For Protocol Amendment 5 of RTOG 0415, A Phase III Randomized Study of Hypofractionated 3D-CRT/IMRT Versus Conventionally Fractionated 3D-CRT/IMRT in Patients with Favorable-Risk Prostate Cancer

NCI/Local Protocol #: RTOG-0415/RTOG 0415

NCI Protocol Version Date: December 18, 2014 (*Broadcast Date: January 20, 2015*)

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
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<tbody>
<tr>
<td>Cover/Schema Pages</td>
<td>• Due to the transition to the National Clinical Trials Network (NCTN), “Radiation Therapy Oncology Group,” “RTOG Headquarters,” and “RTOG” were replaced with “NRG Oncology”.</td>
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<tr>
<td></td>
<td>• Contact information was updated for Dr. Dignam.</td>
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<td></td>
<td>• This amendment was added to the Document History Table.</td>
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<tr>
<td>Appendix I/ Sample Consent</td>
<td>No changes</td>
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</table>
For **Protocol** Administrative Update of RTOG 0415, A Phase III Randomized Study Of Hypofractionated 3D-CRT/IMRT Versus Conventionally Fractionated 3D-CRT/IMRT In Patients With Favorable-Risk Prostate Cancer

NCI/Local Protocol #: RTOG-0415/RTOG 0415

NCI Protocol Version Date: December 23, 2010  *Update Broadcast Date: May 1, 2014*

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
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<tbody>
<tr>
<td>6.8 Appendix VI (CTSU)</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>
</tr>
<tr>
<td>Title page</td>
<td>The Update Date was changed.</td>
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SUMMARY OF CHANGES
Amendment 4, Version Date: December 23, 2010
(Broadcast: January 11, 2011)

RTOG 0415, "A Phase III Randomized Study of Hypofractionated 3D-CRT/IMRT Versus Conventionally Fractionated 3D-CRT/IMRT in Patients With Favorable-Risk Prostate Cancer"

Study Chair: W. Robert Lee, MD, MS; 919-668-7342; lee00255@mc.duke.edu

RTOG 0415 has been amended as follows:

As mandated by CTEP, CTCAE version 3.0 reporting requirements will be converted to CTCAE version 4 for grading of all adverse events reported via AdEERS beginning January 1, 2011.

- Changes were made to Section 6.8.1 (AdEERS Reporting Requirements and RTOG Reporting Requirements) of the protocol. All case report forms will continue to use CTCAE version 3.0.

Note: REFERENCES to CTCAE, version 3.0, may remain in the protocol. These are appropriate, as treatment decision for patients enrolled on this study were based on that version.

Other Changes

Section 6.8.2: This section was amended as required by CTEP to instruct sites to report AML or MDS via AdEERS. In Appendix VI, CTSU Logistics, under "Serious Adverse Event (SAE) Reporting", item 4 was amended to be consistent with this change.
RTOG 0415, "A Phase III Randomized Study of Hypofractionated 3D-CRT/IMRT Versus Conventionally Fractionated 3D-CRT/IMRT in Patients With Favorable-Risk Prostate Cancer"

**Study Chair:** W. Robert Lee, MD, MS; 919-668-7342; lee00255@mc.duke.edu

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**RTOG 0415** has been amended as follows:

**Title page:** The name and contact information for the Senior Statistician for the study were added to amend the protocol to current RTOG standards.

**Eligibility Checklist, page 3, question 24:** A subquestion was added asking sites to specify the reason for a patient's refusal to participate in the quality of life component of the study to amend the protocol to current RTOG standard text.

In addition, the subquestion asking if the patient agrees to the use of Medicare data for research and asking for the patient's social security number was deleted. The RTOG Health Services Research and Outcomes (HSRO) Committee has decided not to routinely collect social security numbers for Medicare patients for the EQ-5D. Cost utility analysis will be done by means of modeling costs. The "note" in **Section 4.1** was deleted to be consistent with this change.

**Section 2.2:** Some of the secondary objectives were inadvertently misnumbered in a prior amendment of the study. Sections 2.2.5-2.2.8 were appropriately renumbered to correct this.

**Sections 5.1.1 and 5.1.2** were amended to the current RTOG standard text.

**Section 5.1.3:** The current RTOG standard text for Regulatory Pre-Registration Requirements was added.

**Section 5.2:** In the 6th paragraph, the new e-mail address for RTOG web support was provided.

**Section 6.0:** The first sentence was amended for clarity to read, "IMRT is allowed for institutions credentialed by the RTOG for IMRT".

**Section 6.8:** In the heading, the word, "Therapy", was added after "Radiation" to amend the protocol to current RTOG standard text.

**Section 6.8.1** was amended to the current RTOG standard text.
Section 10.0: The first paragraph was added to amend the protocol to current RTOG standard text.

Sections 10.1: "Tissue Bank at LDS Hospital" was replaced with "Biospecimen Resource at the University of California San Francisco". This change also was made in Appendix VI, "CTSU Logistics".

Sections 10.1, 10.2.3, 10.3.3.1, 10.5, 10.6.1, and Appendix IV: REFERENCES to the RTOG Tissue Bank were amended to RTOG Biospecimen Resource. In addition, in the heading of the tables in Section 10.3.4, the phrase, "Tissue Bank", was deleted.

Section 10.3.2: The 3 "Optional" sections were formatted as Sections 10.3.2.1-10.3.2.3 for clarity. Section 10.3.2.1 was amended at the request of the RTOG Biospecimen Resource to indicate that a paraffin-embedded tissue block is preferred and to provide options if the block cannot be obtained. Corresponding changes also were made in the table in Section 10.3.4, in the first row.

Section 10.3.3.1: In the 1st bulleted item, "submitted tissue specimen" was replaced by "submitted paraffin tissue block" for clarity.

Section 10.3.3.2: In the bulleted item, the temperature of -20° was corrected to -80° C.

Section 10.3.4, In the 2nd table, "Optional Specimens for Submission", the shipment information in the last column was clarified to "Fresh tissue sent frozen on dry ice via overnight carrier".

Section 10.4 and Appendices IV and V: The shipping address and/or contact information was updated from LDS Hospital to the RTOG Biospecimen Resource.

Section 11.1: The footnote "h", inadvertently omitted next to "Utilization of Sexual Medications/Devices" was added.

Section 11.3.2: The schedule for drawing PSA in each follow-up visit was corrected to be consistent with Sections 11.1 and 12.1.

Section 11.8: The "Note" was added to amend the protocol to the current RTOG standard text.

Section 13.1.2: A secondary endpoint, inadvertently omitted, was added (9th bulleted item) to correspond to Section 2.2.6.

The following changes were made to Appendix I:

- Under "Before you begin the study", the 2nd bulleted item was amended to include the required tissue submission for central review.
Under "Risks and side effects related to radiation", urinary obstruction was deleted from "Rare but Serious", as it is already listed correctly under "Less Likely" risks.

The "Consent Form for Cost Study" was deleted as the RTOG Health Services Research and Outcomes (HSRO) Committee has decided not to routinely collect social security numbers for Medicare patients for the EQ-5D and because patients are asked to complete the EQ-5D in the "Consent Form for Quality of Life Study" (one of the 4 questionnaires).

In the 3rd paragraph of the "Consent Form for Use of Tissue and Blood for Research", the 1st sentence was corrected to include blood drawn prior to and "during treatment". In addition, in the 2nd sentence, the amount of blood was corrected from 4 tablespoons to 4 teaspoons.

**Appendix II**: The Karnofsky Performance Scale was deleted, and in the Zubrod Performance Scale table, parenthetical REFERENCES to Karnofsky scores were deleted, as the Zubrod is the performance scale being used in the study.
RTOG 0415, A Phase III Randomized Study of Hypofractionated 3D-CRT/IMRT Versus Conventionally Fractionated 3D-CRT/IMRT in Patients With Favorable-Risk Prostate Cancer

Study Chair: W. Robert Lee, MD, MS; 919-668-7342; lee00255@mc.duke.edu

RTOG 0415 has been updated as follows:

Section 12.2: Under "Summary of Dosimetry Digital Data Submission", "T5" and "Copy to HQ and ITC" were added next to the Daily Treatment Record for clarity.

Appendix VI (CTSU Logistics): The CTSU hours of operation were changed from 8:00 am-8:00 pm to 9:00 am-5:30 pm Eastern Time in the following places:

- Page 1, under "Address And Contact Information For RTOG-0415, CTSU Patient Registration";
- Page 2, under "CTSU Procedures for Patient Enrollment, #3".
RTOG 0415, A Phase III Randomized Study of Hypofractionated 3D-CRT/IMRT Versus Conventionally Fractionated 3D-CRT/IMRT in Patients With Favorable-Risk Prostate Cancer

Study Chair: W. Robert Lee, MD, MS; 919-668-7342; lee00255@mc.duke.edu

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RTOG 0415 has been revised as follows:

Sample Consent (Appendix I):

- Under "Before you begin the study", 1st paragraph: The sentence, "This will be up to your study doctor", was deleted.
- Under "During the study", 3rd paragraph: The sentence, "A computer program will place you in one of the study groups", was deleted.
- Under "Can I stop being in the study?", 3rd paragraph: The beginning of the sentence, "The study doctor may stop you from taking part" was revised to "The study doctor may decide to take you off this study".
SUMMARY OF CHANGES
Amendment 2, Version Date: September 20, 2007

RTOG 0415, A Phase III Randomized Study of Hypofractionated 3D-CRT/IMRT Versus Conventionally Fractionated 3D-CRT/IMRT in Patients With Favorable-Risk Prostate Cancer

Study Chair: W. Robert Lee, MD, MS; 919-668-7342; lee00255@mc.duke.edu

RTOG 0415 has been amended as follows:

Title Page:
- Dr. Lee's contact information was updated.
- SWOG's endorsement of this trial was added; the contact information was added for Dr. Gregory P. Swanson, the SWOG Co-Chair.

Index: Appendix IV was revised; Appendix V was added and the previous Appendix V is now Appendix VI.

Introduction:
- Sections 1.9 and 1.9.1 were added to provide a rationale for the SNPs analysis.
- The reference numbers in Section 1.10 were revised as a result of the addition of the REFERENCES in Sections 1.9 and 1.9.1. For example, reference 16 is now reference 35.

Section 2.2.8: A translational research objective was added to the study.

Section 3.0:
- 3.1.5.1: The reference to Section 3.2.6 was corrected to 3.2.7.
- 3.1.5.2: The reference to Section 3.2.7 was corrected to 3.2.8.

Section 4.1: A "note" regarding the Cost Study Component of the QOL assessment was added for clarity and for consistency with the revisions made in the consent (Appendix I).

Section 6.0:
- 6.3.6: The reference to Section 6.4.9 was corrected to 6.3.10.
- 6.8.1: The text under "RTOG Reporting Requirements/Adverse Events and Serious Adverse Events" was revised per current RTOG standards.
Section 10.0: The sentence in parentheses was revised per the following changes in Section 10.

- **10.3:** Was revised to include the collection and banking of specimens for SNPs analysis and per current RTOG standard.
- **10.4:** The contact information for LDS Hospital was updated.

Section 11.8: The reference numbers were revised as a result of the addition of REFERENCES to Section 1.0. For example, reference 34 is now reference 53.

Section 13.0:

- **13.1.2:** Consistent with Section 2.2.8, a translational research secondary endpoint was added.
- Reference numbers were revised as a result of the addition of REFERENCES to Section 1.0. For example, reference 48 is now reference 67.

REFERENCES: REFERENCES 16-34 were added for consistency with Sections 1.9 and 1.9.1. The subsequent REFERENCES, previously REFERENCES 16-63, were renumbered, and are now REFERENCES 35-82.

Consent (Appendix I)*:
The Informed Consent document was divided into four sections: consent for main study, QOL study, cost study, and tissue collection/banking. The QOL and cost components were divided for clarity: Patients may participate in both, either, or neither of these parts of the trial and still participate in the main study.

- Under "Consent Form for Use of Tissue and Blood for Research"
- The website address in the second paragraph was updated.
- The third paragraph under "About Using Tissue and Blood for Research" was revised to include banking of blood for future research; "one" tablespoon of blood was revised to "four" tablespoons of blood.
- Blood" was included in the fourth paragraph, in addition to "tissue", for clarity.
- Under "Making Your Choice", statement 3 was added to include the SNP analysis; and the original statement 3 is now statement 4.

*Tissue 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. (Separate document)

Appendixes IV and V: Instructions for tissue and blood collection were added.

Appendix VI: The original Appendix V is now Appendix VI.
SUMMARY OF CHANGES
Amendment 1, Version Date: January 24, 2007

RTOG 0415, "A Phase III Randomized Study of Hypofractionated 3D-CRT/IMRT Versus Conventionally Fractionated 3D-CRT/IMRT in Patients With Favorable-Risk Prostate Cancer"

Study Chair: W. Robert Lee, MD, MS; 336-713-6505; wrlee@wfubmc.edu

At the request of the Cancer Trials Support Unit (CTSU), RTOG 0415 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 0415, A Phase III Randomized Study of Hypofractionated 3D-CRT/IMRT Versus Conventionally Fractionated 3D-CRT/IMRT in Patients With Favorable-Risk Prostate Cancer

Study Chair: W. Robert Lee, MD, MS; 336-713-6505; wrlee@wfubmc.edu

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**RTOG 0415** has been updated as follows:

**Title Page:** Contact information for Dr. Amin was updated.

**Section 3.2.1 through 3.2.9.6:** The numbering of these sections was corrected to 3.2.2 through 3.2.10.6.

**Section 6.3.6:** The dagger symbol in the Arm 2 table was deleted because it was inadvertently included.

**Section 6.8.1**

- Definition of an SAE: All REFERENCES to "drug" were deleted because this trial does not have a drug component. As a result, the reference to CTEP guidelines was deleted because it refers to trials with a drug component.
- Criteria for AdEERS Reporting Requirements for Adverse Events and Serious Adverse Events That Occur Within 30 Days of the Date of the Last Protocol Treatment (Table): The reference to footnote 1 was deleted because it was inadvertently included.

**Section 10.4:** Contact information for LDS Hospital was updated.

**Section 12.1:** The collection times for the HRQOL component was corrected to 6, 12, 24 months and 5 years to match the times specified elsewhere in the protocol.

**Section 12.2.1:** The zip code for ITC was updated.

**Section 13.4.10:** CDUS information was added based on NCI's current analysis plan.

**Section 13.5:** An asterisk was inserted at the bottom of the concluding table because it was inadvertently omitted.

**Appendix I/Sample Consent/What other choices do I have if I do not take part in this study?:** "3D" was replaced by "three-dimensional" for consistency with terminology used earlier in the consent.
NOTE: These are editorial/administrative changes to the protocol. NCI now requires that these changes be documented on the protocol title page with the date of the update noted as "Update Date," not as an amendment.

An updated protocol is available on the RTOG website: www.rtog.org