# RADIATION THERAPY ONCOLOGY GROUP

# RTOG 0621

# ADJUVANT 3DCRT/IMRT IN COMBINATION WITH ANDROGEN SUPPRESSION AND DOCETAXEL FOR HIGH RISK PROSTATE CANCER PATIENTS POST-PROSTATECTOMY: A PHASE II TRIAL

**Study Chairs (6/22/09)**


**Principal Investigator**/Radiation Oncology
Mark Hurwitz, M.D.
Harvard Medical School
Dana-Farber/Brigham & Women's Cancer Center
75 Francis Street, ASB1 L2
Boston, MA 02115
Phone: (508) 235-5700/Fax: (508) 235-5432
E-mail: mhurwitz@lroc.harvard.edu

Medical Oncology Co-Chair
Oliver Sartor, M.D.
Tulane Medical School
1430 Tulane Ave., S1-42
New Orleans, LA 70112
Phone: (504) 988-2750/Fax: (504) 988-5059
E-mail: osartor@tulane.edu

Medical Physics Co-Chair
Ying Xiao, Ph.D.
Bodine Center for Cancer Treatment
Thomas Jefferson University Hospital
111 South 11th Street
Philadelphia, PA 19107
Phone: (215) 955-1632/Fax: (215) 955-0321
E-mail: ying.xiao@jeffersonhospital.org

Senior Statistician
Daniel Hunt, PhD
Radiation Therapy Oncology Group/ACR
1818 Market Street, Suite 1600
Philadelphia, PA 19103
Phone: (215) 940-8825/Fax: (215) 928-0153
E-mail: dhunt@acr.org

Urology Co-Chair
Bobby Shayegan, MD, FRCS (C)
McMaster Institute of Urology
50 Charlton Avenue East
Hamilton, ON L8N 4A6
Phone: 905-522-1155 x33982/ Fax: 905-308-7310
E-mail: shayeb@mcmaster.ca



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

**INDEX**

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## SCHEMA

| **Androgen Suppression** | **+** | **External Beam Radiation** | **+** | **Docetaxel** |
|---|---|---|---|---|
| **LHRH Agonist**<br><br>**AND**<br><br>**Non-Steroidal Antiandrogen** (Flutamide TID or bicalutamide daily**)**<br><br>**6 months duration** | | **Starting 8 weeks after initiation of androgen suppression**<br><br>**66.6 Gy/1.8 Gy/fraction** | | **Starting 3-6 weeks after completion of radiation**<br><br>**75 mg/m$^2$ i.v. Day 1 of each 21-day cycle**<br><br>**x 6 cycles** |

Please refer to sections 6.0 and 7.0 for details of radiation and drug administration.

**Patient Population**: (See Section 3.0 for Eligibility)
Pathologically proven diagnosis of adenocarcinoma of the prostate meeting one of the following combinations:

- Gleason score ≥ 7 at the time of prostatectomy and PSA nadir > 0.2ng/ml;
- Gleason score ≥ 8 at the time of prostatectomy and T classification ≥ T3a.

**Required Sample Size: 76**

**RTOG Institution #** _____

**RTOG 0621** **ELIGIBILITY CHECKLIST (4/8/08)**

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

____(Y) 1. Has the patient had a radical prostatectomy for adenocarcinoma less than or equal to 12 months from registration?

____(Y) 2. At the time of prior prostatectomy, did the patient demonstrate one of the following?

- Gleason ≥ 7and post-operative PSA nadir > 0.2 ng/ml with any pT classification
- Gleason ≥ 8, post-operative PSA nadir ≤ 0.2 ng/ml and ≥ pT3a classification.

____(Y) 3. Was the pre-registration PSA done within 6 weeks (42 days) of registration?

____(Y) 4. Is the Zubrod performance status 0 or 1?

____(Y) 5. Is the patient's age greater than or equal to 18?

____(N) 6. Does the patient have lymph node or distant metastases?

____(Y) 7. Did the patient have a history and physical exam within 8 weeks prior to registration?

____(Y) 8.Was a bone scan done within 16 weeks prior to registration showing no evidence of osseous metastases?

____(Y) 9. Was a CT or MRI of the pelvis done within 16 weeks prior to registration showing that no pelvic lymph nodes were greater than 1.5 cm in greatest dimension or if the enlarged lymph node is biopsied, is it negative?

____(Y) 10. Was a CBC with differential done within 28 days prior to registration?

____(Y) 11. Is the absolute neutrophil count (ANC) greater than or equal to 2,000 cells/$mm^3$?

____(Y) 12. Is the platelet count greater than or equal to 100,000 cells/$mm^3$?

____(Y) 13. Is the hemoglobin greater than or equal to 8.0 g/dl?

____(Y) 14. Were serum testosterone, ALT, AST, alkaline phosphatase and bilirubin levels obtained within 28 days prior to registration?

____(Y) 15. Was the patient evaluated by a medical oncologist prior to registration and approved for study participation?

____(N) 16. Does the patient have a prior invasive malignancy (except for non-melanomatous skin cancer) that has not been disease free for greater than or equal to a 3 year period?

____(N) 17. Has the patient received prior chemotherapy for prostate cancer?

__(N/Y) 18. Has the patient received prior chemotherapy of a different cancer (other than prostate cancer)?

____(Y) If yes, was the chemotherapy administered more than 3 years prior to registration?

**(Continued on the next page)**

____(N) 19. Has the patient received prior androgen deprivation for the treatment of prostate cancer?

____(N) 20. Has the patient received prior radiotherapy to the region of the prostate that would result in overlap of radiation therapy fields?

____(N) 21. Does the patient have any active, severe co-morbidity such as: unstable angina and /or congestive heart failure requiring hospitalization within the last 6 months; a transmural myocardial infarction within the last 6 months; an acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration; exacerbation of chronic obstructive pulmonary disease (COPD) or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration; acquired immune deficiency syndrome (AIDS) as based upon current CDC definition or any prior allergic reaction to the study drugs involved in this protocol?

____(N) 22. Is the patient's ALT or AST greater than 1.5 times the institutional upper normal limit?

____(N) 23. Is the patient's alkaline phosphatase greater than 2.5 times the institutional upper normal limit?

____(N) 24. Is the patient's total bilirubin greater than 1.2 times the institutional upper normal limit?

**The following questions will be asked at Study Registration:**

**3DCRT or IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION**

_____ 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 patient provided study-specific consent prior to study entry

_____ 5. Patient's Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]

_____ 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

_____ 12. Patient's Country of Residence

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

**(Continued on the next page)**

**RTOG Institution #** _____

**RTOG 0621** **ELIGIBILITY CHECKLIST (6/22/09)**

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

_____ 14. Patient's Insurance Status

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

_____ 16. Calendar Base Date (Start date of androgen suppression)

_____ 17. Registration date: This date will be populated automatically.

_____ 18. Highest Gleason score in radical prostatectomy specimen of ≥ 7?

_____(Y) 19. Medical Oncology consultation pre-registration?

_____(Y/N) 20. Tissue/Blood/Urine kept for cancer research?

_____(Y/N) 21. Tissue/Blood/Urine kept for medical research?

_____(Y/N) 22. Allow contact for future research?

_____(N/Y) 23. Will IMRT be used?

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

Radical prostatectomy (RP) is a widely utilized treatment for prostate cancer. While a majority of patients with favorable risk features do well, those with high-risk features identified either initially or at the time of surgery have a substantial risk of recurrence of their disease. Radiation therapy has become increasingly popular as a strategy to eradicate residual local disease post-prostatectomy. Single institutional studies examining the role of salvage radiation once there is evidence of disease recurrence, typically identified by a rising PSA, have consistently shown that early institution of treatment once recurrence is defined leads to better outcomes.[1-7] Furthermore, the use of adjuvant radiation therapy (ART) in patients with high risk of recurrence but with an undetectable PSA has yielded the most promising rates of freedom from disease in retrospective series. [8-14]

Three randomized trials have now been completed assessing the role of post-prostatectomy ART with improvement in several disease outcome parameters but not overall survival. The results of the European Organization for Research and Treatment of Cancer trial (EORTC 22911) included patients with pathologic T3 (pT3) disease and/or positive surgical margins. With median follow-up of 5 years, biochemical progression-free survival was significantly improved from 53% to 74% with ART. Clinical progression-free survival as well as freedom from locoregional failure were also improved with ART but not distant failure.[15] Two additional phase III studies reported in abstract form have yielded similar results. A German study, ARO 96-02 found a 21% improvement in biochemical progression-free survival at 4 years with ART (81%) vs. a wait and see approach (60%) for patients with pT3 disease.[16] The Southwest Oncology Group (SWOG) also assessed the impact of ART for patients with pT3 disease with metastasis-free survival as the primary endpoint. With median follow-up of 9.7 years, no statistically significant improvement in metastasis-free survival 71% vs. 61% or overall survival 74% vs. 63% was noted with ART vs. a wait and see approach; however, significant improvement was noted in PSA-free survival, 47% vs. 23% and relapse-free survival, 67% vs. 48%.[17]

While a trend towards improved overall survival was noted in the SWOG study with long-term follow-up, to date no significant impact on overall survival has been demonstrated with ART. The relatively low radiation doses used in these studies, typically in the range of 60–64 Gy may in part be the reason for this lack of survival benefit but given the lack of impact on metastatic disease, it seems most likely the absence of effective systemic therapy in combination with ART for these patients at high risk of harboring micrometastatic disease may be the reason for lack of impact on survival. The present study is designed to provide an initial assessment of efficacy of combining radiation therapy with systemic therapy, including androgen suppression therapy (AST) and docetaxel.

In patients receiving primary radiation treatment for high-risk clinically localized disease, commonly defined as T3 and/or Gleason ≥ 8, addition of AST has been associated with improved overall survival. In an EORTC phase III study Bolla and colleagues found significant improvement in overall survival with the addition of 3 years of AST to radiation for patients with T3 and/or high-grade disease. Actuarial 5-year overall survival with radiation plus goserelin versus radiation alone was 79% and 62%, respectively; disease-free survival was 85% and 48%, respectively. These differences were highly statistically significant. An update of this trial with a median follow-up of 61 months sustains these findings.[18] In a study performed through the Dana-Farber Cancer Institute at Harvard, patients with intermediate to high risk clinically localized disease were randomized to either radiation alone or radiation plus 6 months of total androgen suppression. An improvement in overall survival with the addition of androgen suppression was noted with a 5-year overall survival of 88% in patients receiving radiation plus 6 months of androgen suppression vs. 78% with radiation alone.[19] The Trans-Tasman Radiation Oncology Group (TROG) also found a survival advantage to the addition of 6 months of AST to radiation for primary treatment of locally advanced prostate cancer as defined as ≥ T2b disease. Eight hundred, eighteen men were randomized to radiation alone or with either 3 or 6 months of AST. Compared with no AST, 3 months of AST improved local failure, biochemical failure-free survival, disease-free survival, and freedom from salvage treatment. In addition to improvement in these endpoints, compared to radiation alone, 6 months of AST also resulted in decrease in distant failure and improved prostate cancer specific survival.[20]

Several retrospective analyses have indicated potential advantage to AST in combination with salvage[21-24] or adjuvant radiation therapy.[25] Researchers at Stanford first reported that transient AST and radiation may improve freedom from early biochemical and clinically evident relapse compared to radiotherapy alone in the salvage setting.[21] In a more recent report of 122 patients who received salvage RT after radical prostatectomy, including 53 patients who received a 4-month course of AST, at 5 years, the actuarial bNED rates were 57% for the combined therapy group compared with 31% for the RT alone

group. There was a significant difference in overall survival rates at 5 years, 100% for the combined therapy group compared with 87% for the RT alone group. On multivariable analysis, addition of short-course AST to postoperative RT significantly predicted for bNED and approached significance for overall survival.[22] In regard to ART, the role of AST in combination with relatively low dose RT of 50 Gy was explored in a small Japanese series which suggested potential benefit on cancer control without clear impact on survival in this small series of patients.[25]

The finding of survival benefit with docetaxel in patients with hormone refractory prostate cancer (HRPC) has led to new interest in studying the impact of chemotherapy with this agent in patients with high-risk clinically localized disease. In a study conducted by the Southwest Oncology Group (SWOG) in HRPC, docetaxel and estramustine was compared with mitoxantrone and prednisone in a large phase III study. The docetaxel and estramustine arm resulted in an increase in overall survival of 17.5 months vs. 15.6 months.[26] In a multi-institutional phase III study assessing single agent docetaxel, TAX 327, 1006 men with HRPC were randomized to receive prednisone with either 12mg/m$^2$ mitoxanthrone every 3 weeks, 75mg/m$^2$ docetaxel every 3 weeks, or 30mg/m$^2$ docetaxel weekly. Patients receiving docetaxel on the every-3-week regimen had significantly improved overall survival as compared to mitoxanthrone, 18.9 months vs. 16.5 months with a hazard ratio for death of 0.76. Weekly docetaxel did not result in significantly better survival than mitoxanthrone.[27] Importantly, estramustine has been associated with significant toxicity including an increase in thromboembolic events on RTOG 99-02 requiring premature closure of this first randomized trial of chemotherapy in primary treatment of high-risk clinically localized disease. The finding of survival advantage with single agent docetaxel therefore has provided new impetus for exploring the role of docetaxel in treatment of high-risk localized disease. In early 2006, RTOG 0521, a phase III trial assessing the impact of docetaxel in combination with radiation and AST for primary treatment of high-risk clinically localized prostate cancer opened for accrual. Similar to patients eligible for RTOG 0521, there are patients in the post-prostatectomy setting with high risk of micrometastatic disease including those with pT3 or high-grade disease.

In contemplating use of adjuvant systemic therapy in addition to radiation as opposed to radiation alone it is important to identify patients at greatest risk of failure despite ART. Recent updates of SWOG 8794 and EORTC 22911 suggest that while many patients benefit from ART alone there are subsets of patients with significant short-term risk of failure despite radiation alone.[28, 29] In a recent update of SWOG 8794, patients with pathologic Gleason 8 disease, or those with persistently detectable PSA post-prostatectomy, representing 28% of enrolled patients, had a risk of disease progression by 3 years in the range of 45-55% despite ART.[28] A retrospective analysis from Johns Hopkins assessing prostate cancer specific mortality post-prostatectomy found the 15-year actuarial prostate cancer specific survival rate after biochemical recurrence in patients with recurrence at 3 years or less was 41% compared to 87% in patients with recurrence more than 3 years after radical prostatectomy. On multivariate analysis a shorter time from surgery to prostate specific antigen recurrence was associated with an increased risk of prostate cancer death (3 years or less versus more than 3 years, RR 2.70).[30] It is important to note that the subset of patients described above from the SWOG analysis had an approximately 50% risk of failure at 3 years despite not only surgery but also ART and therefore are likely to be at much greater risk of death from prostate cancer than those identified in the Johns Hopkins series. Given the significant risk of death from prostate cancer in this group despite aggressive local therapy, assessment of combined local and systemic therapy is warranted in this patient population.

## 2.0 OBJECTIVES

### 2.1 Primary Objective

**2.1.1** To assess whether the addition of androgen suppression therapy (AST) and docetaxel to adjuvant radiation therapy (ART) improves freedom from progression (FFP) as defined as PSA < 0.4 ng/ml, and no clinical failure (local-regional, or distant failure) at 3 years

### 2.2 Secondary Objectives

**2.2.1** To assess freedom from local-regional progression, distant metastases, disease-free survival, prostate cancer specific survival, non-prostate cancer specific survival, overall survival, and time to biochemical (PSA) failure

**2.2.2** To evaluate treatment-related “acute” and “late” toxicity based on CTCAE, v3.0

**2.2.3** To evaluate the relationship of genomic and proteomic biomarkers to the primary and secondary clinical endpoints utilizing archival prostatectomy tissue and pretreatment and prospectively collected serum/plasma

## 3.0 PATIENT SELECTION

**NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED**

### 3.1 Conditions for Patient Eligibility (6/22/09)

**3.1.1** Pathologically proven diagnosis of adenocarcinoma of the prostate gland at the time of prior radical prostatectomy meeting one of the following combinations:

- Pathologic Gleason ≥ 7 and post-operative PSA nadir > 0.2 ng/ml with any pT classification;
- Pathologic Gleason ≥ 8, post-operative PSA nadir ≤ 0.2 ng/ml and ≥ pT3a classification.

Enrollment must occur within 1 year from radical prostatectomy.

**3.1.2** Study entry PSA must be obtained within 6 weeks (42 days) prior to registration.

**3.1.3** Zubrod Performance Status 0-1

**3.1.4** Age ≥ 18

**3.1.5** Appropriate stage for protocol entry, including no lymph node or distant metastases (N0, M0), based upon the following minimum diagnostic workup:

**3.1.5.1** History/physical examination within 8 weeks prior to registration

**3.1.5.2** Bone scan and CT or MRI of the pelvis (use of contrast is at the discretion of the treating physician) within 16 weeks prior to registration with no evidence of osseous metastases and no pelvic lymph nodes > 1.5 cm in greatest dimension unless the enlarged lymph node is biopsied and negative.

**3.1.6** CBC/differential obtained within 28 days prior to registration on study, with adequate bone marrow function defined as follows:

**3.1.6.1** Absolute neutrophil count (ANC) ≥ 2,000 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** Testosterone obtained within 28 days prior to registration on study

**3.1.8** Serum ALT, AST, alkaline phosphatase, bilirubin obtained within 28 days prior to registration on study

**3.1.9** Evaluation and approval for study participation by a medical oncologist prior to registration

**3.1.10** Patient must provide study-specific informed consent prior to study entry.

### 3.2 Conditions for Patient Ineligibility (6/22/09)

**3.2.1** Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years

**3.2.2** Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowed if administered > 3 years previously. See Section 3.2.1.

**3.2.3** Prior androgen deprivation for treatment of prostate cancer. Prior use of hormonal agents such as finasteride or dutasteride for treatment of benign prostatic hypertrophy is allowed.

**3.2.4** Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields

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

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

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

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

**3.2.5.4** Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration

**3.2.5.5** 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. Protocol-specific requirements may also exclude immuno-compromised patients.

**3.2.5.6** ALT, AST > 1.5x institutional upper normal limits; alkaline phosphatase > 2.5x institutional upper normal limits; and total bilirubin > 1.2x institutional upper normal limits, obtained within 28 days prior to registration.

**3.2.6** Prior allergic reaction to the study drug(s) involved in this protocol.

## 4.0 PRETREATMENT EVALUATIONS/MANAGEMENT (6/22/09)

Not applicable to this study.

## 5.0 REGISTRATION PROCEDURES

### 5.1 Preregistration Requirements for IMRT Treatment Approach (6/22/09)

**5.1.1** In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the Radiological Physics Center (RPC) web site. Visit http://rpc.mdanderson.org/rpc and select "Credentialing" and "Credentialing Status Inquiry".

An IMRT phantom study with the RPC must be successfully completed (if the institution has not previously met this IMRT credentialing requirement). Instructions for requesting and irradiating the phantom are available on the RPC web site at http://rpc.mdanderson.org/rpc/; select "Credentialing" and "RTOG". Upon review and successful completion of the phantom irradiation, the RPC will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement. Subsequently, RTOG Headquarters will notify the institution that the site can enroll patients on the study.

**5.1.2** The institution or investigator must complete a new IMRT Facility Questionnaire and send it to RTOG for review prior to entering any cases, and set up an SFTP account for digital data submission, both of which are available on the Image-Guided Center (ITC) web site at http://atc.wustl.edu. Upon review and successful completion of the "Dry-Run" test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study.

### 5.2 Preregistration Requirements for 3DCRT Treatment Approach (6/22/09)

**5.2.1** Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in 3DCRT Quality Assurance Guidelines may enter patients to this study.

**5.2.1.1** The new Facility Questionnaire (one per institution, available on the ATC website at http://atc.wustl.edu) is to be sent to RTOG for review prior to entering any cases. Upon review and successful completion of a "Dry-Run" QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study. Institutions that have previously enrolled patients on 3DCRT trials of this same disease site may enroll patients on this study without further credentialing.

### 5.3 Regulatory Preregistration Requirements (6/22//09)

**5.3.1** **U.S. and Canadian sites** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), with the completed CTSU-IRB/REB Certification Form, http://www.rtog.org/pdf_file2.html?pdf_document=CTSU-IRBCertifForm.pdf, prior to registration of the institution's first case:

- IRB/REB approval letter;
- IRB/REB approved consent (English and native language version*);
  ***Note**: Institutions must provide certification of consent translation to RTOG Headquarters
- IRB/REB assurance number.

**5.3.2** *Pre-Registration Requirements FOR CANADIAN INSTITUTIONS*

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.

**5.3.3** *Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS*

**5.3.3.1** **For institutions that do not have an approved LOI for this protocol:**
International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc

**5.3.3.2** **For institutions that have an approved LOI for this protocol:**

All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

**5.3.4** *Pre-Registration Requirements for the Initial Shipment of Docetaxel*: **(4/8/08)**

**5.3.4.1** US and Canadian Institutions

All pre-registration requirements must be met before calling to register the first case.

**U.S. institutions** must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, http://www.rtog.org (next to the protocol). U.S. 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.

**Canadian institutions** must use the Canadian Study Agent Shipment Form (SASF), which can be accessed in the Canadian Information Section on the RTOG web site, at http://www.rtog.org/members/CanadaInfo/0621/0621drug_order.html. The Canadian SASF must be submitted to CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified.

All 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.

**5.3.4.2** Non-Canadian International Institutions

Please refer to your LOI Approval Notification.

Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study. Before drug can be provided your institution must comply with all pre-registration requirements and certifications and provide all necessary documentation listed in your LOI Approval Notification document. After receipt of written approval of submitted LOI forms from RTOG Headquarters, International 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) and 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.

## 5.4 Registration

**5.4.1** *Online Registration*

Patients can be registered only after eligibility criteria are met.

Each individual user 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://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp).
- 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 (http://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.

Institutions can contact RTOG web support for assistance with web registration: websupport@phila.acr.org.

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, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site's user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

## 6.0 RADIATION THERAPY/FUNCTIONAL IMAGING

**Radiation therapy must begin 8 weeks (±2 weeks) after initiation of androgen suppression.**

### 6.1 Dose Specifications

The prostate bed will receive 66.6 Gy at 1.8 Gy/fraction. A 1.8 Gy variation in prescribed dose is allowed (64.8 – 68.4 Gy).

### 6.2 Technical Factors

Either 3D-conformal radiotherapy (3DCRT) or intensity modulated radiotherapy (IMRT) may be used. For 3DCRT, an arrangement using at least 4 fields but no more than 6 fields should be used. For IMRT, no specific field arrangement is required. Megavoltage irradiation with energies of ≥ 6 MV are required.

### 6.3 Localization, Simulation, and Immobilization

Usage of immobilization techniques such as foam leg immobilizers or thermoplastic molds are highly recommended but not required for 3DCRT but are required for IMRT.

### 6.4 Treatment Planning/Target Volumes

(See also Section 6.7.)

**6.4.1** Pelvic and Prostate Bed Planning for 3DCRT

Contrast may be used for simulation but can distort the anatomy slightly and so is not recommended. The bladder should be reasonably full for simulation, keeping in mind that patients will not be able to maintain as full a bladder during radiotherapy. CT-simulation will be performed using 3-5 mm cuts from the top of the sacrum to below the ischial tuberosities.

**6.4.1.1** *Pelvic Field Planning for 3DCRT*

Using the Clinical Target Volume 1 (CTV1) will include the pelvis. CTV1 will generally involve utilizing a 4-field technique. The CTV1 will extend inferiorly from the top of the penile bulb to at a minimum superiorly the bottom of the sacro-iliac joint and at most superiorly to the L5-S1 interspace. Lateral borders will be at least 1 cm lateral to the pelvic brim. In the lateral fields care should be taken to adequately cover the external and internal 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. The CTV1 should be treated to 45 Gy.

**6.4.1.2** *Prostate Bed Planning for 3DCRT*

The CTV2 will encompass the prostate bed. The seminal vesicles or remnants thereof, if identified on CT or MRI as being present, should be included in the CTV2 in their entirety to at least 50.4 Gy and may be treated to full dose at the discretion of the treating physician. The immediate peri-prostatic bed clips, if present, should receive the full dose. The CTV2 will extend inferiorly from the top of the penile bulb to just above the pubic symphysis superiorly at a minimum (at least for the anterior-most portion of the bladder). Laterally, the CTV2 will extend from the medial edge of one obturator internus muscle to the other. Anteriorly and posteriorly the CTV2 will include the entire bladder neck until above the pubic symphysis, where a gradual reduction of the anterior bladder is made. The CTV2 may be increased (not decreased) beyond these limits in order to encompass the entirety of the prostate based on pre-prostatectomy imaging information when available. In addition, the superior, lateral, and posterior extent of the CTV2 should be increased initially as needed to cover any defined remnants of the seminal vesicles, which should be included in the CTV2 to at least 50.4Gy. After 50.4 Gy a conedown to the prostate bed alone is then allowed,

although the seminal vesicles may be treated to full dose at the discretion of the treating physician. If there are no defined remnants of the seminal vesicles identified on the simulation CT then the prostate bed alone will serve as the CTV2 starting at 45 Gy.

The Planning Target Volume 1 (PTV1) and PTV2 margins should be a minimum of 0.8 cm and a maximum of 1.5 cm in all dimensions. A margin for penumbra (usually 0.5-0.7 cm beyond the PTV) should be added such that ≥95% of the PTV1 and PTV2 receive the prescribed dose. The maximum dose heterogeneity allowable in the PTV1 and PTV2 will be 7%; a variation will be >7% and a violation >12%.

The posterior blocked margin at the bladder neck-rectum interface should not include the entire width of the rectum in the PTV2. The rectum will be outlined from the anterior flexion of the rectosigmoid superiorly to the ischial tuberosities inferiorly. Excluding the CTV2, the entirety of the remaining bladder will be outlined. The femoral heads should be outlined down to the region between the greater and lesser trochanters.

**6.4.2** Pelvic and Prostate Bed Planning for IMRT

The CTV1, CTV2, and PTV1, PTV2 will be the same as for 3DCRT; there is no need to add additional margin for penumbra. Use of 3DCRT to treat the CTV1 and IMRT to treat the CTV2 is allowed. A series of dose-volume histograms (DVHs) will be generated and analyzed to determine the adequacy of the plan. At least 95% of the PTV should receive the prescribed dose; a variation will be noted if <95% to 90% of the PTV receives the prescribed dose, and a protocol violation will be noted if <90% of the PTV receives the prescribed dose. The dose marker levels for bladder and rectum have been modeled after prior studies in men treated definitively with IMRT for prostate cancer. [31-32]

**6.4.2.1** The plan will be deemed acceptable under the following conditions. The maximum dose heterogeneity allowable in the PTV will be 15%; a variation will be >15% and a violation >25%. Since the dose is prescribed to the minimum isodose line of the PTV, the dose variability is seen in portions of the target volume receiving higher than the specified dose. Less than or equal to 25% and 50% of the rectum should receive ≥66.6 Gy and ≥50 Gy, respectively. Less than or equal to 40% and 60% of the bladder (minus prostate bed CTV1) should receive ≥66.6 Gy and ≥50 Gy, respectively. The criteria for the bladder have been relaxed because the dosimetric relationship of volume exposed to the specified marker doses is much less clear and the entirety of the bladder is often included in the CTV1. A variation will be noted if up to an additional 7.5% of the rectal and bladder volumes receive above the target doses specified. The inclusion of rectal volumes beyond these constraints will be considered a protocol violation. The inclusion of bladder volumes beyond these constraints will be considered a secondary protocol variation; it will not be considered a protocol violation. For IMRT, no specific field arrangement is required.

## 6.5 Critical Structures (6/22/09)

The normal structures to be contoured will include bladder, rectum, bilateral femora (to the level of ischial tuberosity), penile bulb, and skin. Contours of normal structures should be present on all CT slices on which they appear. Software with an interpolation function may be used with the accuracy of interpolations confirmed by the treating radiation oncologist. If IMRT is used to treat the CTV1 small bowel within the field should also be contoured and dose tracked. 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. The large and small bowels 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 (http://itc.wustl.edu) to view examples of target and normal tissue contours.

## 6.6 Documentation Requirements

**6.6.1** The ITC will facilitate the review of GTV, CTV, PTV, and designated organs at risk (critical structures) on, as a minimum, the first five cases submitted by each institution. After an institution has demonstrated compliance with the protocol, future cases will receive ongoing remote review.

**6.6.2** The institution will archive treatment prescription and verification images for later review by the study chair if requested. At least one port film or pretreatment alignment film per field along with the digital reconstructed radiographs (DRRs) from the treatment planning program or,

alternatively, a simulation verification radiograph shall be acquired and kept for evaluation if requested except where geometrically impractical.

**6.6.3** The ITC will display, and compare with hard copies, isodose distributions for the axial and coronal planes (or multiple axial planes as outlined in QA Guidelines) through the planning target volume to verify correct digital submission and conversion.

**6.6.4** The ITC will compare the submitted DVHs for the PTV, designated critical structures, and unspecified tissues with DVHs calculated by the ITC.

## 6.7 Compliance Criteria

| **3DCRT** | **Dose Goal (Prescription, Gy) (Dp)** | **PTV Volume Receiving Goal Dose** | **PTV Dose Heterogeneity (D2-D98)/Dp** | | **Minimum CTV Dose (Gy)** |
|---|---|---|---|---|---|
| | | | No Variation | Minor Variation | |
| Target Volume 1 | 66.6±1.8 | ≥95% | ≤7% | 8-12% | 66.6±1.8 |
| Target Volume 2 | 50.4 | ≥95% | ≤7% | 8-12% | 50.4 |

| **IMRT** | **Dose Goal (Prescription, Gy) (Dp)** | **PTV Volume Receiving Goal Dose** | | **PTV Dose Heterogeneity (D2-D98)/Dp** | | **Minimum CTV Dose (Gy)** |
|---|---|---|---|---|---|---|
| | | No Variation | Minor Variation | No Variation | Minor Variation | |
| Target Volume 1 | 66.6±1.8 | ≥95% | 90-94% | ≤15% | 16-25% | 66.6±1.8 |
| Target Volume 2 | 50.4 | ≥95% | 90-94% | ≤15% | 16-25% | 50.4 |

| **IMRT** | **Volume Receiving ≥66.6 Gy** | | **Volume Receiving ≥50 Gy** | |
|---|---|---|---|---|
| Normal Organ Limit | No Variation | Minor Variation | No Variation | Minor Variation |
| Bladder | ≤40% | 41-47.5% | ≤60% | 61-67.5% |
| Rectum | ≤25% | 26-32.5% | ≤50% | 51-57.5% |

| **Assessment** | **Per Protocol** | **Variation, Acceptable** | **Deviation, Unacceptable** |
|---|---|---|---|
| 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 |

## 6.8 R.T. Quality Assurance Reviews

The Radiation Oncology Co-Chair, Mark Hurwitz, M.D., will perform an RT Quality Assurance remote review after complete data for the first 20 cases enrolled has been received at ITC. Dr. Hurwitz will perform the next remote review after complete data for the next 20 cases enrolled has been received at ITC. 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 has been received at ITC, whichever occurs first. These reviews will be ongoing and performed remotely.

## 6.9 Radiation Therapy Adverse Events (6/22//09)

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.

**6.10 Patient Preparation**

Bowel preparation with enema prior to simulation is strongly encouraged.

**6.11 Radiation Adverse Event Reporting**

See Sections 7.9 for Adverse Events and 7.10 for Adverse Event Reporting Guidelines.

## 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

**7.1.1** Androgen Suppression

Patients will receive androgen suppression (AS) (LHRH agonist and oral antiandrogen) for 6 months starting within 6 weeks after registration. Radiation therapy will begin 8 weeks (±2 weeks) after the initiation of hormone treatment and will be given as specified in Section 6.0.

**7.1.2** Chemotherapy

Patients will also receive six cycles of docetaxel beginning 3-6 weeks 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 but doses of dexamethasone may be altered at the treating physician's discretion after the first cycle).

**7.1.3** Duration of Treatment

As outlined above, AS will be administered for a total of 6 months; docetaxel treatments will be planned every 21 days for a total of six cycles.

### 7.2 LHRH Agonists (such as leuprolide, goserelin, buserelin, triptorelin)

**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** Administration

LHRH analogs are administered with a variety of techniques and durations, including subcutaneous insertion of a solid plug in the abdominal wall (Zoladex), intramuscular injection (Lupron), or subcutaneous injection (Eligard). The manufacturer's instructions should be followed to achieve a total duration of 6 months of treatment with a LHRH analogue (i.e., 6 injections of a 1-month formulation, 2 injections of a 3-month formulation, 1 injection of a 6-month formulation).

**7.2.3** Adverse Events

Consult the package insert for comprehensive adverse events (AEs) information. Class-related adverse events are 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 adverse event of LHRH analogs is vasomotor hot flashes; edema, gynecomastia, bone pain, thrombosis, and gastrointestinal disturbances have also 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 adverse events 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, muscle mass and strength loss, hair changes, penile length and testicular volume loss, increased cholesterol, hypertension, diabetes exacerbation, emotional lability, increased risk of cardiovascular events, including fatal myocardial infarction, nausea, vomiting, and, rarely, allergic generalized rash and difficulty breathing.

**7.2.4** Storage

LHRH analogs should be stored as directed by the commercial supplier.

**7.2.5** Supply

Commercially available (Note: Buserelin is not commercially available in the United States. It is commercially available for use in Canada and other countries.)

**7.2.5.1** **Non-Canadian International Institutions (6/22/09, 7/9/09)**

Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study.

## 7.3 Flutamide (Eulexin)

**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** 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 at the same time as the LHRH analogue (+/- minus 1 week) approximately 8 weeks prior to radiotherapy and continued for a total period of 6 months. The last day of the flutamide should be 180 days after the first dose. Administration will be suspended only if there is an apparent or suspected toxicity from the drug. (See Section 7.3.4.) During radiotherapy interruptions, flutamide will be continued.

**7.3.3** Adverse Events

Consult the package insert for comprehensive adverse event information. The reported adverse events 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 adverse events include impotence and loss of libido, fatigue, and, rarely, photosensitivity.

**7.3.4** 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 adverse event 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 ≥ 2x upper institutional limit of normal, flutamide must be discontinued.

**7.3.5** Storage

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

**7.3.6** Supply

Commercially available

**7.3.6.1** **Non-Canadian International Institutions (6/22/09, 7/9/09)**

Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study.

## 7.4 Bicalutamide (Casodex)

**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.[33-34]

**7.4.2** Administration

Bicalutamide is administered orally at a dose of one 50 mg tablet per day. Bicalutamide will begin at the same time as the LHRH analogue (+/- one week) approximately 8 weeks prior to radiotherapy and continued for a total period of 6 months. The last day of the bicalutamide should be 180 days after the first dose. Administration will be suspended only if there is an

apparent or suspected reaction to the drug. During radiotherapy interruptions, bicalutamide will be continued.

**7.4.3** Adverse Events

Consult the package insert for comprehensive adverse event 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 6 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.

**7.4.4** Dose Modifications

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

**7.4.5** Storage

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

**7.4.6** Supply

Commercially available

**7.4.6.1** **Non-Canadian International Institutions (6/22/09, 7/9/09)**

Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study.

## 7.5 Docetaxel (Taxotere)

**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** Administration

Dosage per schedules in Section 7.1.2. 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.

**7.5.3** Adverse Events

Consult the package insert for comprehensive adverse event information.

**7.5.3.1** *Hematologic*

Neutropenia (virtually in 100% of patients given 100 mg/m$^2$) leukopenia, thrombocytopenia, anemia, febrile neutropenia

**7.5.3.2** *GI*

Nausea and vomiting, diarrhea, stomatitis, abdominal pain, constipation, ulcer, esophagitis, GI hemorrhage, intestinal obstruction, ileus, loss of appetite, taste changes

**7.5.3.3** *Cardiac*

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)

**7.5.3.4** *GU*

Blood in urine (rare)

**7.5.3.5** *Respiratory*

Dyspnea, acute pulmonary edema, ARDS

**7.5.3.6** *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

**7.5.3.7** *Hypersensitivity*

Flushing, localized skin reactions, severe hypersensitivity reactions characterized by hypotension, bronchospasm, or generalized rash/erythema

**7.5.3.8** *Musculoskeletal*

Myalgia, arthralgia, muscle cramps, muscle weakness

**7.5.3.9** *Neurologic*

Paresthesia, dysesthesia, pain in patients with anthracycline-resistant breast cancer; distal extremity weakness

**7.5.3.10** *Reactions at Infusion Site*

Hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis, extravasation, mild swelling of the vein

**7.5.3.11** *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)

**7.5.4** Dose Modifications

**7.5.4.1** *Hematologic Adverse Events*

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, scheduled treatment. Dose modification is for the next cycle and all subsequent cycles.

There will be no dose escalations once a dose reduction has occurred with docetaxel. No more than two dose reductions can occur. If more than two dose reductions are required the docetaxel should be discontinued and the patient followed as per protocol.

Docetaxel must not be administered until granulocyte count is ≥ 1,500 cell/mm$^3$ and platelet count ≥100,000 as measured either the day before, or day of, docetaxel administration. If counts are below these levels, re-check weekly and retreat using parameters outlined below (based on the originally scheduled date of docetaxel administration, i.e., 3 weeks after the prior docetaxel dose). If the neutropenia/thrombocytopenia does not resolve to a point that allows chemotherapy dosing by 15 days of a scheduled chemotherapy date, discontinue protocol chemotherapy.

**Table 1: % Calculated Dose**

| | | **Platelet Count** | | |
|---|---|---|---|---|
| | | ≥ 100K | 75-99K | < 75K |
| **ANC (x 1000)** | ≥ 1.5 | 100% | 75% | 50% |
| | 1.0 - 1.499 | 75% | 75% | 60% |
| | < 1.0 | 60% | 60% | 60% |

**7.5.4.2** *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.

**Table 2: Docetaxel Dose Modification for Elevated Liver Function on Day of Treatment**

| | **AST/ALT:** | | |
|---|---|---|---|
| **ALK PHOS:** | ≤ ULN | >1x but ≤ 1.5 x | > 1.5x ULN |
| ≤ ULN | 100% | 100% | Hold* |
| > 1x but ≤ 2.5x | 100% | 100% | Hold* |
| > 2.5x but ≤ 5x | 100% | 75% | Hold* |
| > 5x ULN | Hold* | Hold* | Hold* |

*Hold until AST/ALT recovered, repeat weekly for a maximum 21 days, and then re-treat at a reduced dose (reduce docetaxel dose by 25%) when AST/ALT are <1.5 X ULN as measured the day before, or day of, docetaxel administration. Use reduced dosage for all subsequent cycles in that patient. Note, no more than two dose reductions can occur; each dose reduction should be 25% of the prior cycle dosing. If more than two dose reductions are required, discontinue docetaxel and follow patient as per protocol.

**7.5.4.3** *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.

**7.5.4.4** *Stomatitis*

If any grade stomatitis is present on Day 1 of any cycle, treatment should be withheld until stomatitis has completely resolved; however, more than 15 days of delay beyond a scheduled chemotherapy date should result in discontinuation of protocol chemotherapy administration. If Grade 3/4 stomatitis occurs at any time, the dose of docetaxel should be reduced by 25% for subsequent cycles.

**7.5.4.5** *Hypersensitivity Reactions*

There are no dose reductions for hypersensitivity reactions.

**Table 3: 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 i.v. with or without dexamethasone 10 mg i.v.; 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 i.v. premedication with an antihistamine and a glucocorticoid such as dexamethasone 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 i.v. with or without dexamethasone 10 mg i.v. 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 |

**7.5.4.6** *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.

**7.5.4.7** *Other Non-Hematologic Adverse Events*

For other Grade 3 and 4 adverse events, treatment should be withheld until the adverse events resolve to Grade 1 or less, then restarted (if medically appropriate) with a 25% dose reduction.

**7.5.5** 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.

**7.5.6** Supply **(4/8/08)**

**7.5.6.1** Sanofi-Aventis will supply docetaxel free of charge to patients entered on this trial in U.S and Canadian institutions.

All pre-registration requirements must be met before calling to register the first case.

**U.S. institutions** must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, http://www.rtog.org (next to the protocol). U.S. 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.

**Canadian institutions** must use the Canadian Study Agent Shipment Form (SASF), which can be accessed in the Canadian Information Section on the RTOG web site, at http://www.rtog.org/members/CanadaInfo/0621/0621drug_order.html. The Canadian SASF must be submitted to CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified.

All 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.

**7.5.6.1.1** **Non-Canadian International Institutions (6/22/09)**

Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study. Before drug can be provided your institution must comply with all pre-registration requirements and certifications and provide all necessary documentation listed in your LOI Approval Notification document.

**7.5.7** Distribution

**7.5.7.1** *U.S. Institutions* **(4/8/08, 6/22/09)**

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.

The drug supply will not be shipped by Sanofi-Aventis until the patient has been registered. Sanofi-Aventis generally ships drug Mondays through Thursdays. RTOG will notify Sanofi-Aventis, to initiate each of these shipments after registration of the patient. Drug shipments may not be immediate if the protocol includes a delay in the initial dosing. Drug will be delivered in time for the patient's first dose. Each institution is responsible for notifying the RTOG Regulatory Associate at 215-574-3185 if the drug does not arrive on the expected date.

All docetaxel vials must be destroyed at the site according to the protocol and site regulations. Destruction can only occur after accountability has been performed and documented and any discrepancies have been investigated and satisfactorily explained. The site should keep all supporting documentation. Additional questions about supply and delivery should be directed to:

**Sanofi-Aventis**
**Yasir Nagarwala, MD**
**(908) 981-4871; FAX: (908) 203-7697**
**clinsupplies@sanofi-aventis.com**

**7.5.7.2** *Canadian Institutions* **(4/8/08, 6/22/09)**
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 CTSU Regulatory Office (Fax 215-569-0206) prior to registering the first patient. Headquarters will fax the completed form to Sanofi-Aventis Canada once all regulatory documents are received. Please allow one week prior to registering your first case to receive your shipment.

Sanofi-Aventis Canada will ship medication and shipping documents via specialized 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.

The drug supply will not be shipped by Sanofi-Aventis until the patient has been registered. Sanofi-Aventis generally ships drug Mondays through Thursdays. Canadian and International shipments may require additional time. RTOG will notify Sanofi-Aventis Canada, to initiate each of these shipments after registration of the patient. Drug shipments may not be immediate if the protocol includes a delay in the initial dosing. Drug will be delivered in time for the patient's first dose. Each institution is responsible for notifying the RTOG Regulatory Associate at 215-574-3185 if the drug does not arrive on the expected date.

All docetaxel vials must be destroyed at the site according to the protocol and site regulations. Destruction can only occur after accountability has been performed and documented and any discrepancies have been investigated and satisfactorily explained. The site should keep all supporting documentation. Additional questions about supply and delivery should be directed to:

**Sanofi-Aventis Canada**
**Planner, Clinical Supplies**
**Phone: 514-956-6165**
**Fax: 514-856-8722**

**7.5.7.2.1** *Non-Canadian International Institutions* **(6/22/09)**
Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study. Before drug can be provided your institution must comply with all pre-registration requirements and certifications and provide all necessary documentation listed in your LOI Approval Notification document.

**7.5.8** Re-Supply for U.S. and Canadian Institutions
To receive docetaxel re-supply, complete the "Request for Clinical Medication" form included in each drug shipment, and fax it to Sanofi-Aventis, 908-635-5941, as per the instructions on the form.

## 7.6 Dexamethasone

**7.6.1** Description
Corticosteroid, glucocorticoid-type

**7.6.2** Administration
To reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reaction, premedication with dexamethasone is required for all patients receiving docetaxel therapy. One of two regimens can be used, 8 mg orally twice daily for 6 doses, starting 24 hours before the planned dose of chemotherapy, or 8 mg orally at 12, 3, and 1 hour(s) prior to docetaxel. An intravenous dose of dexamethasone may be given on the day of chemotherapy for antiemetic support. Individual physicians can modify this corticosteroid dosing during a second or subsequent cycle of docetaxel if the first dose of docetaxel was safely administered with one of these prescribed regimens.

**7.6.3** Adverse Events
Consult the package insert for comprehensive adverse event information.

**7.6.3.1** *Cardiac*
Hypertension

**7.6.3.2** *Musculoskeletal*
Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis

**7.6.3.3** *GI*
Weight gain, increase in appetite

**7.6.3.4** *Dermatologic*
Impaired wound healing

**7.6.3.5** *Neurologic*
Mood changes, difficulty sleeping

**7.6.3.6** *Hormonal*
Addison's disease; increased blood sugar content, possibly resulting in diabetes

**7.6.3.7** *Ophthalmic*
Cataracts, glaucoma

**7.6.3.8** *Other*
Increased risk of infection

**7.6.4** Dose Modifications
Dexamethasone may be dose modified at the discretion of the treating physician after the first dose of docetaxel is safely administered using one of the prescribed regimens noted above.

**7.6.5** Storage
Store at room temperature.

**7.6.6** Supply
Commercially available

**7.6.6.1** **Non-Canadian International Institutions (6/22/09, 7/9/09)**
Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study.

## 7.7 Accountability

Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines.

## 7.8 Modality Review

**7.8.1** 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/Acceptable Variation, Not Per Protocol, and Not Evaluable**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

**7.8.2** Dr. Sartor will perform a Quality Assurance Review after complete data for the first 20 cases enrolled have been received at RTOG Headquarters. Dr. Sartor will perform the next review after complete data for the next 20 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.

## 7.9 Adverse Events (12/23/10)

As of January 1, 2011, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4, for grading of all adverse events reported via AdEERS; **all case report forms will continue to use CTCAE version 3.0**. A copy of the CTCAE version 4 can be downloaded from the CTEP home page (http://ctep.cancer.gov) or the RTOG web site (http://www.rtog.org/members/toxicity/main.html). All appropriate treatment areas should have access to a copy of the CTCAE version 4.

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.

**7.9.1 Adverse Events (AEs) (6/22/09)**

**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*. January 2005.]

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 7.9 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.**

**7.9.2 Serious Adverse Events (SAEs) (6/22/09) — 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 adverse 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 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.

**7.9.3 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 via the AdEERS system within 30 days of AML/MDS diagnosis. If you are reporting in CTCAE version 4, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy.

## 7.10 AdEERS Expedited Reporting Requirements (6/22/09)

CTEP defines expedited AE reporting requirements for phase 2 and 3 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 2 and 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 Commercially Available Agents [LHRH Agonists, flutamide, bicalutamide, docetaxel] in this Study**

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

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with a Commercially Available agent 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.

**Please see exceptions below under section entitled "Additional Instructions or Exceptions."**

March 2005

**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 with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

**Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercially Available Agent:**
Expected Grade 4 ANC and platelet toxicity from docetaxel should be excluded from AdEERS reporting.

## 8.0 SURGERY

All patients must have undergone radical prostatectomy prior to being considered for enrollment in this study.

## 9.0 OTHER THERAPY

### 9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

**9.1.1** Antiemetics

Please refer to current ASCO guidelines for antiemetic regimens regarding the use of docetaxel.

**9.1.2** Growth Factors

FDA approved growth factors to support either neutrophil recovery or hemoglobin may be used in conjunction with protocol treatment at the discretion of the treating physician. FDA approved growth factors to support neutrophil counts are encouraged for patients experiencing significant neutropenia after docetaxel chemotherapy.

## 10.0 TISSUE/SPECIMEN SUBMISSION (6/22/09)

**For patients who have consented to participate in the tissue/blood/urine component of the study (See Appendix I).**

**NOTE: Patients must be offered the opportunity to participate in the tissue/blood/component.**
If the patient consents to participate in this component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. **Note**: Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

### 10.1 Tissue/Specimen Submission

The RTOG Biospecimen Resource at the University of California 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 Biospecimen Resource 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.

**10.2 Specimen Collection for Tissue Banking for Biomarker Studies (6/22/09) (Strongly Recommended)**

**For patients who have consented to participate in the tissue/blood/urine component of the study (See Appendices V and VI).**

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

**10.2.1.1** A paraffin-embedded tissue block of the tumor (most preferred). If the block cannot be obtained, then 10-15 unstained slides (please use charged or "Plus" slides) from the block of the tumor. Tissue block 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 block or slides contain(s) 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, buffy coat cells and urine

See Appendices V and VI for the tissue, blood, and urine collection kits and instructions.

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; the RTOG protocol number, the patient's case number, and method of storage, for example, stored at -80° C, must be included.

**10.2.1.2.1** *Timing of serum collection*

Serum collection should be done prior to initiation of hormonal therapy, on Day 1 of radiation therapy, Day 1 of chemotherapy, and at 1 month after completion of chemotherapy.

**10.2.1.2.2** *Serum collection and processing*

- Serum specimens will be collected in red-top tubes (10 mL tubes). A total of 20cc should be collected for each time point.
- After allowing the serum to clot, keep serum tubes at 4° C until processing (tubes may be on ice up to 2 hrs). Centrifuge specimens at 1000 x g (approximately 2500 RPM for standard clinical centrifuge) at 4° C for 10 minutes.
- Using sterile techniques to avoid contamination, aliquot 0.5-1 mL serum into cryovials and freeze. Take great care to collect only serum and avoid collecting any solid particulate matter before transferring serum into the cryovials.
- Label each aliquot with study protocol and case numbers, the date and time of collection, specimen type (i.e., serum) and the time point taken.

**10.2.1.3** Specimen Collection Summary **(6/22/09)**

| **Specimens for Tissue Banking** | | | |
|---|---|---|---|
| **Specimens taken from patient:** | **Specimens collected when:** | **Submitted as:** | **Shipped:** |
| A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or 10-15 unstained slides | From pre-treatment 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 | Pre-treatment, Day 1 of RT, Day 1 of chemotherapy, then 1 month after completion of chemotherapy | 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 | Pre-treatment, Day 1 of RT, Day 1 of chemotherapy, then 1 month after completion of chemotherapy | 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 | Pre-treatment | Frozen buffy coat samples in 1 mL cryovials | Buffy coat sent frozen on dry ice via overnight carrier |
| 5-15 mL clean-catch urine | Pre-treatment | A minimum of 5 mL unpreserved urine in a sterile collection container | Urine sent frozen on dry ice via overnight carrier |
| A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment, preferably at least two blocks, containing both cancerous and normal tissue | From pre-treatment radical prostatectomy specimen | Paraffin-embedded tissue blocks containing both normal and cancerous tissue if possible (minimum of two blocks) | Blocks sent at ambient temperature |

**10.3 Submit materials for Tissue Banking as follows: (6/22/09)**

**U.S. Mailing Address: For Non-frozen Specimens Only**
**RTOG Biospecimen Resource**
**University of California San Francisco**
**Campus Box 1800**
**1657 Scott Street, Room 223**
**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; RTOG@ucsf.edu**

**10.4 Reimbursement (6/22/09)**

RTOG will reimburse submitting institutions $300 per case for buffy coat cells, serum, and plasma; $200 per case for a block of material; $100 per case for 10-15 slides; and $50 for urine. 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.

### 10.5 Confidentiality/Storage

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

**10.5.1** 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.

**10.5.2** 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: See Appendix II for a summary of assessments and time frames.

### 11.2 Evaluation During Treatment (6/22/09)

**11.2.1** During androgen suppression, performance status, serum ALT, AST, alkaline phosphatase, and bilirubin should be checked at least monthly.

**11.2.2** Prior to the start of radiation therapy, performance status, CBC/differential and ANC, AST, ALT, alkaline phosphatase, bilirubin, PSA, and testosterone, should be evaluated.

**11.2.3** Prior to the start of chemotherapy, performance status, CBC/differential and ANC, AST, ALT, alkaline phosphatase, bilirubin, PSA, and testosterone level should be evaluated.

**11.2.4** During chemotherapy, performance status, CBC/differential and ANC, AST, ALT, alkaline phosphatase, and bilirubin should be checked at the start of each cycle. CBC/differential and ANC may also be checked on Days 8 and 15 of each cycle.

### 11.3 Evaluation During Follow Up (6/22/09)

**11.3.1** Performance status, PSA, and testosterone should be obtained at the end of RT (4 months) and then every 3 months (until the end of year 2). If a PSA of > 0.4 ng/ml is recorded, a repeat PSA should be obtained to verify progression.

**11.3.2** After year 2, a PSA should be obtained every 6 months for 3 more years, then at least annually for the remainder of the patient's life. If a PSA of > 0.4 ng/ml is recorded, a repeat PSA should be obtained to verify progression. Testosterone levels should be obtained after year 2 only if the testosterone has not previously returned to a normal range (> 240 ng/dL).

**11.3.3** 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.

**11.3.4** Bone scans and a pelvic CT or MRI (use of contrast is at the discretion of the treating physician) are recommended at least yearly, or more often if clinically indicated, after PSA progression to determine rates of metastatic progression.

### 11.4 Measurement of Effect

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

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

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

**11.4.2.2** *Progressive Disease*: This rating will be assigned when there is clinical evidence in the prostate fossa of disease progression or recurrence measured by a clear nodule that is proven by biopsy or a nodule measuring at least 2X2 cm in diameter.

### 11.5 Other Response Parameters

**11.5.1** Biochemical (PSA) Failure

A biochemical (PSA) failure event will be a PSA ≥ 0.40 ng/ml confirmed by a second PSA higher than the first by any amount, or initiation of hormone therapy. Time to failure will be measured from the date of registration to the date of the failure event. Local-regional failure will be defined as biopsy-proven failure.

**11.5.2** Time to Distant Failure

The time to distant failure will be measured from the date of registration to the date of documented metastatic disease. Patients with evidence of PSA failure but a negative prostate fossa biopsy (recommended if a fossa nodule is present but not required) will be considered to have experienced only a distant failure.

**11.5.3** Freedom from Progression

The failure event for this endpoint will be defined as the first occurrence of local-regional failure, distant failure, PSA failure, or death. Time to freedom from progression will be measured from the date of registration to the date of the failure event. This endpoint includes all measures of disease including physical exams, PSA, bone scans, and biopsies.

**11.5.4** Survival

The survival time will be measured from the date of registration 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. Deaths will be classified into prostate cancer or non-prostate cancer related death by the principal investigator.

**11.5.4.1** *Prostate Cancer Related Death*

The failure event for prostate cancer will be defined as:

1. Primary cause of death certified as due to prostate cancer;
2. Death from a complication of therapy, irrespective of disease status;
3. Deaths of patients with hormone-refractory disease unless clear evidence is presented otherwise.

Prostate cancer related death will be measured from the date of randomization to the date of death due to prostate cancer.

**11.5.4.2** *Non-Prostate Cancer Related Death*

Non-prostate cancer related death is defined as any death excluding prostate cancer related death. It will be measured from the date of randomization to the date of death.

## 11.6 Criteria for Discontinuation of Protocol Treatment

Protocol treatment may be discontinued for any of the following reasons:

- 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 7.5.4.1 that do not resolve by Day 15 of cycle or within 15 days of toxicity;
- A delay in protocol treatment ≥ 8 weeks, or as specified in Sections 6.0 and/or 7.0.

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

## 12.0 DATA COLLECTION

**Data should be submitted to:**

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

***If a data form is available for web entry, it must be submitted electronically.**

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 (4/8/08, 6/22/09)

| 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 |
| Initial Follow-Up Form **(F0)** | At 8 weeks from start of androgen suppression therapy and prior to RT start (at 2 months); at the end of RT and prior to chemotherapy start (at 4 months); at 7 and 10 months (at the completion of androgen suppression and chemotherapy) |
| Follow-Up Form **(F1)** | At 13 months, then every three months until the end of year two, then every six months x 3 years, then annually |
| Treatment Summary Form **(TF)** | After each cycle of chemotherapy |

**For protocols involving submission to ITC:**

### 12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1) (6/22/09)

| Item | Due |
|---|---|
| **Preliminary Dosimetry Information (DD)**<br>†Digital Data Submission Form – Treatment Plan submitted to ITC via SFTP account exported from treatment planning machine by Physicist<br>Digital data submission includes the following:<br>▪ CT data, critical normal structures, all GTV, CTV, and PTV contours<br>▪ Digital beam geometry for initial and boost beam sets<br>▪ Doses for initial and boost sets of concurrently treated beams<br>▪ Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan | Within 1 week of start of RT |
| Digital Data Submission Information **(DDSI)** – Submitted online (Form located on ATC web site, http://atc.wustl.edu/forms/ddsi/ddsi.html) | |

| | |
|---|---|
| Hard copy isodose distributions for total dose plan as described in QA guidelines† **(T6)** | |
| **NOTE: Sites must notify ITC via e-mail (itc@castor.wustl.edu) after digital data is submitted. The e-mail must include study and case numbers or, if the data is phantom, "dry run" or "benchmark".** | |
| **Final Dosimetry Information**<br>Radiotherapy Form **(T1) [copy to HQ and ITC]**<br>Daily Treatment Record **(T5) [copy to HQ and ITC]**<br>Modified digital patient data as required through consultation with Image-Guided Therapy QA Center | Within 1 week of RT end |

†Available on the ATC web site, http://atc.wustl.edu/

**NOTE**: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.

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

Digital data submission may be accomplished using media or the Internet.

For network submission: The SFTP 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 media submission: Please contact the ITC about acceptable media 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

### 13.1 Study Endpoints

**13.1.1** Primary Endpoint **(6/22/09)**

Freedom from progression (FFP): Failure for FFP will be the first occurrence of biochemical failure by PSA ≥ 0.4 ng/ml over the nadir PSA confirmed by a second PSA higher than the first by any amount, clinical failure (local, regional or distant), and death from any cause. The primary endpoint FFP rate by 3 years is defined as the proportion of patients without a FFP failure by 3 years from the registration among all eligible patients at baseline.

**13.1.2** Secondary Endpoints

**13.1.2.1** To assess the following clinical outcomes:

- Local-regional progression: See Section 11.4.
- Distant metastasis: See Section 11.5.2.
- Prostate cancer specific survival: See Section 11.5.4.
- Non-prostate cancer specific survival: See Section 11.5.4.
- Overall survival: See Section 11.5.4.
- Time to biochemical (PSA) failure: See Section 11.5.1.

**13.1.2.2** Incidence of "acute" adverse events (based on CTCAE, v3.0): The first occurrence of worst severity of the adverse event ≤ 90 days of the completion of treatment (3 weeks after the last planned docetaxel dose).

**13.1.2.3** Time to "late" Grade 3+ adverse events (based on CTCAE, v3.0): The time of a first late adverse event occurrence of the Grade 3+ adverse event between 91 days and 730 days from the completion of treatment (3 weeks after the last planned docetaxel dose) will be evaluated.

**13.1.2.4** Prognostic value of genomic and proteomic markers for the primary and secondary clinical endpoints

### 13.2 Sample Size **(6/22/09)**

The primary goal of this study is to estimate the rate of FFP by 3 years of the addition of androgen suppression therapy (AST) and docetaxel to adjuvant radiation therapy (ART) in men receiving post-prostatectomy

We expect that ≥ 50% of patients will experience a FFP failure event without treatment post-prostatectomy, which is a projected rate by a recent update of SWOG 8794. AST + docetaxel + ART will be considered to have superior therapeutic efficacy vs. ART alone if the failure rate is ≤ 30% at 3 years thereby warranting further investigation. The rate of FFP at 3 years is denoted as $p_t$. The null hypothesis ($H_0$) is that AST and docetaxel + ART after prostatectomy will yield a FFP rate at 3 years ≤ 50% versus the alternative hypothesis ($H_A$) that AST and docetaxel + ART after prostatectomy will improve the FFP rate at 3 years by 20%. The hypotheses are:

$$H_0: p_t \leq 0.5 \text{ vs. } H_A: p_t \geq 0.7$$

The sample size, 69, is calculated based on the above hypotheses with Fleming's Multiple Testing Procedure[35] at a significance level of 0.025 with 90% statistical power. Adjusting the number of cases for ineligible or unanalyzable cases by 10%, **a maximum of 76 patients is required for this study.** With three stage testing and a sample size of 76 patients, the actual type I and II error rates are 0.015 and 0.083, respectively.

### 13.3 Patient Accrual

Based upon patient accrual in previous RTOG prostate studies, there will be negligible accrual during the initial 6 months while institutions are obtaining IRB approval. The patient accrual is projected to be 3 patients per month considering the previous RTOG prostate study RTOG 9601 and the characteristics of this patient population. The total accrual of RTOG 9601 was 840 and the monthly accrual was 14 patients per month. About 18% of patients in RTOG 9601 have similar patients' characteristics (Gleason score >7) with this study. We expect to complete accrual in 3 (> 2.7 years) years. If at 21 months after study activation the average monthly accrual between months 16 and 21 is less than 1 patient, the feasibility of completing the study will be discussed with the study chairs, the RTOG GU Cancer Committee chair, and the RTOG Executive Committee. If the accrual rate is higher than the projected rate, we will amend the protocol to reflect the actual accrual rate.

## 13.4 Analysis Plan

### 13.4.1 Primary Endpoint **(6/22/09)**

We hypothesize that the addition of androgen suppression therapy (AST) and docetaxel to adjuvant radiation therapy (ART) will improve freedom from progression (FFP) at 3 years by 20% in men at high risk of failure post-prostatectomy despite use of ART. A failure event for FFP is defined as biochemical (PSA) failure (a PSA ≥ 0.40 ng/ml confirmed by a second PSA higher than the first by any amount, or initiation of hormone therapy), clinical failure (local-regional or distant failure), or death from any cause by 3 years from registration. The FFP rate, pt, is defined as the proportion of patients without a failure event for FFP by 3 years from the registration among all eligible patients at baseline. The stopping and continuation rules in Table 1 will be applied for the interim analyses. If at any stage, we stop and reject the null hypothesis ($H_0$) and show that a FFP rate may be at least 70%, we would conclude that the AST and docetaxel + ART is effective, stop the accrual (if applicable) and report the result. If we stop and reject the alternative hypothesis ($H_A$) at any stage, claiming that a FFP rate may be less than 50%, we stop the accrual (if applicable) and conclude that the treatment is not effective and report the result. If we continue until the last stage, we will conclude that the AST and docetaxel + ART is effective or not effective. We will report the conclusion of the primary endpoint when all patients have at least 3 years of follow-up from the registration unless we stop at any interim stage. The FFP rate by 3 years will be calculated as the number of patients who do not have FFP failure events by 3 years divided by the total number of analyzable patients at the evaluation time point.

**Table 1: Number of FFP Events for Stopping and Continuation Rules**

| Number of analyzable patients* | Stop and reject $H_0$: $p_t \leq 0.5$ | Continue Accrual | Stop and reject $H_A$: $p_t \geq 0.7$ |
|---|---|---|---|
| 23 | ≥ 21 | 10-20 | ≤ 9 |
| 46 | ≥ 32 | 27-31 | ≤ 26 |
| 69 | ≥44 | N/A | ≤ 43 |

* Analyzable patients are defined as eligible patients who received any protocol treatment with at least 3 years follow-up from registration

If a Grade 5 adverse event definitely, probably, or possibly related to treatment is reported within 2 years from the registration, it will be reviewed by the study chairs, the study statistician, the RTOG GU Cancer Committee chair, and the RTOG Executive Committee. CRFs, source documentation, and a statistical report summarizing the study data will be reviewed as soon as possible. During this review, accrual will be suspended (if applicable). Following this review, the study chairs, the study statistician, the RTOG GU Cancer Committee chair, and the RTOG Executive Committee will discuss the findings and make a decision about amending and/or continuing the study.

Multivariate logistic regression[36] will be used to model the association of factors with the occurrence of FFP. Both unadjusted and adjusted odds ratios and the respective 95% confidence interval will be computed. At least, clinical T-stage, baseline PSA, Gleason score, and age (and other factors as appropriate) will be adjusted for in this analysis.

### 13.4.2 Clinical Outcomes

All eligible patients who received any protocol treatment will be included in the outcome analyses. For all secondary clinical outcome endpoints (see Section 13.1.2.1), all patients will be followed for a minimum of 3 years. The time to failure will be measured from the date of registration to the date of the event of interest (see Section 11.5). The overall survival rate will be estimated using the Kaplan-Meier method.[37] Local-regional progression, distant failure, prostate cancer specific survival, non-prostate cancer specific survival, and biochemical failure rates will be estimated using the cause-specific hazard rate approach[38,39] to estimate other survival/failure distributions of interest. Time to failure of interest will be modeled by Cox proportional hazards regression.[40] Unadjusted and adjusted hazard ratios and the respective 95% confidence intervals will be computed. At least clinical T-stage, PSA, Gleason score, and age (and other factors as appropriate) will be adjusted for in this analysis.

**13.4.3** To Evaluate Treatment-Related Adverse Events (based on CTCAE, v 3.0.)

Adverse events are evaluated by the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The treatment-related attribution includes definitely, probably, or possibly related to treatment. The acute adverse events will be the first occurrence of the worst severity of the adverse event ≤ 90 days of the completion of protocol treatment (3 weeks after the last planned docetaxel dose) and a late adverse event is defined as an adverse event occurring more than 90 days from the end of protocol treatment. We will evaluate the acute adverse events when all patients have at least 90 days of follow-up from the end of protocol treatment. The time of a first late adverse event occurrence of the Grade 3+ adverse events between 91 days and 730 days from the completion of treatment will be evaluated. We will evaluate the late adverse events when all patients have at least 730 days of follow-up from the end of protocol specified treatment. Patients will be tabulated by type, grade, and attribution of adverse event. Multivariate logistic regression[36] will be used to model the distribution of acute treatment-related adverse events. Both unadjusted and adjusted odds ratios and the respective 95% confidence interval will be computed. The distribution of time to late Grade 3+ adverse events will be estimated using the Kaplan-Meier method[37] and tested using a log-rank test[38,39] with the significance level of 0.05. If no such late adverse event is observed until the time of the analysis, the patient will be censored at the time of the analysis. A multivariate Cox regression model[40] will be used to adjust for covariates. Both unadjusted and adjusted hazard ratios and the respective 95% confidence interval will be computed. At least, clinical T-stage, baseline PSA, Gleason score, and age (and other factors as appropriate) will be adjusted for in the multivariate analysis.

**13.4.4** Prognostic Value of Genomic and Proteomic Markers for the Primary and Secondary Clinical Endpoints

At the time of data maturity of this study, we will propose specific details of the markers to be investigated. We will address the assays that will be used and a list of specific correlative aims with appropriate statistical considerations. The following is a general guideline for the statistical consideration for this analysis. A genomic or proteomic biomarker will be categorized into two subgroups based upon previously defined (or hypothesized) cut-off points and these two groups will be referred to as favorable and unfavorable risk groups. The patients with genomic and proteomic biomarkers will be compared with the patients without a value for that biomarker to determine if there are any differences with respect to distribution of pre-treatment characteristics. We want to know if there is a difference in survival rate between these two groups. The null ($H_0$) and alternative ($H_A$) hypotheses for survival distribution (S) are

$H_0$: $S_0(t) \geq S_1(t)$ vs. $H_A$: $S_0(t) < S_1(t)$, where t is time

Tests will be performed to see if one group is statistically significantly better than the other in the primary endpoint and secondary endpoints that are related to time to failure of interest. However, the selection of the cut-off point for each biomarker is not established. If the hypothesized cut-off points do not yield statistical significance, other cut-off points may be evaluated. Therefore, various cut-off points are evaluated for their statistical significance. To correct the problem from the multiple testing, the Bonferroni correction will be used.

The overall survival will be estimated by the Kaplan-Meier method and will be tested for the difference between the favorable and unfavorable groups using the log-rank test. We will use the cause-specific hazard rate approach to estimate other survival/failure distributions and test the survival/failure difference between the two groups using the cause-specific log-rank test.[41]

**13.4.5** Interim Reports

Interim reports will be prepared every 6 months until the final analysis. In general, the interim reports will include information about:

Patient accrual rate with projected completion date

Pretreatment characteristics of patients accrued

The frequencies and grades of adverse events due to protocol treatment

**13.4.6** CDUS Reporting

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

## 13.5 Inclusion of Minorities

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 the accrual statistics from RTOG prostate cancer

9601, we project that 87% of the men in the study will be White, 9% will be African American, 1% will be Hispanic, 1% will be Asian, none will be Native Hawaiian or Pacific Islanders, and < 1% will be American Indian or an Alaskan Native. Table 2 lists the projected accrual for each ethnic and racial group.

**Table 2: Projected Distribution of Gender and Minorities**

| **Ethnic Category** | **Gender** | | |
|---|---|---|---|
| | **Females** | **Males** | **Total** |
| Hispanic or Latino | N/A | 1 | 1 |
| Not Hispanic or Latino | N/A | 75 | 75 |
| **Ethnic Category: Total of all subjects** | N/A | 76 | 76 |
| **Racial Category** | | | |
| American Indian or Alaskan Native | N/A | 1 | 1 |
| Asian | N/A | 1 | 1 |
| Black or African American | N/A | 6 | 6 |
| Native Hawaiian or other Pacific Islander | N/A | 0 | 0 |
| White | N/A | 67 | 67 |
| Others and Unknown | | 1 | 1 |
| **Racial Category: Total of all subjects** | | 76 | 76 |

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# APPENDIX I

## RTOG 0621

## Informed Consent Template for Cancer Treatment Trials
## (English Language)

### Adjuvant 3DCRT/IMRT in Combination with Androgen Suppression and Docetaxel for High Risk Prostate Cancer Patients Post-Prostatectomy: A Phase II Trial

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 prostate cancer that has been treated surgically and it has been determined that you have a 50% or greater risk of recurrence of your prostate cancer within 3 years following surgery.

**Why is this study being done?**

The purpose of this study is to find out what effects a combination of local (radiation therapy) and systemic (hormonal therapy and chemotherapy) treatments has on the risk of recurrence of your prostate cancer.

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

About 76 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.

- History and physical exam, including an assessment of your ability to carry out activities of daily living (which will include questions such as whether you are able to feed, bathe, and dress yourself)
- Bone scan
- CT (computed tomography) scan and/or MRI (magnetic resonance imaging) of the pelvis. A CT scan is a study using x-rays to look at one part of your body. An MRI is imaging using a strong magnetic field to look at one part of your body.
- Routine blood studies (for blood count, liver function, and to measure testosterone) to be obtained by vein (IV)
- A blood test to determine your prostate specific antigen (PSA; a value that helps determine the aggressiveness of your prostate cancer). About 2 teaspoons of

blood will be drawn from a vein. At least two PSA tests spaced by 2 months must be obtained after surgery to remove the prostate. Your doctor also may draw another PSA before the start of treatment for a baseline value.

- Evaluation by a medical oncologist

**During hormone therapy, radiation therapy, and chemotherapy treatment…(6/22/09)**

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. They are being done more often because you are in this study.

- Routine blood studies (for blood count, liver function, and to measure testosterone and PSA) to be obtained by vein (IV)

Eight weeks before starting your radiation treatments, you will receive commercially available hormone treatments. There are two parts to the hormone therapy. You will take injections (LHRH agonists: leuprolide or goserelin) either under the skin or in the muscle, and you will take a pill, either flutamide (Eulexin) three times per day or bicalutamide (Casodex) once per day. 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 or bicalutamide will be given on the same schedule during radiation as before radiation began. Once radiation is completed, hormone treatment with the LHRH agonist and flutamide or bicalutamide will be continued for about 2 more months for a total of 6 months.

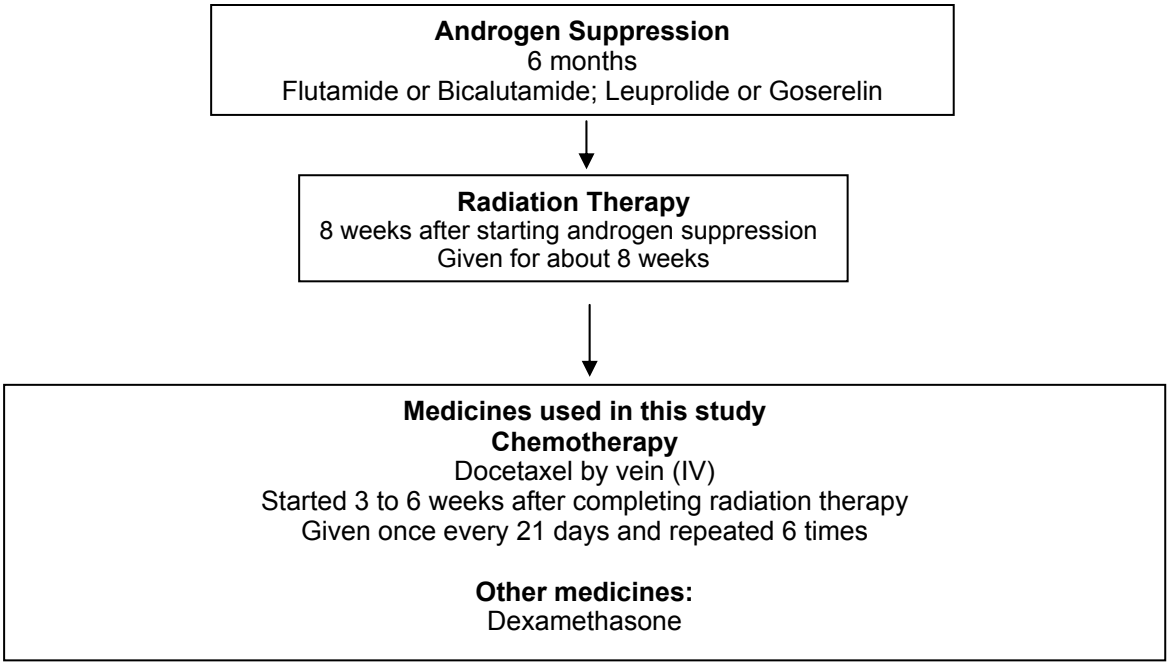
Beginning 3-6 weeks after radiation ends, you will receive a chemotherapy drug: docetaxel (Taxotere). The first day you will be given docetaxel through a needle in a vein in your arm for one hour. You will also be given a drug called dexamethasone in one of two ways: twice daily by mouth for 6 doses beginning 24 hours before docetaxel or a dose given at 12, 3, and 1 hour(s) before docetaxel to try to prevent some of the side effects of docetaxel. You may be given a dose of dexamethasone by vein in your arm on the day you receive docetaxel to try to prevent or decrease vomiting (throwing up). Docetaxel will be given every 3 weeks (21 days) for a total of 6 times. These drugs will be given to you as an outpatient (no hospital stay).

**When you are finished receiving treatment…(6/22/09)**

When you are finished with treatment including hormonal therapy, radiation therapy, and chemotherapy you will have follow-up visits with your doctor(s) every 3 months for 2 years, then every 6 months for years 3 through 5 after finishing treatment, then yearly after 5 years. At each visit a prostate specific antigen (PSA) will be drawn by vein (about 2 teaspoons of blood). The schedule of follow-up visits and the PSA blood test are part of routine follow-up care. In addition, your testosterone level will be checked by drawing blood every 3 months until the end of year 2 following completion of the treatment. After the end of year 2, your testosterone level will be checked only if your doctor thinks it is necessary.

## Study Plan (6/22/09)

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.




### How long will I be in the study? (6/22/09)

Once enrolled on the study you will be given hormonal therapy medicines that block the production and effectiveness of the male hormone testosterone. You will be asked to take a hormonal therapy pill (flutamide or bicalutamide) by mouth every day for a total of 6 months. In addition to taking flutamide or bicalutamide, you will receive a second hormonal therapy drug (leuprolide or goserelin) which is given as a shot once every month or every 3 months for a total of 6 months. Approximately 8 weeks after your first hormonal therapy shot you will begin your radiation treatment. Radiation treatment will be given 5 days a week for almost 8 weeks.

About 3-6 weeks after your radiation therapy is completed you will begin chemotherapy. You will receive one chemotherapy drug: docetaxel (Taxotere). The first day you will be given docetaxel through a needle in a vein in your arm for one hour. You will also be given a drug called dexamethasone in one of two ways: twice daily by mouth for 6 doses beginning 24 hours before docetaxel or a dose given at 12, 3, and 1 hour(s) before docetaxel to try to prevent some of the side effects of docetaxel. You may be given a dose of dexamethasone by vein in your arm on the day you receive docetaxel to try to prevent or decrease vomiting (throwing up). Docetaxel will be given every 3 weeks (21 days) for a total of 4 months.

After you are finished with your treatment, the study doctor will ask you to visit the office for follow-up exams every 3 months for 2 years, then every 6 months for years 2 through 5 after finishing treatment, and then yearly after 5 years. We would like to keep track of your medical condition for the rest of your life. We would like to do this by either seeing you in the doctor's office or calling you on the telephone once a year to see how you are doing. Keeping in touch with you and checking on your condition every year helps us look at the long-term effects of the study.

**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 him/her. Another reason to tell your study 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, researchers 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 radiation or 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.

**HORMONE THERAPY**

**A. Risks and side effects related to LHRH agonists (leuprolide and goserelin) include those that are:**

**<u>Likely</u>**

- Hot flashes or sweating episodes
- Impotence and loss of libido (sex drive), which can be permanent
- Weight gain

**<u>Less Likely</u>**

- Dizziness
- Breast swelling or tenderness
- Diarrhea
- Unusual taste in the mouth
- Skin redness or hives
- Increased thirst and urination
- Anemia
- Loss of bone density
- Loss of muscle 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 or onset of diabetes (high blood sugar)
- Nausea
- Vomiting
- Changes in the texture of your hair
- Feelings of depression or other emotional changes
- Increased percentage of body fat

**Rare but serious**

- Allergic generalized rash and difficulty breathing
- Increased risk of heart attacks and/or heart rhythm problems

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

**Likely**

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

**Less Likely**

- Anemia
- Breast swelling and tenderness
- Diarrhea (for bicalutamide)
- Photosensitivity (sensitivity of the skin to light)

**Rare but serious**

- Liver function changes

## CHEMOTHERAPY

**A. Risks and side effects related to docetaxel (Taxotere) include those which are:**

**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
- Excess tearing in the eyes

**Less Likely**

- Sweating
- Fever and chills
- Headache
- Weight gain
- Muscle cramps
- Hives
- Local skin reactions
- Flushing
- Ulcers of the stomach or esophagus
- Abdominal pain
- 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 (6/22/09)**

- 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
- Pulmonary embolism (a blockage of an artery in the lung)

**B. Risks and side effects related to dexamethasone include those which are:**

**Likely**

- Difficulty sleeping
- Increase in the sugar content of your blood, possibly resulting in diabetes
- Increased blood pressure
- Skin bruising

**Less Likely**

- Increase in appetite
- Weight gain
- Mood changes
- Impaired skin healing
- Increased risk of infection
- Osteoporosis (a disorder in which the bones become increasingly brittle and subject to fracture)

**Rare but serious**

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

## RADIATION THERAPY

**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:** If semen cannot be released from the penis during an orgasm following surgery to remove the prostate, there are no reproductive risks. If semen can be released during an orgasm, the patient needs to use birth control while on this study because the drugs and radiation in this study can affect an unborn baby.

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 researchers 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 researchers learn more about chemotherapy in addition to radiation therapy and hormone therapy as a treatment for 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 including the possibility of receiving radiation and/or hormonal therapy without chemotherapy
- Taking part in another study
- Getting no treatment

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

**Will my medical information be kept private?**

Data are housed at RTOG Headquarters in a password-protected database. 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 (RTOG)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Designated representatives from Sanofi-Aventis, the manufacturer of docetaxel (Taxotere)
- A Data Monitoring Committee (DMC) that regularly meets to monitor safety and other data related to the study

**What are the costs of taking part in this study?**

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.

Sanofi-Aventis will supply docetaxel free of charge to patients participating in this study. However, you or your health plan may need to pay for costs of the supplies for drug administration and personnel who give you the docetaxel. Also, if you should need to take the drug much longer than is usual, it is possible that the supply of free drug that has been supplied to the study institution could run out. If this happens, your study doctor will discuss with you how to obtain additional drug from the manufacturer and you may be asked to pay for it.

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 study 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).*

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

**You can say "yes" or "no" to [each of] the following study[ies]. Below, please mark your choice [for each study].**

*Consent Form for Use of Tissue, Blood, and Urine for Research*

**About Using Tissue, Blood, and Urine for Research**
At the time of surgery, prostate and other body tissues (possibly including lymph nodes) were removed to do some tests to determine the extent of your cancer. The results of these tests have been used to aid in determining the plan for your care following surgery.

We would like to use 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.rtog.org/tissue%20for%20research_patient.pdf.

In addition, if you agree to participate in this part of the study, you will have blood drawn and urine collected before you start treatment, during treatment, and at completion of treatment.

We would like to keep about 2 tablespoons of blood and 5 tablespoons of urine at each of these times for future research. If you agree, this blood and urine will be kept to be used in research to learn more about cancer and other diseases

Your tissue, blood, and urine 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 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, blood, and urine for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

If you decide now that your tissue, blood, and urine 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. Then any tissue that remains will no longer be used for research and 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 study doctor/institution 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 is used for genetic research (about diseases that are passed on in families). Even if your tissue, blood, and urine are used for this kind of research, the results will not be put in your health records.

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

**Benefits**

The benefits of research using tissue 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**

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. **(6/22/09)**

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:
   - Tissue ☐Yes ☐ No
   - Blood ☐Yes ☐ No
   - Urine ☐Yes ☐ No

2. My specimens 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), as follows:
   - Tissue ☐Yes ☐ No
   - Blood ☐Yes ☐ No
   - Urine ☐Yes ☐ No

3. 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: STUDY PARAMETER TABLE (See Sections 11.2 & 11.3 for details) [4/8/08]

| | Pre-Treatment | During Treatment | | | | | Follow-Up |
|---|---|---|---|---|---|---|---|
| | | During Androgen Suppression | Prior to start of Radiation Therapy | At completion of Radiation Therapy | Prior to start of Chemo-therapy | During Chemo-therapy | As indicated in Section 11.3 |
| Pathology | X | | | | | | |
| History/physical | X | | | | | | |
| Performance status | X | X | X | X | X | X | X |
| Bone Scan | X | | | | | | X |
| Pelvic CT or MRI | X | | | | | | Recommend |
| CBC w/ diff & ANC | X | | X | | X | X | |
| Serum ALT, AST, Alk phos, bilirubin | X | X | X | | X | X | |
| PSA | X | | X | | X | | X |
| Testosterone | X | | X | | X | | X |
| Consultation with Medical Oncologist | X | | | | | | |
| Adverse event evaluation | X | X | X | X | X | X | X |

## APPENDIX III (6/22/09)

### ZUBROD PERFORMANCE SCALE

| | |
|---|---|
| **0** | **Fully active, able to carry on all predisease activities without restriction .** |
| **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.** |
| **2** | **Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.** |
| **3** | **Capable of only limited self-care, confined to bed or chair 50% or more of waking hours.** |
| **4** | **Completely disabled. Cannot carry on self-care. Totally confined to bed.** |
| **5** | **Death.** |

## APPENDIX IV

### 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 V (6/22/09)
## Blood Collection Kit and Instructions

**Instructions** for use of serum, plasma, or buffy coat collection kit:

This kit includes:

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

**Serum:**

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

Process:

1. Allow one 5ml red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM at 4° Celsius for 10 minutes.
3. Aliquot a minimum of 0.5 ml serum into each of the four 1ml cryovials labeled with the RTOG study and case numbers, collection date and time, and clearly mark specimens as "serum".
4. Place cryovials into biohazard bag.
5. Store serum at –80° Celsius until ready to ship.

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

**Plasma:**

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

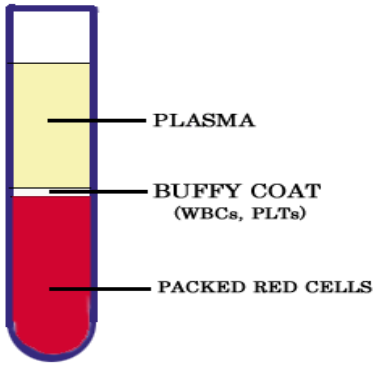
Process:

1. Centrifuge specimen within one hour of collection in a standard clinical centrifuge at ~2500 RPM at 4° Celsius for 10 minutes.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
3. Carefully pipette and aliquot a minimum of 0.5ml plasma into each of the 1ml cryovials labeled with the RTOG study and case numbers, collection date and time, and clearly mark specimens as "plasma".
4. Place cryovials into biohazard bag.
5. Store plasma at a minimum –80° Celsius until ready to ship.

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

**Buffy coat:**

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




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

Process:

1. Centrifuge EDTA (purple top) tube within one hour of collection in a standard clinical centrifuge at ~2500 RPM at 4° Celsius for 10 minutes.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
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 the 1ml 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 and time of collection.
5. Place cryovials into biohazard bag.
6. Store buffy coat samples frozen until ready to ship.

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

Shipping/Mailing:

- Include all RTOG paperwork in pocket of biohazard bag.
- Ship specimens overnight Monday-Thursday. Avoid shipping on a weekend or around a holiday.
- Place frozen specimens and the absorbent shipping material in the Styrofoam cooler and fill with dry ice (if appropriate; double-check temperature sample shipping temperature). 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.*
- For questions regarding collection/shipping, contact the RTOG Biospecimen Resource (contact information below).

**Ship: Specimens and all paper work as follows:**

**U.S. Mailing Address: <u>For Non-frozen Specimens Only</u>**
**RTOG Biospecimen Resource**
**University of California San Francisco**
**Campus Box 1800**
**1657 Scott Street, Room 223**
**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**

## APPENDIX VI (6/22/09)
## Urine Collection Kit Instructions

**This Kit contains:**

- One (1) Sterile Urine collection cup
- Biohazard bags
- Shipping Label(s)

**Urine Specimens:**

Preparation for collecting **Urine:**

- A clean catch urine specimen will be collected.

Process

- To collect the specimen, use the following instructions:
  - Males should wipe clean the head of the penis and females need to wipe between the labia with soapy water/cleansing wipes to remove any contaminants.
  - After urinating a small amount into the toilet bowl to clear the urethra of contaminants, collect a sample of urine in the collection cup.
  - After 10-25 mL urine has been collected, remove the container from the urine stream without stopping the flow of urine.
  - Finish voiding the bladder into the toilet bowl.
  - Place the cap on the collection cup and tighten the container. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- Label the specimen with the RTOG study and case number, collection date and time, timepoint of collection, and clearly mark specimen as "urine".
- If available, use parafilm to seal the cap of the urine cup and to prevent leakage.
- Place urine cup into biohazard bag and seal the bag.
- Immediately freeze urine sample at -20ºC.
- Store specimens frozen at -20ºC until ready to ship.

**Shipping Instructions for all specimens:**

**Urine Specimens**: Urine cups must be wrapped in an absorbent material (e.g., paper towels) and placed in an airtight plastic freezer bag (i.e., re-sealable bag). Urine specimens may be sent in batches, if within 30 days of collection. Pack the frozen specimens in a heavy grade Styrofoam box with dry ice (4-5 lbs/2-2.5 kg minimum). Seal the box with plastic tape. All RTOG paperwork should be placed in a plastic bag, sealed, and taped to the outside of the Styrofoam box. Pack the Styrofoam box in a cardboard box. Note: Specimens requiring specific infectious precautions should be clearly labeled, with specific sources of infectious concerns listed, if known. Mark the outer cardboard box "biohazard".

Send specimens by overnight express to the address below. Specimens only should be shipped **Monday through Wednesday** to prevent thawing due to delivery delays. Saturday and holiday deliveries will not be accepted. Samples received thawed will be refrozen and held. A notification will be sent immediately to the Principal Investigator and Clinic Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date, if possible.

**Notes:**

- *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 as follows:

**U. S. Postal Service Mailing address: For Non-frozen Specimens Only**
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
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
**Telephone:** 415-476-RTOG (7864) **Fax:** 415-476-5271 **Email:** RTOG@ucsf.edu

## APPENDIX VII (4/8/08)

### RTOG 0621, Docetaxel Shipment

Docetaxel will be shipped by Sanofi-Aventis to U.S. sites and by Sanofi-Aventis Canada to Canadian 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.

All pre-registration requirements must be met before calling to register the first case (see Section 5.0).

**U.S. institutions** must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, http://www.rtog.org (next to the protocol). U.S. sites 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.

**Canadian institutions** must use the Canadian Study Agent Shipment Form (SASF), which can be accessed in the Canadian Information Section on the RTOG web site, at http://www.rtog.org/members/CanadaInfo/0621/0621drug_order.html. The Canadian SASF must be submitted to CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified.
All 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.

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.