RADIATION THERAPY ONCOLOGY GROUP

RTOG 0622

A PHASE II TRIAL OF SAMARIUM 153 FOLLOWED BY SALVAGE PROSTATIC FOSSA 3D-CRT OR IMRT IRRADIATION IN HIGH-RISK, CLINICALLY NON-METASTATIC PROSTATE CANCER AFTER RADICAL PROSTATECTOMY

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

This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.

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A PHASE II TRIAL OF SAMARIUM 153 FOLLOWED BY SALVAGE PROSTATIC FOSSA 3D-CRT OR IMRT IRRADIATION IN HIGH-RISK, CLINICALLY NON-METASTATIC PROSTATE CANCER AFTER RADICAL PROSTATECTOMY

SCHEMA

Pre-local Irradiation Bone-Targeted Treatment
with
Samarium 153 as a single I.V. injection
of 2.0 mCi/kg

R E G I S T E R

Evaluate for toxicity and PSA response
at 12 weeks
Prostatic Fossa 3D-CRT or IMRT Radiation Therapy
(64.8 to 70.2 Gy)

Evaluate for toxicity and PSA response
at 24 weeks
If no response to prior therapy then hormonal therapy

Samarium 153 treatment begins within 2 weeks after registration. Radiotherapy begins 12 weeks after Samarium infusion. See Sections 7.0 and 6.0 for details.

See pre-registration requirements for 3D-CRT or IMRT in Section 5.1.

Patient Population: (3/9/11)

- Pathologically (histologically) proven diagnosis of prostate cancer
- Pathologic stage T2-T4, including no distant metastases (pelvic nodal metastases allowed)
- Post-operative PSA within 4 weeks of study registration meets at least one of the following criteria
  - PSA above 1.0 ng/ml;
  - PSA above 0.2 if the tumor Gleason score is 9 or 10; or
  - PSA above 0.2 with nodal disease

Required Sample Size: 76

RTOG Institution # _____

RTOG 0622 **ELIGIBILITY CHECKLIST (3/9/11)**

Case # _____ (page 1 of 4)

1. _____ (Y) Is there a pathologically (histologically) proven diagnosis of prostate cancer progressing after radical prostatectomy, as indicated by either of the following?
   - Postoperative PSA above 1.0 ng/ml;
   - Postoperative PSA above 0.2 ng/ml with a surgical tumor Gleason Score of 9 or 10; or
   - Postoperative PSA above 0.2 ng/ml with nodal disease
2. _____ (Y) Does the patient have a pathologic state of T2- T4 N0-N1, including no distant metastases, based upon the following minimum diagnostic workup?
   - History and physical examination within 8 weeks prior to registration; and
   - Bone scan negative for metastases within 4 months prior to registration
   - Abdominal imaging negative for metastases within 6 months prior to registration.
3. _____ (Y) Is Zubrod Performance Status 0-1?
4. _____ (Y) Is the patient $\geq$ 18 years old?
5. _____ (Y) Has the CBC/Differential and PSA been obtained within 4 weeks prior to registration, with adequate bone marrow function?
   - Absolute Neutrophil Count (ANC) $\geq$ 1,800 cell/mm^3
   - Platelets $\geq$ 100,000 cells/mm^3
   - Hemoglobin (Hgb) $\geq$ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb of $\geq$ 8.0 g/dl is permitted.)
6. _____ (Y) Has the patient provided study specific consent prior to study entry?
7. _____ (N) Is there biopsy evidence of M1 disease; or presence of neuroendocrine features in any prostate cancer specimen; or prior invasive malignancy (except non-melanomatous skin cancer), unless disease free for a minimum of 3 years?
8. _____ (N) Has the patient received prior systemic chemotherapy for the study cancer (Note: Prior chemotherapy for a different cancer is permitted.); or hormonal therapy initiated within the last 3 months; or prior radiotherapy of the pelvic region that would result in overlap of radiation field?
9. _____ (N) Does the patient have any of the following severe, active co-morbidities?
   - Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months, or;
   - Transmural myocardial infarction within the last 6 months; or

(Continued on the next page)

- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration; or
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects (Note: Laboratory tests for liver function and coagulation parameters, however, are not required); or
- Renal failure (Note: Laboratory tests for renal function, are not required); or
- Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition (Note: HIV testing, however, is not required)

RTOG Institution # _____

RTOG 0622 **ELIGIBILITY CHECKLIST (4/3/08)**

Case # _____ (page 3 of 4)

The following questions will be asked at Study Registration:
3D-CRT/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 study-specific Consent Form was signed? (must be 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)

_____(Male) 11. Gender

_____ 12. Patient's Country of Residence

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

_____ 14. Patient's Insurance Status

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

_____ 16. Calendar Base Date (Samarium 153 injection)

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

(Continued on the next page)

RTOG Institution # _____

RTOG 0622 **ELIGIBILITY CHECKLIST (4/3/08)**

Case # _____ (page 4 of 4)

_____(Y/N) 18. Tissue/Blood/Urine kept for cancer research?

_____(Y/N) 19. Tissue/Blood/Urine kept for medical research?

_____(Y/N) 20. Allow contact for future research?

_____ 21. Height (cm)

_____ 22. Weight (kg)

_____(Y/N) 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 (9/29/09)

Prostate cancer is a common cause of cancer morbidity and mortality. It is estimated that 234,500 new cases of prostate cancer were diagnosed in 2006, and approximately 27,400 will die of disease[1]. Approximately 25% of men with locally advanced prostate cancer develop bony metastatic disease despite aggressive treatment with radiation therapy and hormonal therapy[2]. In fact, the majority of men dying of prostate cancer have bone as the only site of metastasis[3]. Complications from skeletal metastases dominate the clinical course of advanced prostate cancer, and are the primary cause of death in most patients. Because of this predictable pattern of progression, the development and clinical evaluation of bone-targeted therapy will benefit patients.

Multiple clinical trials have evaluated the benefits of bone-targeted radiation therapy in advanced metastatic prostate cancer[4-11]. In particular, beta-emitting radiopharmaceuticals (Samarium 153 and Strontium-89), have been developed that selectively irradiate osteoblastic metastases, with minimal or no effect on normal tissue, by binding to the bone mineral (hydroxyapatite). With these agents, reported palliative response rates have ranged from 55% to 80%[5,7,10,11]. Response duration has been reported to range 2 to 17 weeks, with one study noting that 50% of responses lasted 16 weeks. Less than 10% of patients had National Cancer Institute Toxicity Criteria Grade III/IV bone marrow toxicity.

Recently, Tu et. al. found that bone-targeted radiation therapy with one dose of Strontium-89 and doxorubicin, enhanced anti-tumor activity and improved overall survival in selected patients who responded to sequential chemotherapy[12]. In their study, patients with advanced metastatic androgen-independent prostate cancer who had consolidation bone-targeted radiation therapy after induction chemotherapy had improved time to progression (14 vs. 7 months, $p < 0.0001$) and overall survival (27.7 vs. 16.8 months, $p=0.0001$).

Tu et. al. provided a strong rationale for additional work testing bone-targeted therapy as a valuable treatment paradigm in men with advanced prostate cancer. The benefits of this treatment strategy have yet to be tested in hormone naïve, clinically non-metastatic prostate cancer patients. As the first step to clinically evaluate this innovative approach in this patient population, we designed and conducted a phase I study (activated in March 2003) to determine the maximum tolerated dose (MTD) of Samarium 153 administered sequentially with neoadjuvant hormonal therapy (HT) and external beam radiation (RT) in patients at high risk for subclinical bone metastases[13].

The dose limiting toxicity is grade 3 or higher hematologic toxicity (CTCAE version 3.0 for toxicity). The doses of Samarium 153 ethylenediaminetetramethylenephosphonic acid (EDTMP) assessed in this initial pilot trial ranged from 0.25 mCi/kg to 2.0 mCi/kg. These doses were selected because they have been shown effective in advanced metastatic patients. A total of 29 have enrolled in our study, with all patients completing acute toxicity evaluation. We have administered doses as high as 2.0 mCi/kg of Samarium 153 with only 2 cases of grade 3 toxicity. After the administration of Samarium 153, all patients tolerated prostatic external beam irradiation without any delays or untoward complications. **Thus, the MTD of Samarium 153 is 2.0 mCi/kg which is estimated to be approximately equivalent to an effective bone surface radiation dose of 50.0 Gy.**

This clinical trial will study patients who are likely to harbor subclinical bony metastases, and have an increased risk of distant metastases and disease-specific death. The study group will include post-prostatectomy patients with an isolated PSA failure above 2.0 ng/ml or a Gleason score 9 or 10 with postoperative PSA profile rising above 0.2 ng/ml. These risk factors have been shown in multiple studies to be associated with a high likelihood of biochemical progression following prostatic fossa irradiation for an isolated PSA elevation[14-16]. It is hypothesized that in such patients the PSA elevation is driven predominantly by subclinical bony metastases and that the administration of bone-targeted therapy with Samarium 153 should result in a measurable decline in the PSA.

To test this hypothesis, Samarium 153 will be administered alone as a single 2.0 mCi/kg injection, and the post-therapy PSA profile will be closely followed for 12 weeks. This time frame was selected because in our phase I study the hematologic profile of most patients returned to baseline by 12 weeks. In addition, it is expected that this period is a reasonable timeframe to observe a biochemical response to the bone-targeted treatment. Patients will be monitored for a PSA response as defined by a 30% or greater decline in the baseline PSA value within 12 weeks of Samarium 153 administration. A response rate of 30% is in line with responses after salvage radiation therapy [40]. This definition of response may be a useful surrogate of a decreased risk of prostate cancer death[17].

At 12 weeks, all patients will undergo postoperative prostatic fossa irradiation, with doses ranging from 64.8 Gy to 70.2 Gy. At this point in time, the addition of hormonal therapy, or the use of pelvic field irradiation will be prohibited. The benefit of these two treatment modalities, in combination with prostatic fossa irradiation, remains controversial[18].

1.1 SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) AND NORMAL TISSUE TOXICITY (3/9/11)

RT produces its biological effects mainly through the generation of short lived but highly reactive DNA radicals that evolve into stable, long-lived DNA lesions such as DSBs[19] or through interactions with the plasma membrane[20], leading to cell death. The total number of gene products currently known to be involved in determining cellular radiosensitivity is well over 100 and growing[21]. Several groups have reported analysis of genetic variants of individual candidate genes potentially implicated in normal tissue radiosensitivity[22,23]. A more powerful search approach, in the post-genome era, would be to screen patients for a large number of genes that could impact on radiosensitivity. Variations in the sequence of the human genome can comprise repeating sequences such as variable number of tandem repeats (VNTRs), short tandem repeats (STRs) and SNPs[24]. Although the human genome is ~99.9% identical among individuals, the ~0.1% variations (the vast majority of which are SNPs) tend to be heritable and stable[25]. It is postulated that these variations in the genome explain phenotypic differences between individuals and may also serve as a genetic blueprint for susceptibility to disease and cellular responses to pharmacologic agents[26, 27]. SNP-types associated with a higher risk of radiation-induced normal tissue toxicity would comprise a predictive molecular signature of radiation injury, and would have broad applicability in patient selection for radical radiotherapy.

Several groups have reported preliminary results in their analysis of the association between candidate SNPs and late toxicity after RT for breast cancer[28-33]. An association between TGFB1 -509T and +869C alleles and fibrosis was found by Quarmby et al, while Andreassen et al found TGFB1 position -509 and codon 10 to be associated with fibrosis. The latter study also found associations between other DNA damage-related SNPs (SOD2 (codon 16), XRCC3 (codon 241), XRCC1 (codon 399)) and clinical late toxicity. Recently, in a different breast cancer patient cohort, Andreassen et al[32] found statistically significant associations between the *TGFB1* codon 10 Pro allele (P=0.005) as well as the *TGFB1* position -509 T allele (P=0.018) and increased risk of late breast fibrosis as indicated by breast appearance. The functional significance of either the *TGFB1* codon 10 Pro allele or the *TGFB1* position -509 T allele is currently unclear. However, recently Andreassen et al[34] failed to replicate these earlier associations in a study where DNA was obtained from formalin fixed paraffin embedded tissue samples in a different cohort of breast cancer patients. In order to avoid false positive associations, SNP-association studies should be validated in larger, well-defined cohorts of homogeneously treated patients.

The correlation of SNPs and pelvic normal tissue toxicity was reported by De Ruyck et al[35, 36] examined SNPs in *XRCC1*, *XRCC3*, *TGFB*1 position -509, *TGFB1* codon 10 and *OGG1*. Patients with three or more risk alleles in *XRCC1* and *XRCC3* had a significantly increased risk of developing late pelvic GI/GU toxicity (odds ratio 10.10, p = 0.001). Damaraju et al[37] analysed 53 SNPs in *BRCA1, BRCA2, ESR1, XRCC1, XRCC2, XRCC3, NBS1, RAD51, RAD52, LIGIV, HAP1, ATM, BCL2, TGFβ-1, MSH6, XPD (ERCC2), XPF (ERCC4), GRL, CYP1A1, CYP2C19, CYP3A5, CYP2D6, CYP11B2, and CYP17* genes from a cohort of 83 men who had undergone 3-dimensional conformal RT for prostate cancer. Significant univariate associations with late rectal or bladder toxicity (grade 2+) were found for *XRCC3* A>G 5' UTR NT 4541, *LIGIV* T>C Asp568Asp, *MLH1* C>T, Val219Ile, *CYP2D6*4* G>A splicing defect, mean rectal and bladder dose, dose to 30% of rectum or bladder, and age <60 years. In a Cox multivariate analysis, significant associations with toxicity were found for *LIGIV* T>C, Asp568Asp; *XPD* G>A, Asp711Asp; *CYP2D6*4* G>A, splicing defect; mean bladder dose >60 Gy, and dose to 30% of rectal volume >75 Gy. These data suggest an association between candidate SNPs and late pelvic radiation toxicity.

1.1.1 PROPOSAL FOR BANKING OF WHOLE BLOOD SPECIMENS FOR SNP ANALYSIS

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

2.0 OBJECTIVES

2.1 Primary Objective

2.1.1 To assess the effectiveness of Samarium 153 administration, as determined by a 30% decline in the PSA within 12 weeks, as compared to baseline, in a population of men with high risk, clinically non-metastatic prostate cancer after a radical prostatectomy.

2.2 Secondary Objectives

2.2.1 To assess the proportion of patients completing protocol treatment

2.2.2 To evaluate hematological toxicity at 12 weeks

2.2.3 To evaluate any Samarium 153-related adverse events at 12 weeks

2.2.4 To evaluate the "acute" and "late" radiation therapy related events having occurred up to 24 weeks from the end of radiation therapy

2.2.5 To compare the freedom from progression (FFP) rate at 2 years to that predicted by the Kattan Nomograms

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

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (3/9/11)

3.1.1 Pathologically (histologically) proven diagnosis of prostate cancer progressing after radical prostatectomy as indicated by one of the following:

- Postoperative PSA rising above 1.0 ng/ml;
- Postoperative PSA rising above 0.2 ng/ml with a surgical tumor Gleason score of 9 or 10; or
- Postoperative PSA rising above 0.2 ng/ml with nodal disease

3.1.2 Pathologic stage T2 -T4 N0 - N1, including no distant metastases, based upon the following minimum diagnostic workup:

3.1.2.1 History/physical examination within 8 weeks prior to registration

3.1.2.2 Bone scan negative for bone metastases within 4 months prior to registration

3.1.2.3 Abdominal imaging negative for metastases within 6 months prior to registration

3.1.3 Zubrod Performance Status 0-1

3.1.4 Age ≥ 18 years

3.1.5 CBC/differential and PSA obtained within 4 weeks prior to registration, with adequate bone marrow function defined as follows:

3.1.5.1 Absolute Neutrophil Count (ANC) ≥ 1,800 cells/mm^3

3.1.5.2 Platelets ≥ 100,000 cells/mm^3

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

3.1.6 Patient must be able to provide study specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility

3.2.1 Biopsy evidence of M1 disease

3.2.2 Presence of neuroendocrine features in any prostate cancer specimen

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

3.2.4 Prior systemic chemotherapy for the study cancer (Note: Prior chemotherapy for a different cancer is permitted.)

3.2.5 Hormonal therapy initiated within the last 3 months

3.2.6 Prior radiotherapy to the pelvic region that would result in overlap of radiation therapy fields

3.2.7 Severe, active co-morbidity, defined as follows:

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

3.2.7.2 Transmural myocardial infarction within the last 6 months

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

3.2.7.4 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects (Note: Laboratory tests for liver function and coagulation parameters, however, are not required for entry into this protocol.)

3.2.7.5 Renal failure ((Note: Laboratory tests for renal function, however, are not required for entry into this protocol.)

3.2.7.6 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition (Note: HIV testing is not required). The need to exclude patients with AIDS is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

4.1 Histologic evaluation with Gleason score determination is mandatory

4.2 Mandatory laboratory studies *(obtained within 4 weeks prior to study entry)*: ALT, alkaline phosphatase, BUN, creatinine, testosterone

4.3 Pelvic lymph node assessment *(within 6 months prior to study entry)* by one of the following procedures: pelvic CT or MRI, ProstaScint, or pelvic lymph node dissection or sampling procedure *(either via laparotomy or laparoscopically)*.

5.0 REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements FOR ALL INSTITUTIONS (9/29/09)

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

5.1.1 Pre-Registration Requirements for 3D-CRT Treatment Approach

All institutions that have previously been credentialed to submit protocol compliant cases to prior RTOG 3D-CRT prostate trials may register patients on this trial. All other institutions that have met the technology requirements and that have provided the baseline physics information described in the Quality Assurance Guidelines (see RPC web site at http://rpc.mdanderson.org/rpc/) may enter patients into this study.

5.1.2 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 3D-CRT trials of this same disease site may enroll patients on this study without further credentialing.

5.1.3 Pre-Registration Requirements for IMRT Treatment Approach

In order to utilize IMRT, the institution must have met specific technology requirements and have provided the 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. Sites can access the web site at http://rpc.mdanderson.org/rpc/ and select "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.

5.1.4 The institution or investigator must complete a new IMRT Facility Questionnaire and send it to RTOG for review prior to entering any cases, and/or 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" 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.

5.2 Pre-Registration Requirements for Shipment of Samarium 153 (4/20/12)

5.2.1 **U.S. and Canadian sites** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, https://www.ctsu.org/readfile.aspx?fname=public/CTSU-IRBcertif_Final.PDF, prior to registration of the institution's first case:

- IRB/REB approval letter;
- IRB/REB assurance number;
- IRB/REB approved Informed Consent (English version)
- Radioactive Materials License
- Health Canada's TPD forms (Canadian institutions only)
- Study Agent Shipment Form

5.2.1.1 Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved RTOG will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

5.2.2 **Note:** 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/Researchers/InternationalMembers.aspx .

Approved international sites fax copies of the documentation below to RTOG Headquarters (Fax 215-574-0300) along with the completed International REC Certification Form (http://www.rtog.org/Researchers/InternationalMembers.aspx) prior to registration of the institution's first case:

- REC approval letter
- Informed Consent (English Version)
- Federalwide Assurance (FWA) number

5.2.3 To order Samarium 153 lexidronam:

A Word version of the Samarium 153 Lexidronam Release Form for this study is available on the RTOG web site, www.rtog.org, next to the protocol. **U.S., Canadian and approved international institutions** must complete this form electronically and send as an attachment via email to Customer Service at Bristol-Myers Squibb Medical Imaging (BMSMI), mics@bms.com, once a patient has been registered. Required regulatory documents (see Section 5.2.1) must be received before drug can be shipped. See Section 7.4 for further instructions regarding Samarium ordering.

5.3 Registration (4/20/12)

Patients can be registered only after eligibility criteria are met.

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

- The Investigator must have completed Human Subjects Training and been issued a certificate (Training is available via http://phrp.nihtraining.com/users/login.php).
- The institution must complete the Password Authorization Form at https://crcuserreg.acr.org/Registration/App_Web/USERACCOUNT/Login.aspx?Site=3 . RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

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

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient's record.

Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

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

Institutions can contact RTOG web support for assistance with web registration: websupport@acr.org **or** 800-227-5463 ext. 4189 **or** 215-574-3189.

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 (NOTE: INTENSITY MODULATED RT [IMRT] IS ALLOWED)

6.1 Dose Specifications

Radiation therapy (RT) will be delivered to 64.8-70.2 Gy, using either 3D-CRT (prescribed to the isodose encompassing the PTV) or IMRT (minimum dose to the PTV) treatment. RT will begin 12 weeks (+/- 1 week) following Samarium 153 administration. Daily tumor doses will be 1.8 – 2.0 Gy per day, 5 days per week x 7-8 weeks.

6.2 Treatment Equipment (See 6.3 for IMRT Treatment)

6.2.1 Megavoltage equipment is required with photon energies of ≥ 6 MV *(≥ 10 MV is preferred)*. The minimum source-to-axis *(SAD)* distance will be 100 cm. Any treatment technique *(field arrangement)* capable of producing the required dose distribution will be acceptable, with the following exceptions: *(1)* Perineal boost will not be permitted, and *(2)* AP/PA technique will not be permitted except for photon energies ≥ 24 MV photons. Typical field arrangements will be 4-6 field technique for the prostatic fossa volume.

6.3 Target Volumes

6.3.1 An urethrogram is strongly recommended, but not required, to establish the urethral-vesicular anastamosis. If the urethrogram is not done with the planning CT scan, then an AP simulation radiograph can be submitted with the planning CT.

6.3.2 A treatment planning CT scan will be required to define the clinical (prostatic fossa) and planning target volumes and the critical normal structures (See Section 6.4). The treatment planning CT will be acquired with the patient set up in the same position as for daily treatments. Each patient will be positioned in the supine position. The CT scan of the pelvis should start at or above the iliac crest down to the perineum. All tissues to be irradiated must be included in CT scan. CT scan thickness should be ≤ 0.5 cm through the region that contains the target volumes (i.e., from the bottom of the sacroiliac joints down to the penile urethra). The regions above and below the target volume region may be scanned with slice thickness ≤ 1.0 cm.

It is advised that extreme rectal filling not be present at the time of the planning CT scan. A distended rectum can introduce a systematic patient positioning error that may increase the probability of missing the PTV. If a full bladder is present at the time of the planning CT scan, the patient should be able and advised to maintain a full bladder through the course of his radiation treatments.

The CTV and PTV, and normal tissues must be outlined on all CT slices in which the structures exist. For patients receiving forward planned 3D-CRT beam's eye view display must be used to design beam aperture.

6.4 Treatment Planning/Target Volumes

6.4.1 The definition of volumes will be in accordance with the ICRU Report #62: Prescribing, Recording, and Reporting Photon Beam Therapy.

6.4.2 The Clinical Target Volume **(CTV)** is defined by the physician as all microscopic disease with the use of a planning CT, urethrogram, clinical and pathological information. The CTV for the purposes of this protocol is the prostatic fossa, extending from the seminal vesicle stump to urethral-vesicular junction. The lateral extent should be limited by the body of the ischium and its musculature.

6.4.3 The Planning Target Volume **(PTV)** will provide a margin around the CTV to compensate for the variability of treatment set up and internal organ motion. A minimum of 4 mm around the CTV is required to define the PTV. Superior and inferior margins (capping) should be 4-10 mm depending on the thickness and spacing of the planning CT scan. Careful consideration should be made when defining the 4-10 mm margin in three dimensions.

6.4.4 Treatment will be given to the PTV using three-dimensional conformal fields shaped to exclude as much of the bladder and rectum as possible. Field arrangements will be determined by 3D planning to produce the optimal conformal plan in accordance with volume definitions. The treatment plan used for each patient will be based on an analysis of the volumetric dose including dose-volume histogram (DVH) analyses of the PTV and critical normal structures.

6.4.5 A portal image of each field of 3-D radiotherapy or orthogonal images that localize the isocenter placement of IMRT must be obtained on the first day of therapy but should not be submitted.

6.4.6 Weekly verification or orthogonal images are required to be taken, but not submitted.

6.5 Doses (9/29/09)

6.5.1 In IMRT treatment planning, the prescription dose is the minimum dose to the PTV. The maximum dose to the PTV should not exceed the prescription dose by more than 7% (inhomogeneity ≤ 7%) and will be scored as per protocol: ≤ 7%; variation acceptable: > 7 to ≤ 10%; deviation unacceptable: > 10%. It is expected that IMRT may result in more heterogeneity in dose coverage than forward planned 3D-CRT. Minor variations as described are acceptable.

6.5.2 3D-CRT or IMRT
For conformal treatment planning: The dose should be prescribed to the minimum target dose *(i.e. to the highest isodose volume)*, which encompasses the CTV).

6.5.3 Prostatic fossa target volume (CTV) will receive the total dose of 64.8 Gy to 70.2 Gy.

6.6 Critical Normal Structures

6.6.1 The normal tissue volume to be contoured will include bladder, rectum, bilateral femora (to the level of ischial tuberosity), penile bulb, and skin. The normal tissues will be contoured and considered as solid organs. The bladder should be contoured from its base to the dome and the rectum from the anus (at the level of the ischial tuberosities) for a length of 15 cm or to the rectosigmoid flexure. This generally is below the bottom of the sacroiliac joints. The tissue within the skin and outside all other critical normal structures and PTV's is designated as unspecified tissue. See the ATC Web site to view examples of target and normal tissue contours.

6.6.2 Custom shielding or multileaf collimation must be used in conjunction with conformal planning to restrict the dose to the normal structures. Dose volume histograms (DVHs) must be generated for all critical normal structures, with the exception of skin. Portions of the bladder and rectum may, by necessity, receive the full dose as the PTV, however, careful 3D planning must be performed to ensure that the volume of the bladder and rectum receiving the full dose is kept to a minimum.

6.6.3 Average dose to entire rectum shall not exceed 55 Gy. Portions of the anterior rectal wall will, by necessity, receive the same dose as the prostatic fossa.

6.7 Radiation Toxicity

6.7.1 All patients will be seen weekly by their radiation oncologist during radiation therapy. Any observations regarding radiation reactions should be recorded and should include attention toward the following adverse side effects:

6.7.1.1 Skin reactions.

6.7.1.2 Small bowel or rectal irritation manifesting as abdominal cramping, diarrhea, rectal urgency, hematochezia.

6.7.1.3 Bladder complications including urinary frequency, dysuria, hematuria, urinary tract infections, and incontinence.

6.7.1.4 All serious adverse events will be reported via the AdEERS reporting system per Section 7.12.

6.8 Compliance Criteria

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

6.9 R.T. Quality Assurance Reviews

The Radiation Oncology Co-Chair, Richard Valicenti, M.D., will perform an RT Quality Assurance Review remotely after complete data for the first 20 cases enrolled have been received at ITC. Dr. Valicenti will perform the next review after complete data for the next 20 cases enrolled have 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 have been received at ITC, whichever occurs first. These reviews will be on going and performed remotely.

6.10 Radiation Adverse Event Reporting

See Section 7.12 for specific Adverse Event Reporting.

7.0 RADIOPHARMACEUTICAL THERAPY: QUADRAMET® (SAMARIUM 153 LEXIDRONAM)

Samarium 153 treatment must begin within 2 weeks (+/- 3 days) after registration.

Treatment

7.1 Dose definition — **The Samarium 153 lexidronam dose for this study is 2.0 mCi/kg.**

7.2 Technique of administration — Samarium will be given as single IV injection over 5 minutes through a secure indwelling catheter and followed with a saline flush.

- The dose should be measured by a suitable radioactivity calibration system, such as a radioisotope dose calibrator, immediately before administration.
- The dose of radioactivity to be administered and the patient should be verified before administration of Quadramet®. Patients should not be released until their radioactivity levels and exposure rates comply with federal and local regulations.
- **The patient should ingest (or receive by i.v. administration) a minimum of 1 Liter (4 cups) of fluids prior to injection and should void as often as possible after injection to minimize radiation exposure to the bladder.**
- Quadramet® contains calcium and may be incompatible with solutions that contain molecules that can complex with and form calcium precipitates. Thaw at room temperature before administration and use within 8 hours of thawing.

7.3 Study Agent

Quadramet® is a therapeutic agent consisting of radioactive samarium and a tetraphosphonate chelator, ethylenediaminetetramethlyenephosphonic acid (EDTMP). Quadramet® is formulated as a sterile, non-pyrogenic, clear, and colorless to light amber isotonic solution of Samarium 153 lexidronam for intravenous administration. Quadramet® does not contain a preservative. Each milliliter contains 35 mg EDTMP●H20,5.3 mg Ca [as Ca (OH)2], 14.1 mg Na [as NaOH], equivalent to 44 mg Ca/Na EDTMP (anhydrous calc.), 5-46 µg Samarium (specific activity of approximately 1.0-11.0mCi/µg Sm), and 1850 ± 185 MBq (50 ± 5 mCi) of Samarium 153 at calibration. The ionic formula is 153 Sm+3 $\mathbf{(CH_2N(CH_2P0_3H^2)_2]_2}$ and the ionic formula weight is 581.1 Dalton (pentasodium form, 696). The pH of the solution is 7.0 to 8.5.

Quadramet® is supplied frozen in a single-dose glass vial containing 3 ml with 5550 MBq (150 mCi) of Samarium 153 at calibration (NDC#50419-209-03).

The vial is shipped in a lead shield; a package insert is included. The drug product expires 48 hours after the time of calibration noted on the label, or 8 hours after thawing, whichever is earlier.

7.4 Supply

Samarium Sm-153 lexidronam (Quadramet®) is available commercially (Cytogen Corporation; manufactured by Bristol-Myers Squibb Medical Imaging-BMSMI) and currently has FDA approval for the treatment of symptomatic bony metastases. Samarium Sm-153 lexidronam will be supplied to patients on study free of charge. Sites using a central radiopharmacy will be responsible for the radiopharmacy fee. Sites can choose to take delivery directly from BMSMI for this study in order not to incur a central radiopharmacy preparation fee.

The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

The Study Agent Shipment Form must be submitted to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. Each institution must also provide a copy of their Radioactive Materials License prior to study start so that an account number for drug supply can be established. This must be done prior to registration of the institution's first case.

The Study Agent Shipment Form for US and Canadian sites must be submitted to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. **Note: International sites must receive written approval of submitted LOI Forms from RTOG Headquarters prior to submitting documents to local ethics committee for approval. See http://www.rtog.org/Researchers/InternationalMembers.aspx. Approved international institutions must submit the Study Agent Shipment Form 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.**

Samarium 153 lexidronam is produced only one day per week (Tuesday), which allows for administration Wednesday through Friday of the same week. It expires at 12:00 noon, EST. The drug will not be shipped until the patient has been registered and the RTOG 0622 Samarium 153 Lexidronam Release Form has been received at BMSMI. A Word version of the Samarium 153 Lexidronam Release Form for this study is available on the RTOG web site, www.rtog.org, next to the protocol. Completed forms should be sent via email to Customer Service at BMSMI (mics@bms.com). Forms can be sent to BMSMI, Monday through Friday except for New Year's Day, Memorial Day, July 4, Labor Day, Thanksgiving and Christmas Day. The product ships Tuesday through Thursday each week. Each institution is responsible for notifying the RTOG Regulatory Associate at 215-574-3185 if the drug does not arrive on the expected date.

Unused supplies at the sites must be disposed of in accordance with institutional policy for radioactive waste. Additional questions about supply and delivery should be directed to: **Customer Service at BMSMI, 800-362-2668.**

7.5 Storage

Samarium 153 lexidronam will be stored in the radioisotope lab in the Department of Nuclear Medicine or Radiation Oncology. Quadramet® is approved for distribution to persons licensed pursuant to the Code of Massachusetts Regulations 105 CMR 120.500 for the uses listed in 105 CMR 120.537 or under equivalent licenses of the U.S. Nuclear Regulatory Commission, an Agreement State or a Licensing State. It is to be stored frozen at -10 to 20^0 C in a lead-shielded container. Storage and disposal of Quadramet® should be controlled in a manner that complies with the appropriate regulations of the government agency authorized to license the use of this radionuclide.

7.6 Physical Characteristics

Samarium 153 is produced in high yield and purity by neutron irradiation of isotopically enriched Samarium Sm 152 oxide ($^{152}Sm_3O_3$). It emits both medium-energy beta particles and low energy gamma photons, and has a physical half-life of 46.3 hours (1.93 days). Samarium 153 has

average and maximum beta particle ranges in water of 0.5 mm and 3.0 mm, respectively. The primary radiation emissions of Samarium 153 are shown in the following table.

Beta	640	30%
Beta	710	50%
Beta	810	20%
Gamma	103	29%

* Maximum energies are listed for the beta emissions; the average beta particle energy is 233 keV.

7.7 Clinical Pharmacology

Quadramet® (Samarium Sm-153 EDTMP) has an affinity for bone and concentrates in areas of bone turnover in association with hydroxyapatite. In clinical studies employing planar imaging techniques, more Quadramet® accumulates in osteoblastic lesions than in normal bone with a lesion-to-normal bone ratio of approximately 5. The mechanism of action of Quadramet® in relieving the pain of bone metastases is not known.

Distribution: Human protein binding has not been studied; however, in dog, rat and bovine studies, less than 0.5% of Samarium153 EDTMP is bound to protein. At physiologic pH, >90% of the complex is present as $^{153}Sm[EDTMP]^{-5}$ and <10% as $^{153}Sm[EDTMP]^{-4}$. The octanol/water partition coefficient is $<10^{-5}$.

Skeletal Uptake: The greater the number of metastatic lesions, the more skeletal uptake of Sm-153 radioactivity. The relationship between skeletal uptake and the size of the metastatic lesions has not been studied. The total skeletal uptake of radioactivity was 65.6% ± 15.5% of the injected dose in 453 patients with metastatic lesions from a variety of primary malignancies. In a study of 22 patients, the total skeletal uptake of radioactivity ranged from 56.3% in a patient with 5 metastatic lesions to 76.7% in a patient with 52 metastatic lesions. If the number of metastatic lesions is fixed, over the range 0.1 to 3.0 mCi/kg, the % ID taken up by bone is the same regardless of the dose.

Metabolism: The complex formed by Samarium and EDTMP is excreted as an intact, single species that consists of one atom of the Sm-153 and one molecule of the EDTMP, as shown by an analysis of urine samples from patients (n=5) administered Samarium Sm-153 EDTMP. Metabolic products of Samarium Sm-153 EDTMP were not detected in humans.

Elimination: For Quadramet®, calculations of the % ID detected in the whole body, urine and blood were corrected for radionuclide decay. The clearance of activity through the urine is expressed as the cumulated activity excreted. The whole body retention is the simple reciprocal of the cumulated urine activity.

Blood: Clearance of radioactivity from the blood demonstrated bi-exponential kinetics after intravenous injection in 19 patients (10 men, 9 women) with a variety of primary cancers that were metastatic to bone. Over the first 30 minutes, the radioactivity (mean ± SD) in the blood decreased to 15% (±8%) of the injected dose with a t ½ of 5.5 min (±1.1 min). After 30 minutes, the radioactivity cleared from the blood more slowly with a t ½ of 65.4 min (±9.6 min). Less than 1% of the dose injected remained in the blood 5 hours after injection.

Urine: Samarium Sm-153 EDTMP radioactivity was excreted in the urine after intravenous injection. During the first 6 hours. 34.5% (±15.55) was excreted. Overall, the greater the number of metastatic lesions, the less radioactivity was excreted.

7.8 Pharmacodynamics

The beta particle of ^{153}Sm-EDTMP travels an average of 3.1 mm in soft tissue and 1.7 mm in bone. In clinical trials of 78 patients with metastatic bone lesions who had 13 specific bone scan sites evaluated, the presence or absence of ^{153}Sm-EDTMP uptake is similar to the presence or absence of ^{99m}Tc diphosphonate uptake (range 67 to 96% agreement depending upon the blinded reader and the site of the body). Whether the amount of ^{153}Sm-EDTMP uptake varies with the size of the lesion or to the presence of osteolytic components has not been studied. The clinical benefits of ^{153}Sm-EDTMP in patients with osteolytic lesions are not known. The relationship of different tumor cell types to clinical response has not been studied.

7.9 Toxicity

Most of the toxicity data is from the pivotal studies and the literature (6-10). Adverse events were evaluated in a total of 580 patients who received Quadramet® in clinical trials. Of the 580 patients, there were 472 men and 108 women with a mean age of 66 (range 20 to 87). Of these

patients, 472 (81%) had at least one adverse event. In a subgroup of 399 patients who received Quadramet® 1.0 mCi/kg, there were 23 deaths and 46 serious adverse events. The deaths occurred, on average, 67 days (range: 9 to 130) after Quadramet®. Serious events occurred, on average, 46 days (range: 1 – 118) after Quadramet®. Although most of the patient deaths and serious adverse events appear to be related to the underlying disease, the relationship of end stage disease, marrow invasion by cancer cells, previous myelotoxic treatment and Quadramet® toxicity can not be easily distinguished. In clinical studies, two patients with rapidly progressive prostate cancer developed thrombocytopenia and died 4 weeks after receiving Quadramet®. One of the patients showed evidence of disseminated intravascular coagulation (DIC); the other patient experienced a fatal cerebrovascular accident, with a suspicion of DIC. The relationship of the DIC to the bone marrow suppressive effect of Samarium is not known. Marrow toxicity occurred in 277 (48%) patients.

In controlled studies, 7% of patients receiving 1.0 mCi/kg Quadramet® (as compared to 6% of patients receiving placebo) reported a transient increase in bone pain shortly after injection (flare reaction). This was usually mild, self-limiting, and responded to analgesics.
The most common adverse events observed in controlled clinical studies of Quadramet®, are pain flare reaction (7%), cardiovascular (16%), hematologic (27%), bleeding (16 %), and infection (17%).
OVERDOSAGE: Overdosage with Quadramet® has not been reported. An **antidote** for Quadramet® overdosage is not known. The anticipated complications of overdosage would likely be secondary to bone marrow suppression from the radioactivity of ^{153}Sm, or secondary to hypocalcemia and cardiac arrhythmias related to the EDTMP.

7.10 Accountability: RTOG drug accountability records must be maintained at all sites according to Good Clinical Practices and NCI guidelines.

7.11 Modality Review
The Medical Oncology Co-Chair, Oliver Sartor, M.D., will perform a Quality Assurance Review after 4 months of complete data for the first 20 cases enrolled have been received at RTOG Headquarters. Dr. Sartor will perform the next review after 4 months of complete data for the next 20 cases enrolled have been received at RTOG Headquarters. The final cases will be reviewed after this study has reached the target accrual as soon as 4 months of complete data for all cases enrolled have been received at RTOG Headquarters.

7.12 Adverse Events (3/8/11)
Beginning April 1, 2011, this study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for AdEERS reporting of adverse events (AEs). **All AE reporting on the study case report forms (CRFs) should follow grading criteria instructions on the specific CRF.** The CTCAE version 4.0 is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

All adverse events (AEs) as defined in the table below (7.12.4) 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 table below will also be reported via AdEERS. Sites also can access the RTOG web site (http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx) 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.

A 24-hour notification is to be made to CTEP by telephone at 301-897-7497 only when internet connectivity is disrupted. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into AdEERS by the original submitter at the site.

7.12.1 Adverse Events (AEs) (9/29/09)

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: Adverse Event Reporting Requirements. January 2005; http://ctep.cancer.gov/reporting/adeers.html]

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 7.12.4 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.

7.12.2 <u>Serious Adverse Events (SAEs)</u> — 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.**

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

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

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

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.

7.12.3 <u>Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)</u>

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.

7.12.4 AdEERS Expedited Reporting Requirements (9/29/09)

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 Study Agent [Samarium 153] 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."

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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 a commercially available agent.
- 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:

Not applicable to this study.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Androgen Suppression Plan (3/9/11)

Schedule: Patients may receive androgen suppression *(Zoladex or Lupron with or without Casodex or Eulexin [AS])* at the discretion of their physician if the PSA continues to rise after completion of prostatic fossa irradiation. Recommended duration is 2 years or until death.

9.1.1 Zoladex *(goserelin)*

9.1.1.1 *Description*

Zoladex is an LHRH analog with substitutions for the L-amino acid Glycine in positions 6 and 10. These substitutions produce an analog with 50-100 times the potency and longer duration of action than the naturally occurring peptide when assessed in acute animal tests.

9.1.1.2 *Supply*

Zoladex is commercially available. Either 10.8 mg, 3-month formulation or 3.6 mg, 1-month formulation may be used.

9.1.1.3 *Storage*

The Zoladex 3.6 mg depot is supplied with a 16 gauge needle and the Zoladex 10.8 mg depot is supplied with a 14 gauge needle. The unit is sterile and comes in a sealed, light- and moisture-proof package. The pack should be stored at approximately 25° C *(room temperature).* Before being opened, each package must be inspected for damage in which case the syringe must not be used. Being sterile, the syringe should be removed from its package only by the physician/nurse immediately before use.

9.1.1.4 *Administration*

Zoladex may be administered to all patients. If requested by the patient, a local anesthetic, i.e., 0.2 to 0.5 ml of 1% lidocaine hydrochloride may be given intradermally. Zoladex will be injected subcutaneously using an aseptic technique. Insert the needle to its full length, pull it back 1cm, then inject. The manufacturer recommends inserting the needle into the subcutaneous fat then changing the direction of the needle so that it parallels the abdominal wall before inserting the needle to its full length. This will create a little pocket for the Zoladex plug so that it does not extend when the needle is withdrawn. After checking to ensure that the depot has been discharged, the used syringe will be discarded in a safe manner. One can ensure that the depot has been discharged by ensuring the tip of the plunger is visible within the tip of the needle. The tear off portion of the depot package label will be removed and affixed to the patients' permanent record. All patients will receive a total of 24 months of androgen ablation. In the event of radiotherapy treatment interruptions, the drug administration will be continued. Administration of drug will be suspended only if there is an apparent or suspected reaction to the drug.

9.1.1.5 *Toxicity*

During routine screening of Zoladex, no significant pharmacological activity was apparent in the cardiovascular, respiratory, central nervous, renal, metabolic, coagulation or gastric acid secretory systems. Studies have shown that serum levels of testosterone can be reduced and maintained within the castrate range resulting in objective evidence of tumor regression. Other than the occasional transient worsening of cancer symptoms *(tumor flare)* due to an initial temporary rise in testosterone serum levels on initiating therapy, no significant toxicity apart from that attributed to castration *(hot flashes, decreased erections, impotence)* has been reported. In general, allergic reactions have been extremely uncommon with Zoladex therapy. There have been isolated reports of urethral obstruction, urticaria, or spinal cord compression.

9.1.2 Lupron *(leuprolide)*

9.1.2.1 *Description*

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone *(GnRH or LH-RH)*. The analog possesses greater potency than the natural hormone. Leuprolide acetate, a LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Human studies indicate that following an initial stimulation, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy. Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors *(prostatic tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats)* as well as atrophy of the reproductive organs.

In humans, administration of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone *(LH)* and follicle stimulating hormone *(FSH)*, leading to a transient increase in levels of the gonadal steroids *(testosterone and dihydrotestosterone in males, and estrone and estradiol in premenopausal females)*. However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. These decreases occur within two to four weeks after initiation of treatment, and castrate levels of testosterone in prostatic cancer patients have been demonstrated for more than five years with continuous drug administration.

9.1.2.2 *Supply*

Leuprolide is commercially available as either 7.5 mg *(one month)*, 22.5 mg *(three month)*, or 30 mg *(four month)* depots for intramuscular injection. Each kit contains a vial of sterile lyophilized microspheres, which is leuprolide incorporated in a biodegradable polymer of polylactic acid. Any formulation may be used.

9.1.2.3 *Storage*

The vial of leuprolide and the ampule of diluent may be stored at room temperature. Product does not contain preservative, discard if not used immediately.

9.1.2.4 *Administration*

Any formulation may be used and administered per package directions.

9.1.2.5 *Toxicity*

In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. The most common side effect of Leuprolide is vasomotor hot flashes; edema, gynecomastia, bone pain, thrombosis, and GI disturbances have occurred.

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms.

9.1.3 Eulexin *(flutamide)*

9.1.3.1 *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 non-steroid anti-androgen that is metabolized into a hydroxylated derivative, which effectively competes with the hydrotestosterone for androgen receptor sites.

9.1.3.2 *Supply*

Flutamide is supplied as 125 mg capsules and is commercially available.

9.1.3.3 *Storage*

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

9.1.3.4 *Administration*

The drug is administered orally at a dose of two 125 mg capsules three times a day for a total daily dose of 750 mg *(six capsules).*

Flutamide will be suspended only if there is an apparent or suspected reaction to the drug. See Section 7.4.6.

9.1.3.5 *Toxicity*

The reported side effects of treatment include diarrhea and anemia. A high percentage of patients treated with flutamide alone developed gynecomastia within 2-8 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.

9.1.3.6 *Dose Modification Schedule*

If gastrointestinal disturbances *(cramps, diarrhea)* occur prior to initiation of radiotherapy, flutamide will be withheld until the side effects subside and then reintroduced at a dose of 250 mg/day increasing the dose *(at 3 day intervals)* to 500 mg/day then to 750 mg/day as tolerated.

If gastrointestinal disturbances occur after administration of radiotherapy, it might be difficult to identify their cause. However, if severity of diarrhea exceeds the level commonly observed during

pelvic irradiation, the toxicity will be ascribed to flutamide and the drug will be permanently discontinued.

ALT will be measured pretreatment, then monthly during oral antiandrogen therapy. If ALT increases ≥ 2 x upper institutional limit of normal, flutamide must be discontinued.

9.1.4 Casodex *(bicalutamide)*

9.1.4.1 *Description*

Casodex *(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, *(+,-)*. Casodex is a racemic mixture with the antiandrogen activity residing exclusively in the *(-)* or **R-**enantiomer. Casodex 50 mg has the status of an approved new drug. Casodex has a long half-life compatible with once-daily dosing. Casodex is well tolerated and has good response rates in phase II trials.[38-39]

9.1.4.2 *Supply*

Casodex is commercially available as a 50 mg tablet.

9.1.4.3 *Storage*

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

9.1.4.4 *Administration*

Casodex is administered orally at a dose of one 50mg tablet per day.

9.1.4.5 *Toxicity*

In animal experiments, birth defects *(abnormal genitalia, hypospadias)* were found in male offspring from female animals dosed with Casodex during pregnancy. Although offspring from male animals dosed with Casodex did not show any birth defects, patients enrolled in this trial are advised to neither cause pregnancy nor to donate sperm while receiving protocol therapy or during the first 3 months after cessation of therapy. The use of barrier contraceptives is advised.

The most frequent adverse events reported among subjects receiving bicalutamide therapy are breast tenderness, breast swelling, and hot flashes.

When bicalutamide 50 mg was given in combination with an LHRH analogue, the LHRH analogue 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%).*

9.1.4.6 *Dose Modification Schedule*

CASODEX SHOULD BE DISCONTINUED IN INSTANCES OF CHEMICAL LIVER TOXICITY. ALT WILL BE MEASURED PRETREATMENT AND THEN MONTHLY DURING ANTIANDROGEN THERAPY. IF THE ALT RISES ≥ 2 X THE INSTITUTIONAL UPPER LIMIT OF NORMAL, CASODEX MUST BE DISCONTINUED.

9.2 Other 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) and documented on each site's source documents as concomitant medication.

10.0 TISSUE/SPECIMEN SUBMISSION

(9/29/09) Note: Patients must be offered the opportunity to participate in the tissue/specimen submission component of the study. If the patient consents to participate in the tissue/specimen 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 General Information (3/9/11)

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.

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

10.2 Specimen Collection for Tissue Banking for Biomarker Studies: Strongly recommended
For patients who have consented to participate in the tissue/blood/urine component of the study (See Appendix VI). (4/20/12)

10.2.1 Sites may submit the following specimens:

10.2.1.1 At least one paraffin-embedded tissue block of the tumor or a 2-mm diameter core of tissue punched from the tissue block containing the tumor with a punch tool and submitted in a plastic tube labeled with the surgical pathology number. If tumor heterogeneity is observed, the submission of multiple blocks or punch biopsies, including tissue from the area having the highest Gleason score, is desirable. **As this is a post-surgical study, numerous FFPE tissue blocks containing the primary tumor should exist.**
Note: A kit with the punch, tube, and instructions can be obtained free of charge from the RTOG Biospecimen Resource (see Appendix VI). Block or core 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 RTOG Biospecimen Resource:

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

10.2.1.2 Serum, plasma, whole blood, and urine
See Appendix VI for the blood and urine collection kits and instructions.
The following must be provided in order for the case to be evaluable for the RTOG Biospecimen Resource: A Specimen Transmittal Form documenting the date of collection of the biospecimen; the RTOG protocol number, the patient's case number, time point of study, and method of storage, for example, stored at -80° C, must be included.

10.2.1.3 Storage Conditions **(9/29/09)**
Store frozen specimens at -80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:
Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).
OR:
Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).
OR:
Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on the Specimen Transmittal Form the storage conditions used and time stored.

10.2.1.4 Specimen Collection Summary

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 a 2 mm diameter core of tissue, punched from the tissue block with a punch tool	From prostatectomy surgical specimens	Paraffin-embedded tissue block or punch biopsy	Block or punch shipped ambient
SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge	Pre-treatment and 6 months after RT completion	Frozen serum samples containing 0.5 mL per aliquot in 1 mL cryovials (five to ten)	Serum sent frozen on dry ice via overnight carrier
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) and centrifuge	Pretreatment and 6 months after RT completion	Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (five to ten)	Plasma sent frozen on dry ice via overnight carrier
DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix	Pre-treatment and week 4 (midway) of RT	Frozen whole blood samples containing 1 ml per aliquot in 1ml cryovials (three to five)	Whole blood sent frozen on dry ice via overnight carrier
10-20 mL clean-catch urine	Pre-treatment and 6 months after RT completion	Two 5-10 mL urine aliquots in 2 sterile 15 ml polypropylene centrifuge tubes. Store frozen at -20° or 80° C	Urine sent frozen on dry ice via overnight carrier

10.2.2 Submit materials for Tissue Banking to:

U.S. Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

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

10.3 Reimbursement (3/9/11)

RTOG will reimburse institutions for submission of protocol specified biospecimen materials sent to the Biospecimen Resource at the University of California San Francisco and other protocol-specified collection repositories/laboratories. After confirmation from the RTOG Biospecimen Resource or other designated repository/laboratory that appropriate materials have been received, RTOG Clinical Trials Administration will authorize payment according to the schedule posted with the Reimbursement and Case Credit Schedule found on the RTOG web site (http://www.rtog.org/LinkClick.aspx?fileticket=Csxzt1v1hEk%3d&tabid=323). Biospecimen

payments will be processed quarterly and will appear on the institution's summary report with the institution's regular case reimbursement.

10.4 Confidentiality/Storage (9/29/09)

(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx for further details.)

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

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

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters:

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

11.2 Evaluation During Radiotherapy Treatment (9/29/09)

Radiotherapy begins 12 weeks (+/- 1 week) after Samarium 153 administration.

11.2.1 A physical exam, weight and performance status, CBC with differential, and PSA will be conducted weekly (the CBC w/ differential and PSA will be collected weekly for 12 weeks after the Samarium infusion).

11.2.2 ALT, alkaline phosphatase, BUN, and creatinine will be assessed monthly, if oral antiandrogen therapy is used.

11.3 Evaluation Following Radiotherapy (9/29/09)

11.3.1 History and physical exam, weight and performance status, CBC with differential, PSA, and testosterone assessments will be conducted at 3 months, 6 months, and 12 months following radiotherapy in the first year, every 6 months for the next 2 years, and annually thereafter.

11.3.2 A pelvic lymph node assessment by CT scan, MRI, ProstaScint, or pelvic lymph node dissection or sampling will be conducted every 6 months for 2 years

11.3.3 A bone scan will be conducted every 6 months for 2 years, and as clinically indicated.

11.4 Measurement of Response

Response will be evaluated in this study using weekly (i.e., for 12 weeks following Samarium infusion) PSA measurements obtained from the same biochemical assay.

Response Criteria: Evaluation of sub clinical target lesions

*Complete Response (CR):	Disappearance of all disease indicators as indicated by a PSA nadir below 0.2 ng/ml
*Partial Response (PR):	At least a 30% decrease in the serum PSA level as measured from baseline,
*Progressive Disease (PD):	At least a 30% increase in the serum PSA level as compared to baseline
*Stable Disease (SD):	Neither sufficient PSA decrease to qualify for PR nor sufficient increase to qualify for PD, taking as reference the baseline PSA

11.5 Criteria for Freedom from Progression (FFP)

A secondary endpoint is FFP, which includes biochemical (PSA) failure at anytime for 2 years after prostatic fossa RT, initiation of systemic therapy, or clinical failure.

11.5.1 Biochemical (PSA) Failure

The biochemical failure endpoint is defined as a rise of 0.2 ng/ml or more above the nadir PSA after completion of RT followed by another higher value, or a continued rise in the serum PSA despite RT.

11.5.2 Clinical Failure

Clinical failure is defined as any evidence of local, regional or distant failure.

11.5.3 Time to FFP

Time to FFP will be measured from the date of registration to the date of documented biochemical progression, clinical failure, or death from any cause.

11.6 Criteria for Local Failure

11.6.1 Local Failure

Local failure is defined as the development of a new palpable abnormality in the prostate bed after enrollment in the protocol. The presence of a palpable abnormality in the prostate bed prior to randomization is not permitted unless it is biopsy proven to be negative for cancer. Needle biopsy is recommended for any new palpable abnormality. Patients who have a normal exam and no evidence of biochemical failure by the primary endpoint will be considered controlled locally. Patients with a new prostatic fossa abnormality and biochemical failure will be considered to have local failure. Patients with a new prostatic fossa abnormality and no evidence of biochemical failure should undergo prostatic fossa biopsy. If salvage therapy is instituted prior to biopsy of a new prostatic fossa abnormality, then these patients will be considered to have had local failure. The presence of palpable disease must be recorded on the data collection forms for follow-up evaluations of the patient.

11.6.2 Biopsy of any new palpable abnormality in the prostatic fossa is recommended to document by histologic criteria the presence of prostatic adenocarcinoma.

11.7 Criteria for Nonlocal Failure

11.7.1 Regional Metastasis

Regional metastasis will be documented if there is radiographic evidence (CT or MRI) of lymphadenopathy (lymph node size ≥ 1.5 cm) in a patient without the diagnosis of a hematologic/lymphomatous disorder associated with adenopathy. Histologic confirmation is not required, although it is recommended in the setting of freedom from biochemical progression.

11.7.2 Distant Metastasis

Distant metastasis will be documented if by imaging (e.g., bone scan, CT, MRI) there is evidence of hematogenous spread.

11.7.2.1 Time to Distant Failure

The time to distant failure will be measured from the date of registration to the date of documented distant disease.

11.8 Criteria for Discontinuation of Protocol Treatment (4/9/10)

- Progression of disease as determined by a rapidly rising PSA after administration of samarium as defined by a PSA doubling time less than 3 months.
- Progression of disease as defined as two consecutive rises in PSA more than 30% above baseline obtained prior to the administration of Samarium-153.
- Severe thrombocytopenia defined as a platelet count of 25,000 cells/mm^3 or less.
- The patient may withdraw from the study at any time for any reason. The institution must notify RTOG Headquarters Data Management about this in writing, and follow the guidelines set forth in the RTOG procedure manual.

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

Item	Due

Demographic Form **(A5)**	Within 2 weeks of study entry
Initial Evaluation Form **(I1)**	Within 2 weeks of study entry
Pathology Report **(P1)** [For studies with pathology]	Within 2 weeks of study entry
Slides/Blocks **(P2)** [For studies with pathology]	Within 2 weeks of study entry
Radiotherapy form (T1) (Copy to ITC and HQ)	Within 1 week of RT end
Treatment Form **(TF)**	1 month after Samarium injection
Follow-up Form **(F1)**	Every three months for one year after Samarium injection; then every 6 months x 2 years, then annually

For protocols involving submission to ITC:

12.2 Summary of Dosimetry Digital Data Submission for 3D-CRT or IMRT (Submit to ITC; see Section 12.2.1)

Item (9/29/09) (4/9/10)	**Due**
Preliminary Dosimetry Information (DD) Digital Data Submission – Treatment Plan submitted to ITC via SFTP account exported from treatment planning machine by Physicist Digital data submission includes the following: • CT data, critical normal structures, all GTV, CTV, and PTV contours **(C1, C3)** • Digital beam geometry for initial and boost beam sets • Doses for initial and boost sets of concurrently treated beams • Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan **(DV)**	Within 1 week of start of RT
Digital Data Submission Information Form **(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 **(T6)**	
NOTE: Sites must notify ITC via e-mail (itc@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 Radiotherapy Form **(T1) [copy to HQ and ITC]** Daily Treatment Record **(T5) [copy to HQ and ITC]** Modified digital patient data as required through consultation with Image Guided Therapy QA Center	Within 1 week of RT end

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@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*

The effectiveness of Samarium 153

13.1.2 *Secondary Endpoints*

13.1.2.1 Completion of protocol treatment

13.1.2.2 Hematological toxicity at 12 weeks

13.1.2.3 Samarium 153-related adverse events at 12 weeks

- Adverse events are evaluated by the NCI Common Terminology Criteria for Adverse Event (CTCAE) version 3.0. The treatment-related attribution includes definitely, probably or possibly related to treatment. The Samarium 153 related adverse event is defined as the following:
- HEMATOLOGIC
  Platelet grade 3-5
  WBC grade 3-5
  Hemoglobin grade 3-5
  Any secondary leukemia's
- HEMORRHAGE/BLEEDING
  Hemorrhage, GI - anus, rectum grade 3-5
  Hemorrhage, GU - bladder, prostate, urethra grade 3-5
- SAMARIUM 153-RELATED GRADE 5 ADVERSE EVENT PRIOR TO TREATMENT OF RADIATION.

13.1.2.4 "Acute" and "late" radiation therapy-related adverse events having occurred up to 24 weeks from the end of radiation therapy.

13.1.2.5 Freedom from progression (FFP) rate at 2 years to that predicted by the Kattan Nomograms

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

13.2 Sample Size

The primary goal of this study is to assess the effectiveness of Samarium 153 administration, as determined by a PSA response within 12 weeks in a population of men with high risk, clinically non-metastatic prostate cancer after a radical prostatectomy. A PSA response for each patient is calculated by (baseline PSA-current PSA)/baseline PSA. Denote p_t as the proportion of patients who have a PSA response to Samarium 153 among all eligible patients. We expect that less than or equal to 10% of patients will have a PSA response if patients are not treated with Samarium 153. We hypothesize that Samarium 153 will improve the proportion of patients who have a PSA response more than or equal to 25% within 12 weeks. The null hypothesis (H_0) is that Samarium 153 is not effective versus the alternative hypothesis (H_A) that Samarium 153 is effective. The hypotheses are:

$$H_0: p_t \leq 0.1 \text{ vs. } H_A: p_t \geq 0.25$$

The sample size is calculated based on the above hypotheses with Fleming's Multiple Testing Procedure[1] at a significance level of 0.019 and 91% statistical power. At these type I and II error rates, 69 patients will detect a proportion of patients who have a PSA response to Samarium 153 of no more than 10% under the null hypothesis and at least 25% under the alternative hypothesis. Adjusting the number of cases for ineligible or unanalyzable cases by 10%, **a maximum of 76 patients is required for this study.**

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 2 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. 17% of patients in RTOG 9601 have similar patient's characteristics with this study. We expect to complete accrual in 4 (> 3.7 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, RTOG GU Cancer Committee chair, and 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 (3/9/11)

13.4.1 Primary endpoint

The primary objective is to assess the effectiveness of Samarium 153 administration, as determined by a PSA response within 12 weeks in a population of men with high risk, clinically non-metastatic prostate cancer after a radical prostatectomy. A PSA response is defined as a 30% decline in the PSA as compared to baseline PSA. We hypothesize at least 25% of patients will respond to Samarium 153 within 12 weeks in a population of men with high risk, clinically non-metastatic prostate cancer after a radical prostatectomy. For the evaluation of effectiveness of Samarium 153, analyzable patients are defined as eligible patients who received Samarium 153 with at least 12 weeks follow-up from the injection. 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 PSA response to the Samarium 153 rate may be at least 25%, we would conclude that the Samarium 153 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 PSA response to the Samarium 153 rate may be less than 10%, we stop the accrual (if applicable) and conclude that the Samarium 153 is not effective and report the result. If we continue until the last stage, we will conclude that Samarium 153 is effective or not effective. We report the conclusion of the primary endpoint when all patients have at least 90 days of follow-up from the end of radiation therapy unless we stop at any interim stage. The rate of a PSA response p_t will be calculated as the number of patients who have a PSA response to Samarium 153 divided by the total number of analyzable patients at the evaluation time point.

< Table 1 Stopping and Continuation Rules for a PSA Response Rate >

Number of analyzable patients*	Stop and reject H_0: $p_t \leq 0.1$	Continue Accrual	Stop and reject H_A: $p_t \geq 0.25$
23	≥ 8	1-7	≤ 0
46	≥ 11	6-10	≤ 5
69	≥13	N/A	≤ 12

* Analyzable patients are defined as eligible patients who received any protocol treatment with at least 12 weeks follow-up from the Samarium 153 injection.

If a grade 5 adverse event definitely, probably or possibly related to treatment is reported within 12 weeks after the Samarium 153 injection, 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[2] will be used to model the association of factors with the occurrence of a PSA response to Samarium 153. Both unadjusted and adjusted odds ratios and the respective 95% confidence interval will be computed. Clinical T-stage, baseline PSA, Gleason score, and age (and other factors as appropriate) will be adjusted for in this analysis.

13.4.2 Secondary endpoints

13.4.2.1 To assess the completion of protocol treatment

The completion of protocol treatment is defined as receiving at least 64.8 Gy radiation after the Samarium 153 injection. The null hypothesis that the proportion of the number of patients who complete the protocol treatment (the Samarium 153 and the radiation therapy) is less than or equal to 0.5 will be tested using an exact test for a binomial proportion. If the true treatment completion proportion is 0.8, then the statistical power of a one-sided 0.378 level exact binomial test of proportion would be 94.1% with the sample size of 26. This corresponds to a rule of 18 or more tissue samples out of 23 completing the protocol treatment. The study sample size, 69, would provide enough power for this endpoint. We evaluated the completion of protocol treatment when all patients have at least 90 days of follow-up from the end of radiation therapy.

13.4.2.2 To evaluate hematologic, Samarium 153-related, and radiation therapy-related adverse events

Adverse events are evaluated by the NCI Common Terminology Criteria for Adverse Event (CTCAE) version 3.0. The treatment-related attribution includes definitely, probably or possibly related to treatment. The treatment-related adverse events are defined in Section 13.1.2.3, including the development of leukemia. The hematologic and Samarium 153 related adverse events are evaluated at 12 weeks from the injection of Samarium 153. An acute adverse event is defined as an adverse event occurring less than 90 days from the end of radiation therapy and a late adverse event is defined as an adverse event occurring more than or equal to 90 days from the end of radiation therapy.

We will evaluate the acute radiation therapy-related adverse events when all patients have at least 90 days of follow-up from the end of radiation therapy. We will evaluate late radiation therapy-related adverse events having occurred up to 24 weeks from the end of radiation therapy. We will evaluate the late adverse events when all patients have at least 24 weeks of follow-up from the end of radiation therapy. Patients will be tabulated by type, grade, and attribution of adverse event. Multivariate logistic regression[2] 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. Clinical T-stage, baseline PSA, Gleason score, and age (and other factors as appropriate) will be adjusted for in this analysis.

13.4.2.3 To compare the freedom from progression (FFP) rate at 2 years with that predicted by the Kattan Nomograms

The freedom from progression (FFP) rate at 2 years will be compared to that predicted by the Kattan Nomograms as cited by Stephenson et al.[40] The FFP failure event 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 by 2 years from registration. The FFP rate at 2 years is defined as the proportion of patients with a FFP failure by 2 years from the registration among all eligible patients at baseline. It will be tested using a two-sided exact test for a binomial proportion at the significance level of 0.05.

13.4.3 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 grade of adverse events due to protocol treatment

13.4.4 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.

13.4.5 Plan for monitoring the toxicity of Samarium 153

Treatment-related (Samarium 153-related) adverse events are defined in 13.1.2.3. We expect that no more than 5% of patients will experience treatment-related (Samarium 153-related) adverse events. Interim reports will be prepared every 6 months until the final analysis. The frequency and grade of adverse events due to protocol treatment are presented to the Data Safety Monitoring Board (DSMB) for their review every 6 months, and they will make a recommendation regarding continuation of this study. Also, this study will be monitored by the CDUS version 3.0. As stated in section 13.4.1, if at any time a grade 5 adverse event definitely,

probably, or possibly related to treatment is reported, 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 necessary. 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 the protocol and/or continuing the study.

13.5 Inclusion of Minorities

In conformance with the National Institute 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 the prior RTOG prostate cancer trial, 9601, we project that 79% of the men in the study are White, 15% are African American, 3% are Hispanic, 1% are Asian, <1% are Pacific Islander and <1% are American Indian or Alaskan Native. The following table lists the projected accrual for each racial group. The table 2 lists projected accrual by race/ethnicity.

< Table 2 Projected Accrual by Race/Ethnicity >

Ethnic Category	**Sex/Gender**		
	Females	Males	Total
Hispanic or Latino	N/A	3	3
Not Hispanic or Latino	N/A	73	73
Ethnic Category: Total of all subjects	N/A	76	76
Racial Category			
American Indian or Alaskan Native	N/A	3	3
Asian	N/A	0	0
Black or African American	N/A	12	12
Native Hawaiian or other Pacific Islander	N/A	0	0
White	N/A	61	61
Racial Category: Total of all subjects	N/A	76	76

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APPENDIX I

Informed Consent Form

RTOG 0622

A PHASE II TRIAL OF SAMARIUM 153 FOLLOWED BY SALVAGE PROSTATIC FOSSA 3D-CRT OR IMRT IRRADIATION IN HIGH-RISK, CLINICALLY NON-METASTATIC PROSTATE CANCER AFTER RADICAL PROSTATECTOMY

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 may have spread to the bone and will not respond to treatment directed to the prostate bed.

Why is this study being done?

The purpose of this study is to find out what effects, good or bad, a bone-targeted radioactive substance has on your prostate cancer. The kind of treatment that most physicians would consider standard for this stage of prostate cancer is radiation therapy. In this study all patients will receive this treatment. In addition, patients will also receive Samarium 153, a radioactive substance. Samarium 153 is currently FDA-approved for the treatment of painful bone metastases, but is an investigational substance in this study because the cancer may not have spread to your bones. It is hoped that Samarium 153 will provide additional benefit. The use of this radioactive substance needs to be tested to determine if it is worthwhile.

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?

If you decide to participate in this study, you will have the following tests and procedures:

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.

- Physical exam with medical history, including Zubrod performance status
- Histological evaluation

- Blood tests, to include a CBC, PSA, liver and kidney function tests and a testosterone level
- Bone scan
- Pelvic lymph node assessment by either CT scan, MRI, ProstaScint or pelvic lymph node dissection or sampling

During the study:

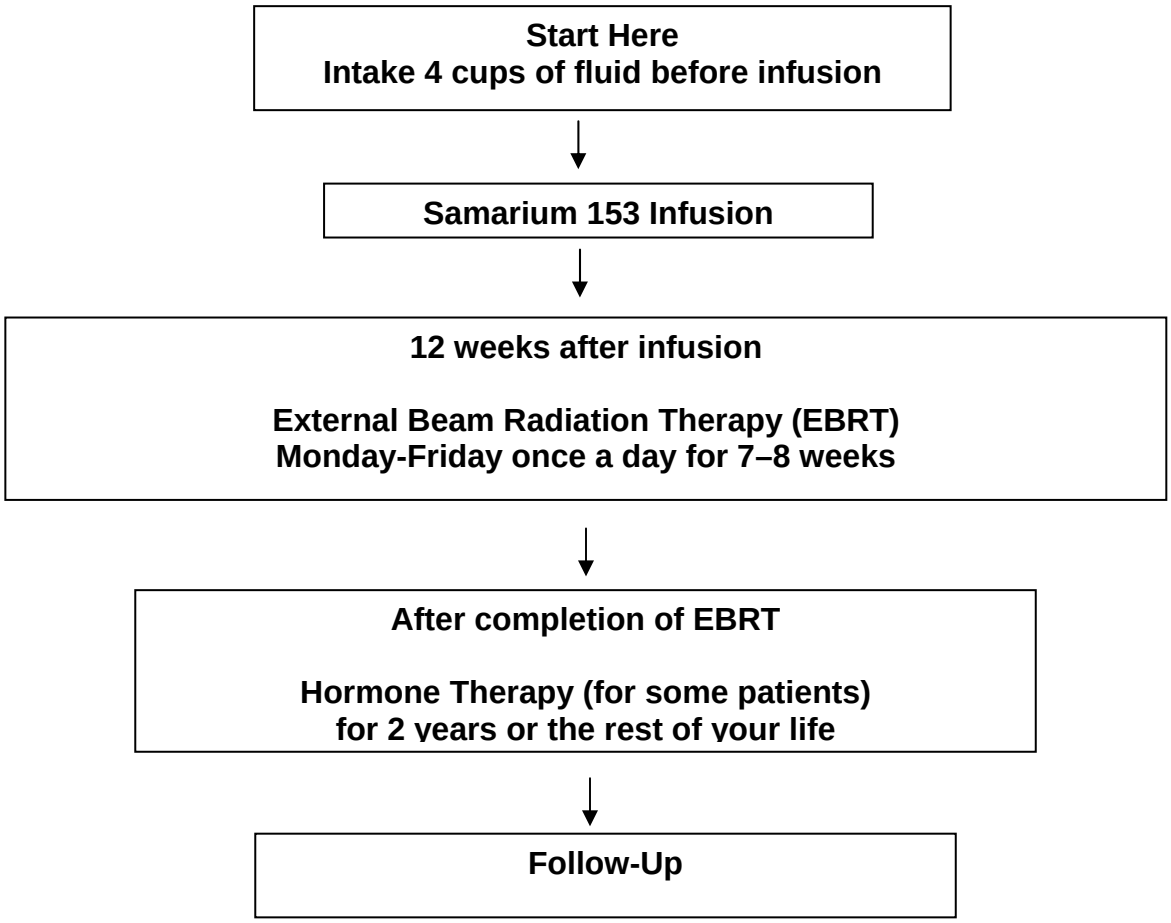
You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study. They will help your study doctor see how the study is affecting your body.

- **(9/29/09)** Blood tests: CBC and PSA every week for 12 weeks after the drug is administered; CBC, PSA, and testosterone at 3 months, 6 months, and 12 months in the first year after radiation is completed, every 6 months for the next 2 years, and yearly thereafter

You will receive standard treatment that consists of external beam radiation treatment. In external beam radiation therapy, a machine delivers radiation to the area of the body affected by the cancer in order to kill the cancer cells. In this study, the radiation will be targeted to the pelvic area of the body where the prostate gland lies (the prostatic fossa). After a discussion with your doctor, you may decide to add hormonal therapy. However, hormonal therapy is not required.

The sequence of this therapy is as follows: You will be given a radioactive substance, Samarium 153, intravenously (IV) as a single dose. The injection will last for approximately 5 minutes. You will drink 4 cups of fluid before the injection and be asked to urinate as frequently as possible after the injection. After the Samarium injection, you will be closely evaluated for 12 weeks. After the 12 weeks you will receive external beam radiation treatments. Radiation is given Monday through Friday, once a day for 7 to 8 weeks. This treatment is given as an outpatient.

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?

When you are finished with the external beam radiation therapy, you will be followed at 3 months, 6 months, and 12 months, then every 6 months for 2 years, and then yearly for the rest of your life.

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 Samarium 153 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. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

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

Risks and side effects related to Samarium 153 include those which are:

Likely
- Nausea
- Vomiting
- Leukopenia (decreased white blood cells, which may increase chance of infection)
- Thrombocytopenia (decreased platelet count, which may cause bleeding)
- Decrease in hemoglobin (which may cause tiredness)

Less likely
- Abdominal pain
- Diarrhea
- Fever and/or chills
- Muscle weakness
- Low blood pressure
- Pain flare reaction (bone pain)
- Cerebrovascular accident (stroke)
- Death

Rare, but serious
- Arrhythmias (irregular heart beat)

Risks Associated with Radiation Therapy:

Very likely
- Reddening or tanning of the skin in the treated area (pelvic area around the prostate)
- Hair loss in the treated area (pelvic area around the prostate)
- Fatigue
- Diarrhea
- Abdominal cramps
- Nausea and vomiting
- Bladder irritation causing urinary frequency; urinary tract infection; painful or difficult urination

Rare, but serious
- Injury to the bladder causing blood in the urine
- Inability to hold urine

- Injury to the bowel and pelvis area
- Permanent inability to achieve an erection

Long term side effects are unknown. The external beam radiation treatment that you will receive uses x-rays that will penetrate your body. Samarium 153 is a radioactive drug that gives off electrons (also called Beta particles) that do not move far in the body, so that their effect is local. Most of the drug is passed through your urine. A licensed medical physician will administer this drug to you. You will not be a radioactive risk to others after the treatment.

Reproductive risks: You should not father a baby while on this study because the drugs in this study can affect an unborn baby. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

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 Samarium 153 will enhance the beneficial effect of usual radiation treatment, there is no proof of this yet. We do know that the information from this study will help researchers learn more about Samarium 153 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. These could include radiation therapy and/or hormones
- Taking part in another study
- Getting no treatment—with this choice your tumor would continue to grow and your disease would spread.

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?

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
- 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 Bristol-Myers Squibb Medical Imaging (BMSMI), the manufacturer of Samarium 153

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.

Cytogen is supplying Samarium 153 at no cost to you. However, you or your health plan may need to pay for costs of the supplies to administer the drug and for the personnel who give you the Samarium 153. If, during the study, Samarium 153 becomes approved for use in your type of prostate cancer, you and/or your health plan may have to pay for drug needed to complete this study.

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].

Use of Tissue, Blood, and Urine for Research (3/9/11)

About Using Tissue, Blood, and Urine for Research

You have had surgery to remove your prostate and your cancer. Your doctors have removed and examined some of this tissue to look at the amount and grade of the cancer and to see if the cancer extended outside of the prostate. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over from your surgery 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 "Providing your Tissue for Research" to learn more about tissue research. This information sheet is available to all at http://www.cancer.gov/clinicaltrials/resources/providing-tissue.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 and six months after you complete radiation treatment. You will also have blood drawn during week 4 of radiation treatment. We would like to keep about two tablespoons of blood and 5 tablespoons of urine. 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. The research that may be done 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, blood and urine will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over tissue and blood 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, blood, and urine. Then any tissue, blood, or urine 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 products or treatments in the future.

Benefits

The benefits of research using tissue, blood, and urine 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 or your participation in the main part of the study.

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

☐ Yes ☐ No

3. 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

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

☐ Yes ☐ No

Where can I get more information? (4/20/12)

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

1-800-4-CANCER (1-800-422-6237)

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 (3/9/11)

RTOG 0622 STUDY PARAMETER TABLE (See Sections 11.2 and 11.3 for details.)

	Pretreatment (may be required for eligibility)				During Samarium & RT Treatment			Follow-Up		
	Within 6 months of Registration	Within 4 months of Registration	Within 8 weeks of Registration	Within 4 weeks prior to Registration	Within 4 weeks prior to Sm-153	Weekly	Monthly	At 3 months, 6 months, and 12 months	q 6 months for 2 years	Annually
History/physical			X			X		X	X	X
Pelvic lymph node assessment	X								X	
Wt. & Performance status				X	X	X		X	X	X
CBC w/ diff, PSA, testosterone				X	X	CBC, PSA only		X	X	X
ALT, Alk Phos, BUN, Cr				X			X			
Bone Scan		X							X	
Adverse event evaluation						X		X	X	X

APPENDIX III (9/29/09)

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).

APPENDIX IV
AJCC STAGING SYSTEM (continued)

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

Study Agent Shipment

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. US and Canadian institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) and fax it, along with the Radioactive Materials License to the CTSU Regulatory Office (Fax 215-569 0206). Pre-approved international institutions must submit the SASF, Radioactive Materials License and documentation of IRB approval to RTOG headquarters (Fax 215-574-0300). This must be done prior to registration of the institution's first case.

The SASF must be processed before the institution is approved to receive drug. Institutions should allow adequate time (7-10 days) to process the SASF form before calling to register the first case. Institutions must also complete the Samarium 153 Lexidronam Release Form electronically and send it as an attachment via e-mail to Customer Service at Bristol-Myers Squibb Medical Imaging (BMSMI), mics@bms.com, once a patient has been registered. Required regulatory documents (see Section 5.2.1) must be received before drug can be shipped. Patient registration, not submission of the SASF, triggers the initial drug shipment. See Section 7.4 for further instructions regarding Samarium ordering.

Note: The SASF and Samarium 153 Lexidronam Release Form for this study are available on the RTOG web site, http://www.rtog.org. (The SASF is located under protocol-specific materials/regulatory resources; the Samarium 153 Lexidronam Release Form is located under Forms).

APPENDIX VI (4/20/12)

APPENDICES FOR RTOG BIOSPECIMEN COLLECTION

RTOG FFPE Specimen Plug Kit Collection
RTOG Blood Collection Kit Instructions
RTOG Urine Collection Kit Instructions

Shipping Instructions:

US Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen or Trackable Specimens
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

- ❑ Include all RTOG paperwork in pocket of biohazard bag.
- ❑ Check that the Specimen Transmittal Form (STF) has the consent boxes checked off.
- ❑ Check that all samples are labeled with the RTOG study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

- ❑ **FFPE Specimens:**
  - o Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  - o FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear the slides shaking it is likely that they will break during shipping.
  - o Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice**.

- ❑ **Frozen Specimens:**
  - o Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - o Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - o Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - o Send frozen specimens via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80° C until ready to ship.

- ❑ **For Questions regarding collection/shipping please contact the RTOG Biospecimen Resource by e-mail: RTOG@ucsf.edu or phone: 415-476-RTOG(7864) or Fax: 415-476-5271.**

APPENDIX VI (continued)

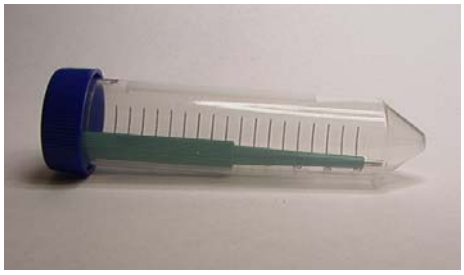
RTOG FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the RTOG Biospecimen Resource. The plug kit contains a shipping tube and a punch tool.

Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

Step 2
Label the punch tool with the proper specimen ID. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or e-mail us if you have any questions or need additional specimen plug kits.



Step 3
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

***NOTE:** If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the RTOG Biospecimen Resource and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.
Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below. For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the RTOG Biospecimen Resource by e-mail: RTOG@ucsf.edu or call 415-476-RTOG(7864)/Fax 415-476-5271.

U.S. Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens or Trackable shipments
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

APPENDIX VI (continued)

RTOG BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood *(as specified by the protocol)*:

Kit contents:

- One Red Top tube for serum (A)
- One Purple Top EDTA tube for plasma (B)
- One Purple Top EDTA tube for Whole Blood (C)
- Twenty-five (25) 1 ml cryovials
- Biohazard bags (3) and Absorbent shipping material (3)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form (STF) and Kit Instructions

PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD:

(A) Serum (if requested): Red Top Tube

- ❑ Label as many 1ml cryovials (5 to 10) as necessary for the serum collected. Label them with the RTOG study and case number, collection date, time, and time point, and clearly mark cryovials "serum".

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the STF.
3. Aliquot 0.5 ml serum into as many cryovials as are necessary for the serum collected (5 to 10) labeled with RTOG study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90° C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90° C until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the STF.

(B) Plasma (If requested): Purple Top EDTA tube #1

- ❑ Label as many 1ml cryovials (5 to 10) as necessary for the plasma collected. Label them with the RTOG study and case number, collection date, time, and time point, and clearly mark cryovials "plasma".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the STF..
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (5 to 10) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma". Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C.
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the STF.

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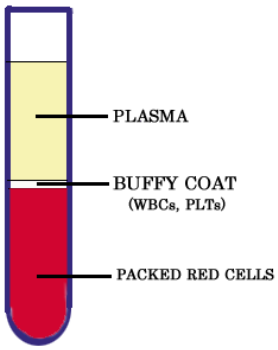
RTOG BLOOD COLLECTION KIT INSTRUCTIONS



(C) Whole Blood for DNA (if requested): Purple Top EDTA tube #2

- ❑ Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the RTOG study and case number, collection date/time, and time point, and clearly mark cryovials "blood".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials as are necessary for the blood collected (3 to 5) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on STF.

Freezing and Storage:

- ☐ Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ❑ Store at -80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- ❑ Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all RTOG paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.

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APPENDIX VI (continued)

RTOG BLOOD COLLECTION KIT INSTRUCTIONS

- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- **For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail RTOG@ucsf.edu or call (415)476-7864.**

Shipping Address:

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-RTOG (7864) or e-mail: RTOG@ucsf.edu

APPENDIX VI (continued)
RTOG URINE COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of urine specimens.

Kit Contents:

- One (1) Sterile Urine collection cup
- Two 7 ml disposable pipettes
- Absorbent paper towel
- Two 15 ml polypropylene centrifuge tubes
- Biohazard bags
- Parafilm for sealing outside of tubes

Preparation and Processing of Urine Specimens:

Process:

- A clean catch urine specimen will be collected. 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.
- Aliquot 5-10 mls of Urine into each of two 15 ml polypropylene centrifuge tubes (disposable pipets are provided in the kit). Do not fill with more than 10 mls to avoid cracking of tubes due to expansion during freezing. Replace the cap and tighten on the tubes. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- Use parafilm to seal the cap around the outside rim of the urine tube to prevent leakage.
- Discard remaining Urine and collection cup.
- Label the specimen with the RTOG study and case number, collection date and time, time point of collection, and clearly mark specimens as "urine".
- Wrap Urine Tubes with absorbent material (paper towels) and place into biohazard bag and seal the bag. Freeze and store Urine samples in a -20°C or -80°C freezer until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED with RTOG study and case numbers, collection date/time, and time point collected (e.g. pretreatment, post-treatment).

Storage and Shipping:

Freezing and Storage:

- ❑ Urine specimens may be sent in batches or with other frozen biospecimens, if within 30-60 days of collection. Store at -20°C or -80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:
  - ▪ Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - ▪ Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
  - ▪ Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all RTOG paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- ❑ Place sealed specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Samples received thawed will be discarded, and a notification will be sent immediately to the Principal Investigator and Clinical Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date.
- ❑ **For questions regarding ordering, collection, or shipping of a Urine Collection Kit, please e-mail RTOG@ucsf.edu or call (415)476-7864 or fax (415) 476-5271.**

Shipping Address: FedEx/UPS/Courier address (For all frozen samples)
RTOG Biospecimen Resource at UCSF
2340 Sutter Street, Room S341, San Francisco, CA 94115
Contact Phone: (415) 476-RTOG(7864)