For Protocol Amendment 7 of RTOG 0521, a Phase III Protocol of Androgen Suppression (As) and 3DCRT/IMRT Vs. As and 3DCRT/IMRT Followed by Chemotherapy With Docetaxel and Prednisone for Localized, High-Risk Prostate Cancer

NCI/Local Protocol #: RTOG-0521/RTOG 0521

NCI Protocol Version Date: December 22, 2014 (Broadcast date: 2/2/2015)

<table>
<thead>
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<th>Section</th>
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| Cover/Schema Pages       | • Due to the transition to the National Clinical Trials Network (NCTN), “Radiation Therapy Oncology Group,” “RTOG Headquarters,” and “RTOG” were replaced with “NRG Oncology”.
|                          | • Contact information was updated for Dr. Hu.                           |
|                          | • Version date was updated.                                             |
| Appendix I/Sample Consent| No changes                                                              |
For Protocol Administrative Update of RTOG 0521, A Phase III Protocol Of Androgen Suppression (AS) And 3DCRT/IMRT Vs. AS And 3DCRT/IMRT Followed By Chemotherapy With Docetaxel And Prednisone For Localized, High-Risk Prostate Cancer

NCI/Local Protocol #: RTOG-0521/RTOG 0521

NCI Protocol Version Date: August 18, 2010  Update Broadcast Date: May 1, 2014

<table>
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<tr>
<td>7.10</td>
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<td>7.11</td>
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<tr>
<td>Appendix V</td>
<td>As required by CTEP, references to the “Adverse Event Reporting System (AdEERS)” have been changed to “CTEP Adverse Event Reporting System (CTEP-AERS)” throughout these sections.</td>
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<td>Title page</td>
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RTOG 0521, A Phase III Protocol of Androgen Suppression (AS) and 3DCRT/IMRT vs. AS and 3DCRT/IMRT Followed by Chemotherapy With Docetaxel and Prednisone for Localized, High-Risk, Prostate Cancer

Study Chair: Howard M. Sandler, MD, MS; Phone: 310-423-4234; Fax: 310-423-6161; E-mail: Howard.Sandler@cshs.org

RTOG 0521 has been amended as follows:

As mandated by CTEP, CTCAE version 3.0 reporting requirements were converted to CTCAE version 4.0.

- Changes were made to Section 7.10 of the protocol.
RTOG 0521, "A Phase III Protocol of Androgen Suppression (AS) and 3DCRT/IMRT vs. AS and 3DCRT/IMRT Followed by Chemotherapy With Docetaxel and Prednisone for Localized, High-Risk, Prostate Cancer"

**Study Chair:** Howard M. Sandler, MD, MS; Phone: 310-423-4234; Fax: 310-423-6161;

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**RTOG 0521** has been updated as follows:

**Section 7.5.2.1:** Biologics, Inc. contact Karl Buer was added in place of Leigh Hancock.
SUMMARY OF CHANGES
Amendment 5: July 28, 2009
(Broadcast August 20, 2009)

RTOG 0521, "A Phase III Protocol of Androgen Suppression (AS) and 3DCRT/IMRT vs. AS and 3DCRT/IMRT Followed by Chemotherapy With Docetaxel and Prednisone for Localized, High-Risk, Prostate Cancer"

**Study Chair:** Howard M. Sandler, MD, MS; Phone: 310-423-4234; Fax: 310-423-6161; E-mail: Howard.Sandler@cshs.org

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RTOG 0521 has been amended as follows:

**Title page:** The contact information for the Principal Investigator, Dr. Sandler, was updated.

Dr. Hunt was added as the RTOG Senior Statistician for this protocol.

**Section 7.0:**

- **7.5.2.1:** The "RTOGDRUG" e-mail address and the contact information for Biologics, Inc. were updated.
- **7.10:** The MedDRA version used for this study is 6.0.

**Section 10.0:**

- **Section 10.2:** Was amended at the request of the RTOG Biospecimen Resource to indicate that a paraffin-embedded tissue block of tumor is preferred and to provide options if the tissue block cannot be obtained. Corresponding changes also were made in the first row of the Specimen Collection Summary table.
- **Section 10.2.1.2:** The temperature of -20° was corrected to -80° C.
- **Section 10.2.2:** "U.S. Postal Service" was added to the Biospecimen Resource mailing address and "DHL" was replaced with "UPS" in the Biospecimen Resource courier address in this section and also in Appendices VI and VII.
- **Section 10.3:** "10-15 slides" was added to the reimbursement paragraph.
RTOG 0521, "A Phase III Protocol of Androgen Suppression (AS) and 3DCRT/IMRT vs. AS and 3DCRT/IMRT Followed by Chemotherapy With Docetaxel and Prednisone for Localized, High-Risk, Prostate Cancer"

Study Chair: Howard M. Sandler, MD; Phone: (734) 936-9338; Fax: (734) 763-7371; E-mail: hsandler@umich.edu

RTOG 0521 has been amended as follows:

Title page: Contact information was updated for 2 co-chairs and all study chairs' information was formatted to RTOG standard. Contact information for the RTOG Senior Statistician for GU studies was added.

Index: Date added next to Appendices VI and VII to indicate revisions to these sections of the protocol.

Eligibility Checklist: Page 1, question 5, the phrase, "and within 180 days of registration" was added for consistency with the PSA eligibility clarification made in Section 3.1.7.

Section 3.0:

- **Section 3.1.1**: Text was added to clarify that patients with diagnoses older than 180 days are eligible with certain conditions.

- **Section 3.1.7**: The time frame for PSA draw was clarified.

- **Section 3.1.8**: The eligibility requirement for bilirubin was corrected.

Sections 5.2, 5.3, and 5.4: Were updated according to current RTOG procedures.

Section 6.0:

- The URL address for the RTOG Prostate Cancer Atlas was added at the beginning of the Section.

- **Section 6.3.1**: The definition of the lymph node target volume was clarified, and the URL address for the RTOG Prostate Cancer Atlas was added. Under "Dose Specification", the dosimetry requirements were corrected for consistency with previous changes to this section.
- **Section 6.3.2**: Under "Dose Specification", the dosimetry requirements were corrected for consistency with previous changes to this section.

- **Section 6.3.5.2**: The definition and contouring instructions for the clinical target volume were clarified, and the URL address for the RTOG Prostate Cancer Atlas was added to the section.

**Section 7.0:**

- **Section 7.5.2**: The URL address for the Canadian SASF was corrected.

- **Sections 7.10 and 7.11**: Adverse event reporting guidelines were updated.

**Section 10.0**: Was revised to reflect the new name, location, and contact information for tissue banking. The name of the facility was revised throughout, and the URL address for the FAQ web page was updated in Section 10.4.

- **Section 10.2.1.3**: Blood collection for SNPs analysis was added to the specimen collection summary table.

- **Section 10.3**: Was revised to reflect current reimbursement amounts for specimens.

**Section 11.1**: The "c" footnote was removed from the "pelvic CT or other lymph node assessment" row, as it refers to bone scans only.

**Section 12.2**: Under "Final Dosimetry Information", the "copy to HQ" instruction to sites was added for clarification.

**Section 13.4.7**: Table 4 was renamed "Projected Distribution of Gender and Minorities", consistent with RTOG standard.

**Appendix I (Consent)**: Under "About Using Tissue and Blood for Research", the third paragraph was revised to clarify the timing of blood collection for banking.

**Appendix V (CTSU Logistics):**

- **Pages 1-2**, the CTSU hours of operation were updated.

- **Page 3**, under "Tissue/Specimen Submission", the RTOG tissue bank name (Biospecimen Resource) and location (University of San Francisco) were updated.

**Appendix VI**: A bulleted item (shipping information) was added.

**Appendix VI and Appendix VII**: Amended to reflect new name, location, and contact information for tissue banking. The name of the facility was revised throughout.
Appendix VIII: The URL address for the Canadian SASF was corrected.
SUMMARY OF CHANGES
Update Date: June 20, 2007

RTOG 0521, "A Phase III Protocol of Androgen Suppression (AS) and 3DCTR/IMRT vs. AS and 3DCTR/IMRT Followed by Chemotherapy With Docetaxel and Prednisone for Localized, High-Risk, Prostate Cancer"

Study Chair: Howard M. Sandler, MD; Phone: (734) 936-9338; Fax: (734) 763-7371; hsandler@umich.edu

RTOG 0521 has been updated as follows:

Title Page:

- The contact information for the Physics/Quality Assurance Co-Chair, James Purdy, PhD, was updated.
- Under the Version Date, a typographical error was revised. The phrase, "Includes Amendment 1-2" was revised to "Includes Amendments 1-3".

Eligibility Checklist:

- "Blood" was deleted from questions 22-23 and questions 25-27 were added for clarity.

Tissue Consent:

- The date, 4/27/07, was added to the top of page 1.
SUMMARY OF CHANGES  
Amendment #3, Version Date: April 27, 2007

RTOG 0521, "A Phase III Protocol of Androgen Suppression (AS) and 3DCTR/IMRT vs. AS and 3DCTR/IMRT Followed by Chemotherapy With Docetaxel and Prednisone for Localized, High-Risk, Prostate Cancer"

Study Chair: Howard M. Sandler, MD; Phone: (734) 936-9338; Fax: (734) 763-7371; hsandler@umich.edu

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RTOG 0521 has been amended as follows:

Title Page: Oliver Sartor, MD, is the Medical Oncology Co-Chair. The contact information for the Urology Co-Chair, Leonard Gomella, MD, was updated.

Index: Revised for consistency with Appendix VI, VII, and VIII.

Eligibility Checklist: Question 19 was revised to correct a typographical error: "pr" was changed to "or".

Introduction: Sections 1.1. and 1.2 were added to provide a rationale for the SNPs analysis.

Section 2.2: A translational research objective was added to the study.

Section 4.2: This section was added for consistency with Section 10.2.

Section 5.3: The drug shipment guidelines were revised per current RTOG procedures.

Section 6.3.1: The dosimetry requirements were revised.

Section 7.1.1.2: Under "Arm 2", a note was added to clarify the timing of chemotherapy administration. Also, a sentence was added regarding administration of prednisone.

Sections 7.3.4 and 7.4.4: The third and fourth sentences, beginning "If the patient has already started LHRH…" and "Radiotherapy should begin…” were added to clarify the start of radiation therapy in relation to hormone therapy.

Section 7.6.6: The sentence was revised to clarify prednisone tapering post-chemotherapy.

Section 7.9: Was updated to show that Dr. Oliver Sartor, the Medical Oncology Co-Chair, will perform the chemotherapy modality review.

Sections 10.1 and 10.2: Revised per current RTOG tissue banking procedures. The
previously numbered 10.2.6 is now numbered 10.2.2.

**Section 10.3:** Revised for clarity.

**Section 11.1:** A "note" was added to footnote "a" of the Study Parameters Table to clarify the timing of assessments.

**Section 13.0:** Reference numbers were revised as a result of the addition of REFERENCES to Section 1.0. For example, reference 22 is now reference 41.

**Section 13.1.2:** Consistent with Section 2.2, a translational research endpoint was added.

**References:** References 22-40 were added for consistency with Sections 1.1 and 1.2. The subsequent references, previously references 22-32, were renumbered.

**Consent (Appendix I)***:

- Under "When you are finished taking the hormone therapy and chemotherapy…", the sentence beginning, "After treatment, if your digital…" was added for consistency with Section 11.
- Under "Hormone Therapy/Risks and side effects related to LHRH agonists…", bone pain and thrombosis were added.
- Under "Consent Form for Use of Tissue for Research"
  - "Blood" was added to the subtitle of the section for consistency with Section 10.
  - The third paragraph was revised to include banking for SNPs analysis; "two teaspoons of blood" was changed to "four teaspoons of blood".
  - Under "Making Your Choice", the word "blood" was removed from statements 1 and 2. Statements 3 and 4 were added for clarity, statement 5 was added to include the SNP analysis, and the original statement 3 is now statement 6.

*Consent:* For currently enrolled patients, a separate, two-page consent form was developed regarding the addition of the SNPs translational research component to the study.

**Appendix VI to VIII:** Appendixes VI and VII were revised per current RTOG procedures and Appendix VIII was renumbered (originally Appendix VII).
RTOG 0521, "A Phase III Protocol of Androgen Suppression (AS) and 3DCTR/IMRT vs AS and 3DCTR/IMRT Followed by Chemotherapy With Docetaxel and Prednisone for Localized, High-Risk, Prostate Cancer"

Study Chair: Howard M. Sandler, MD; (734) 936-9338; FAX (734) 763-7371; hsandler@umich.edu

At the request of the Cancer Trials Support Unit (CTSU), RTOG 0521 has been amended as follows:

Title page: The statement at the bottom of the page regarding patient enrollments from institutions not aligned with RTOG was deleted, and text was added to the subsequent page.

Appendix V: All prior CTSU logistics text was deleted and was replaced with new CTSU logistics.
RTOG 0521, "A Phase III Protocol of Androgen Suppression (AS) and 3DCTR/IMRT vs AS and 3DCTR/IMRT Followed by Chemotherapy With Docetaxel and Prednisone for Localized, High-Risk, Prostate Cancer"

Study Chair: Howard M. Sandler, MD; (734) 936-9338; FAX (734) 763-7371; hsandler@umich.edu

RTOG 0521 has been updated as follows:

Complete instructions for submission of the Study Agent Shipment Form (SASF) for Taxotere (docetaxel) were added in Sections 5.3 and 7.5.2 and in Appendix VII.
SUMMARY OF CHANGES
Update: November 14, 2006

RTOG 0521, "A Phase III Protocol of Androgen Suppression (AS) and 3DCTR/IMRT vs AS and 3DCTR/IMRT Followed by Chemotherapy With Docetaxel and Prednisone for Localized, High-Risk, Prostate Cancer"

Study Chair: Howard M. Sandler, MD; (734) 936-9338; FAX (734) 763-7371; hsandler@umich.edu

RTOG 0521 has been updated as follows:

Index: Appendix VII, Study Agent Shipment Form reference to form on the RTOG web site

Section 7.5.2.1: A section was added about ordering Taxotere free of charge to U.S. institutions

Consent:

- Under "Will my medical information be kept private?": a second bullet was added
  - Qualified representatives of Sanofi Aventis, the company that makes Taxotere
- Under "What are the costs for taking part in this study?": the following sentence was added, "The drug Taxotere will be provided without cost to you by Sanofi Aventis, Inc., however, you or your health plan may need to pay for costs of the supplies and personnel who give you the drug."

Appendix VII: This appendix was added.
RTOG 0521, "A Phase III Protocol of Androgen Suppression (AS) and 3DCTR/IMRT vs AS and 3DCTR/IMRT Followed by Chemotherapy With Docetaxel and Prednisone for Localized, High-Risk, Prostate Cancer"

Study Chair: Howard M. Sandler, MD; (734) 936-9338; FAX (734) 763-7371; hsandler@umich.edu

RTOG 0521 has been amended as follows:

Title Page: The medical oncology co-chair was changed to Oliver Sartor, MD, and his name and contact information were added. The SWOG co-chair's name and contact information were added to the title page, as SWOG has elected to endorse this study through CTSU. The contact information for Mahul B. Amin, MD, was updated.

Index: Appendix VI, "Blood Collection and Kit Instructions" was added, as it was added to the protocol.

Eligibility Checklist: The number of the protocol, 0521, was added to the heading on each page of the Checklist. In addition, under "The following questions will be asked at Study Registration," "Specify modality (3D vs. IMRT)" was added prior to the first question. A new question # 17 was added to correspond to new Section 3.2.11. As a result, subsequent questions on page 2 of the Eligibility Checklist were renumbered as 18 through 21.

Section 3.2.11: Parameters were added for the collection of study entry PSA.

Section 6.6: The cross-reference was changed to Section 7.10 be consistent with the renumbering in Section 7 as described below.

Section 7.1.1.2: A statement of caution was added to the end of this section to provide information concerning agents that may alter patients' metabolizing of docetaxel.

Section 7.5.6.1: A "%" sign was added to the second row of the 100-149K section because it was inadvertently omitted.

Section 7.5.6.2: Dose modifications for liver toxicity were altered to be consistent with the package insert and "black box" warning for docetaxel.

Sections 7.7 through 7.11: These sections were renumbered as Sections 7.6 through 7.10, because the protocol had inadvertently skipped from Section 7.5 to Section 7.7.

Section 7.7.4 (formerly Section 7.8.4): This section was rewritten to allow for
administration of dexamethasone per institutional standards. The last two sentences of the section were deleted.

Section 7.8 (formerly Section 7.9): Under the third bullet, the cross-reference to Section 7.5.7 was changed to Section 7.5.5.

Sections 9.2 through 9.2.1: These sections were added to clarify that aprepitant is not permitted.

Section 10:

- **Section 10.1:** In the last sentence, "/blood" was added for clarity.
- **Section 10.2.5:** The following text was added to this section: "Peripheral Blood will be collected before initiation of treatment by venipuncture and shipped with a Specimen Transmittal Form (see Section 10.2.5.2) using RTOG collection kits. See Appendix VI for detailed collection instructions and collection kit components."
- **Section 10.2.5.1:** This section was amended with a brief description of the new blood collection requirements.
- **Section 10.2.5.2:** Two new sentences were added to the beginning of the section to clarify shipping of tissue specimens. Changes were made in the third sentence to clarify shipping of blood specimens. In the third-to-last sentence, "blood" was deleted, "of specimens" was added after "shipment," and "the RTOG Tissue Bank" replaced "LDS Hospital, Dept. of Pathology."
- **Section 10.2.6:** The contact information was updated for LDS Hospital.
- **Section 10.3:** The first sentence was changed to include "$300 per case for buffy coat cells," and "unstained slides" and "leukocytes" were deleted.

Sections 12.1 through 12.2: The Adverse Event Form (AE) was added in five places under "Items."

Section 12.2.1: The zip code for ITC was corrected.

Section 13.0: The statistical section was amended for clarity and the stopping rules were modified to address a concern about drug tolerability as follows:

Section 13.1: In the first six bullets, the first sentence under each one was deleted.

Section 13.2.2: In the first paragraph, a new second sentence was added to this section and "(H$_0$: OS$_{arm1}(t) \leq OS_{arm2}(t)$, where t is time)" was deleted. In the first sentence of the second paragraph, "ratio" was changed to "rate" and in the last sentence, "or lack-of-data rate of 10% and a" was deleted and "and" was added.

Sections 13.2.3.1, 13.2.3.2, 13.2.3.3, 13.2.3.4: In these sections, "ratio" was changed to "rate." In addition, in Section 13.2.3.4, "disease progression rate" was changed to "disease-free survival rate."
Section 13.3: In the last sentence, "stopping" was changed to "terminating" and "to the RTOG DMC" was added to the end of the sentence.

Section 13.4: "All eligible patients randomized will be included in comparison of treatment arms (intent-to-treat analysis)" was added to this section.

Section 13.4.1: In the fourth sentence, after Arm 2, $\lambda_{o,2}$ - was inserted and OSarm2 was deleted. After Arm 1, $\lambda_{o,1}$ was inserted and OSarm1 was deleted. The null and alternative hypotheses were changed to: $H_0: \lambda_{o,1} \leq \lambda_{o,2}$ vs. $H_A: \lambda_{o,1} > \lambda_{o,2}$

Section 13.4.2.1:

- A new second sentence was added: "Specifically, time to biochemical failure is measured as the time to PSA failure measured from the date of randomization to the date of arise by 2 ng/ml or more above the nadir PSA."
- In the fifth sentence, "survival function" was changed to "time-to-event function" and "also" was deleted.
- In the sixth sentence, "or not" was deleted; after Arm 2, $\lambda_{s,2}$ was inserted and SSarm2 was deleted; after Arm 1, $\lambda_{s,1}$ was inserted and SSarm1 was deleted.
- $H_0: SSarm1(t) \geq SSarm2(t)$ vs. $H_A: SSarm1(t) < SSarm2(t),$ where t is time" was deleted and "$H_0: \lambda_{s,1} \leq \lambda_{s,2}$ vs. $H_A: \lambda_{s,1} > \lambda_{s,2}$" inserted.
- The last sentence was changed to "Risk group defined as the combination of PSA, clinical stage, and Gleason score, race, and age (as appropriate) will be adjusted for in this analysis."

Section 13.4.2.2:

- In the third sentence, after Arm 2, $\lambda_{D,2}$ was inserted and DSarm2 was deleted; after Arm 1, $\lambda_{D,1}$ was inserted and DSarm1 was deleted. The null and alternative hypotheses were changed to " $H_0: \lambda_{D,1} \leq \lambda_{D,2},$ vs. $H_A: \lambda_{D,1} > \lambda_{D,2},$"
- The last sentence of the section was changed to: Risk group defined as the combination of PSA, clinical stage, and Gleason score, race, and age (as appropriate) will be adjusted for in this analysis.

Section 13.4.2.3:

- In the fourth sentence, after Arm 1, $\lambda_{A,1}$ was inserted and ASarm1 was deleted and after Arm 2, $\lambda_{A,2}$ was inserted and ASarm2 was deleted.
- $H_0: ASarm1(t) = ASarm2(t)$ vs. $H_A: ASarm1(t) \neq ASarm2(t),$ where t is time" was changed to

$$H_0: \lambda_{A,1} = \lambda_{A,2} \text{ vs. } H_A: \lambda_{A,1} \neq \lambda_{A,2}$$
Section 13.4.2.5: In the second sentence, "such" was deleted. In the third sentence "a" was deleted. In the third paragraph, fourth sentence, "each" was added and a typo was corrected in "modeled."

Section 13.4.3: "Hypothesis: H₀: OS\text{arm}_1(t) \geq OS\text{arm}_2(t) \text{ vs. } H_\Lambda: OS\text{arm}_1(t) < OS\text{arm}_2(t),\text{ where } t \text{ is time where } OS\text{arm}_1 \text{ and } OS\text{arm}_2 \text{ are the overall survival rate for Arm 1 and Arm 2, respectively}" was changed to "Hypothesis: H₀: \lambda_0,1 \leq \lambda_0,2 \text{ vs. } H_\Lambda: \lambda_0,1 > \lambda_0,2 \text{ where } \lambda_0,1 \text{ and } \lambda_0,2 \text{ are the overall survival rate for Arm 1 and Arm 2, respectively.}"

Section 13.4.4: In the second paragraph, the fourth sentence was deleted and the fifth sentence was rewritten as: "If at any stage, we stop and reject the alternative hypothesis and claim that the grade 4+ adverse event (any) rate may be greater than or equal to 40%, we will temporarily close the study to accrual, gather the relevant source data on the cases with a grade 4+ adverse event (any), prepare a statistical report summarizing the adverse event findings, and present the report to the radiation and medical oncology study chairs for review."

Appendix V: The CTSU Logistics have been amended for consistency with the rest of the protocol.

• Under Data Submission: the last sentence in the second bullet was deleted.
• Under Special Materials or Substudies: Under Radiation Therapy, the T2 was changed to DDSI and "and a copy of this transmittal sent to the CTSU for tracking purposes" was deleted. In the last sentence, the Treatment Summary Form (TF) was changed to Radiation Therapy Form (T1). In addition, information about the Dosimetry Transmittal Form was added. In the sub heading Modality Review, the cross-reference was changed to Section 7.9 to be consistent with the renumbering in Section 7. The sub-heading Specimen Banking was changed to Tissue/Specimen Submission and the first two sentences of the first bullet were rewritten.

• Under Adverse Event (AE) Reporting: The cross-reference was changed to Section 7.10 to be consistent with the renumbering in Section 7 as described above.

Appendix VI: This appendix was added.