For **Amendment 6** to: RTOG 0630, A Phase II Trial of Image Guided Preoperative Radiotherapy for Primary Soft Tissue Sarcomas of the Extremity

**NCI/Local Protocol #: RTOG-0630/RTOG 0630**

**NCI Protocol Version Date: April 3, 2014**

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</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 the protocol.</td>
</tr>
<tr>
<td>Title pages</td>
<td>- On the 1st title page, as required by CTEP, “Radiation Therapy Oncology Group” was replaced with “NRG Oncology”.</td>
</tr>
<tr>
<td></td>
<td>- The contact information for Drs. Wang and Eisenberg was updated.</td>
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<tr>
<td></td>
<td>- On the 2nd title page, the version date and amendment number were changed for this amendment.</td>
</tr>
<tr>
<td>Schema page</td>
<td>As required by CTEP, “Radiation Therapy Oncology Group” was replaced with “NRG Oncology”.</td>
</tr>
<tr>
<td>6.10 and 7.0</td>
<td>- The date and link to the NCI Guidelines were updated.</td>
</tr>
<tr>
<td></td>
<td>- The link to CTCAE, v. 4 was updated.</td>
</tr>
<tr>
<td>Sample Consent</td>
<td>No changes.</td>
</tr>
</tbody>
</table>
SUMMARY OF CHANGES
Update: July 3, 2012
(Broadcast: 7/3/12)

RTOG 0630, "A Phase II Trial of Image Guided Preoperative Radiotherapy for Primary Soft Tissue Sarcomas of the Extremity"

Study Chair: Dian Wang, MD, PhD; 414-805-4496; dwang@radonc.mcw.edu

RTOG 0630 has been updated as follows:

Section 7.0 was updated with instructions for long-term follow up of patients accrued to Cohort A (closed on 1/18/10) and for reporting adverse events and serious adverse events.

Section 10.2.4: The link to the Specimen Transmittal form was updated.

Appendix I: In the 2nd paragraph on the 1st page, the last sentence regarding chemotherapy was deleted to correct the sample consent to be consistent with changes made in Amendment 4.
SUMMARY OF CHANGES
Amendment 5: February 16, 2011
(Broadcast: 2/24/11)

RTOG 0630, "A Phase II Trial of Image Guided Preoperative Radiotherapy for Primary Soft Tissue Sarcomas of the Extremity"

Study Chair: Dian Wang, MD, PhD; 414-805-4496; dwang@radonc.mcw.edu

RTOG 0630 has been amended as follows:

As mandated by CTEP, Section 6.10 has been amended to require the use of CTCAE, version 4 for grading of all adverse events reported via AdEERS as of April 1, 2011.

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

Other Changes
Section 6.11.2: This section was amended as required by CTEP to instruct sites to report AML or MDS via AdEERS.
RTOG 0630, "A Phase II Trial of Image Guided Preoperative Radiotherapy for Primary Soft Tissue Sarcomas of the Extremity"

**Study Chair:** Dian Wang, MD, PhD; 414-805-4496; dwang@radonc.mcw.edu

RTOG 0630 has been amended as follows:

Due to slow accrual for Cohort A (patients receiving chemotherapy and radiation), this cohort was closed. In addition, the sample size of Cohort B (patients receiving radiation alone) was increased to test for a 15% absolute decreased in combined toxicity rate. The following sections were amended for this change:

- **Schema page:**
  - The closure date was added next to "Cohort A";
  - The first paragraph below the table concerning chemotherapy was deleted;
  - In the third paragraph below the table, REFERENCES to Section 7.0 and "Drug Therapy" were deleted;
  - The required sample size was amended.

- **Eligibility Checklist:**
  - Page 1: Question 7, concerning Cohort A patients, and Question 13, concerning chemotherapy, were deleted, and subsequent questions were appropriately renumbered. In addition, question 9 (former question 10) was amended to be consistent with changes in Section 3.1.
  - Page 2: Question 22 concerning Cohort A patients was deleted.
  - Page 3: Question 26 concerning chemotherapy was deleted (and subsequent questions were appropriately renumbered).

- The title, "For Cohort A patients" and selected sections below it (Sections 3.1.10, 3.1.12, 3.1.13, and 3.1.14) were deleted. **Section 3.1.11**, requiring a CBC/differential, was renumbered as 3.1.10 and was retained as a pretreatment requirement to ensure adequate bone marrow function prior to treatment.

- **Section 3.2.9**, listing exclusions for Cohort A patients, was deleted.

- **Section 6.0:** In the second sentence, the phrase, "For Cohort B patients (radiation therapy only)", was deleted. In addition, the third sentence concerning Cohort A patients was deleted.

- **Section 6.1.1:** The third and fourth sentences of the second paragraph concerning patients receiving chemotherapy were deleted.

- **Section 6.1.2.4**, regarding radiotherapy dose when chemotherapy is given, was deleted.

- **Section 6.10.1**, Radiation Adverse Event Reporting, was added.
• **Sections 7.1**, "Chemotherapy", **7.2**, "Adverse Events", and **7.3**, "AdEERS Expedited Reporting Requirements", were deleted, as the study is now a radiation-only trial.

• **Sections 8.2.1, 8.2.2, and 8.4.1**: The phrase, "+/- chemotherapy", was deleted.

• **Section 9.2**: The first sentence was reformatted as Section 9.2.1. Section 9.2.2, prohibiting chemotherapy, was added.

• **Section 11.2** was amended from "Evaluation During Treatment" to "Evaluation During RT".

• **Sections 11.2.1 and 11.2.2**: The phrase, " and/or chemotherapy", was deleted.

• **Section 11.2.3** was amended to require a CBC/differential every other week during radiation treatment (and the subsequent section was appropriately renumbered).

• **Sections 11.4 and 11.6**: The "Note" concerning cycles of chemotherapy was deleted.

• **Section 11.5.2**: At the end of the third paragraph, the parenthetical phrase was amended to refer sites to Sections 6.9 and 6.10 for adverse event information.

• **Section 13.2**: The third paragraph was added.

• **Appendix I** (the sample consent):
  - "How many people will take part in the study?" was amended to explain the closure of Cohort A and to provide the new sample size for Cohort B.
  - Under "What will happen if I take part in this research study?":
    - The third paragraph concerning chemotherapy was deleted;
    - The closure date for Cohort A was added in the fourth paragraph;
    - In the fifth paragraph, "no chemotherapy" was deleted next to "Group B";
    - Under "Before you begin the study", in the seventh bulleted item, the amount of blood collected was amended from 5 to 2 teaspoons. In addition, the last bulleted item, the test of heart function for Group A patients, was deleted.
    - Under "During the study", in the third paragraph, the phrase, "every other week" was added to "Blood tests" to be consistent with changes made in Section 11.2.3; in the fourth paragraph, "Prior to surgery", the fourth bulleted item, "Blood tests", was deleted to be consistent with changes made in Appendix II. The fifth paragraph, "Group A only", was deleted.
    - Under "You will need these tests and procedures in follow-up visits", the last bulleted item, "Blood tests", under "Every 3 months in years 1-2, etc", was deleted.
  - Study Plan: The closure date was added to "Group A".
  - "How long will I be in the study?": The second paragraph regarding patients receiving chemotherapy was deleted.
  - "What side effects or risks can I expect from being in the study?":
    - In the fourth paragraph under "Risks and side effects related to Radiation Therapy", the phrase, "while you are receiving chemotherapy or just after you have chemotherapy", was deleted.
In addition, under Likely Early Side Effects, the REFERENCES to chemotherapy were deleted from the first bulleted item.

- Under "Risks and side effects related to Surgery", the phrase "with/without chemotherapy", was deleted from the first and second paragraphs and from the Less Likely risk.
- The paragraph titled "Risks and side effects related to Chemotherapy" was deleted.
- Under "Reproductive Risks", the phrase, "and chemotherapy if you receive it", was deleted.

- **Appendix II:**
  - Under "Pretreatment", the column titled "Prior to start of RT or chemo" was amended to "Prior to the start of RT".
  - The pretreatment Med Onc Eval, laboratory evaluations (bilirubin, AST/ALT, creatinine, creatinine clearance, Na, K, Cl, HCO3, glucose, Ca, Mg, albumin), and MUGA/echo were deleted to be consistent with changes made in Section 3.1.
  - The required pretreatment CBC/differential & ANC was identified with an "X" versus "Cohort A". In addition, this laboratory assessment was deleted in all other timeframes except "During Radiation Treatment".
  - The heading "During Treatment", was amended to "During Radiation Treatment", and the 2 columns below it titled "Cohort A" were deleted. In addition, for the history/physical under "During Radiation Treatment", the reference to Section 11.2.5 was amended to Section 11.2.4 to be consistent with changes made in Section 11.2.

**Other Changes:**

**Appendix I:** under "How long will I be in the study?", the length of time for radiation treatment was amended from 22-25 days to 25 days.
SUMMARY OF CHANGES
Amendment 3, October 13, 2009
(Broadcast 10/29/09)

RTOG 0630, "A Phase II Trial of Image Guided Preoperative Radiotherapy for Primary Soft Tissue Sarcomas of the Extremity"

Study Chair: Dian Wang, MD, PhD; 414-805-4496; dwang@radonc.mcw.edu

RTOG 0630 has been amended as follows:

Title pages: Dr. Kraybill's e-mail address was updated, and the Senior Statistician was amended.

Eligibility Checklist, page 3:

- Question 14 of this demographic portion of the checklist was amended to current RTOG standard text.
- Questions 19-21 were reformatted to current RTOG standard as Questions 19-25, and subsequent questions were appropriately renumbered.
- No eligibility criteria were changed.

Section 5.4.1 was amended to current RTOG standard text.

Section 5.5: In the 6th paragraph, the e-mail address for RTOG web support was updated.

Section 7.2.2: The 5th paragraph was amended to current RTOG standard text.

The following changes were made to Section 10.0:

Text from Section 10.1 regarding which specimens are required versus optional was moved to Section 10.0 for clarity and emphasis.

- Section 10.1: In the last sentence of the 1st paragraph, the phrase, "when required", was added for clarity.
- Sections 10.3.1.2 and 10.5 were amended to current RTOG Biospecimen Resource standards.
- Section 10.3.2.4 was amended to include current storage instructions for blood specimens.
- Section 10.6: The phrase, "U.S. Postal Service" was added prior to "Mailing Address" for clarity and next to "Courier Address", DHS was replaced with UPS.

Sections 12.2 and 12.2.1: The ITC e-mail address was updated.
Appendix I, under "Making Your Choice": The questions were reformatted to current RTOG standards.

Appendix II: Under "Assessments", electrolytes were added at 2 weeks prior to registration, in order to rule out the grade 3-4 abnormalities listed in Section 3.2.9.5. In addition, the "X" indicating that the Musculoskeletal Tumor Rating Scale (MSTS) should be done "Prior to Surgery" was deleted, as it was inconsistent with the correct timeline for this assessment in Section 11.7.

Appendices V, VI, VII, and VIII were amended to current RTOG Biospecimen Resource standards.
RTOG 0630, "A Phase II Trial of Image Guided Preoperative Radiotherapy for Primary Soft Tissue Sarcomas of the Extremity"

Study Chair: Dian Wang, MD, PhD; 414-805-4496; dwang@radonc.mcw.edu

RTOG 0630 has been amended as follows:

**Title page:** Dr. Kraybill's contact information was updated, and Dr. Pajak's affiliation was updated to the current standard RTOG text.

**Section 4.1.1:** The phrase, "tissue specimens", was clarified to "Representative histology slides".

**Section 5.1.2.1:** The 2nd sentence was amended to the current standard RTOG text.

**Section 5.1.2.2:** The 1st sentence was amended to allow IGRT data from an anonymized patient with either extremity Sarcoma or other extremity disease. The 3rd sentence was amended to require that a minimum of 2 of the 5 pretreatment images have post-shift images.

**Sections 5.2, 5.3, and 5.4** were amended to the current standard RTOG text.

**Section 6.1.1:** In the 2nd paragraph, the 2nd sentence was clarified to read, "More than 99% of the PTV should receive > 97% of the prescribed dose."

**Sections 6.4.1.2 and 6.4.1.3:** The 3rd sentence of each section was corrected by deleting the phrase, "plus a margin of 1 cm".

**Section 6.5:** The 1st sentence of the 2nd paragraph was amended for clarity.

**Section 6.7:** In the 1st row of the table, "< 110%" was corrected to "> 110%".

**Section 6.8** was amended to current standard RTOG text.

**Section 6.9:** The word, "Therapy", was added to the heading to amend the protocol to the current standard RTOG text.

**Section 10.0:** The first paragraph was added to amend the protocol to the current standard RTOG text.
Section 10.2.1 was amended to request "immunohistochemistry slides for morphology and grade in the pre-treatment biopsy specimen and for margin and percentage of viable tumor in the post-RT surgery specimen", as well as the H & E stained slide.

Section 10.2.2 was added to instruct institutions that the Pathology Co-Chair, Dr. Lucas, may request additional slides, if needed, for central review. Subsequent sections were appropriately renumbered.

Section 10.3.1.2: In the 2nd and last sentences, REFERENCES to a tissue block were deleted, as some institutions find it difficult to submit a block of tissue. Sites can submit a 2 mm core of tumor tissue instead of a block. These changes also were made in the Section 10.5 table titled "Tissue Collection at Each Time Point".

Section 11.2.4 was added to provide instructions to institutions regarding determining patients' performance status during treatment.

Section 11.2.5 was added to provide instructions to institutions regarding weekly exams during radiation therapy.

Section 11.4: The "Note" was added to provide instructions to institutions regarding increase in primary tumor size after neoadjuvant chemotherapy.

Section 11.8: The first 2 sentences were added to amend the protocol to current standard RTOG text.

Section 12.2: The timeframe for submission of IGRT images and the IGRT image data set was amended to "within 1 week of RT end".

Appendix I, under "About Using Tissue, Blood, and Urine for Research": The 3rd paragraph was added to make the consent consistent with the collection of cutaneous/subcutaneous tissue requested in Section 10.5.

Appendix II:

- The row, "Adverse Event eval", was deleted to amend the protocol to current RTOG standard text. Sites are directed when to submit adverse events in Section 12.1.

- The row, "Tumor response eval" was deleted as a correction to the table.

- The row, "Tissue, blood, urine for research", was added to be consistent with the recommended (but optional) specimen collection in Section 10.3.

- In the 5th column, a reference was added to Section 11.2.4 for details of determination of the performance status, and the "X" indicating that performance status should be determined weekly during chemotherapy for Cohort A patients was deleted.
In the 7th column, the word, "Weekly" was replaced with a reference to Section 11.2.5 for details regarding documentation of the patient's weight.

Appendix III: 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.
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Appendices V and VI have been combined into a new Appendix V, "Fresh Frozen Tissue Kit and RNAlater™ Preserved Tissue Kit and Instructions", for clarity and updated to the current standards of the RTOG Biospecimen Resource. Other sections updated to be consistent with this change include the following:

- **Index page**: Appendix V was retitled, and Appendix VI was deleted. Subsequent appendices were appropriately renumbered.
- Appendices were appropriately renumbered to be consistent with the Index page in Sections 10.3.1.1, 10.3.1.2, 10.3.1.3, 10.3.2, 10.3.3, and 10.5.
- **Appendices VII-IX** were appropriately renumbered to Appendices VI-VIII.

Other Changes: **Section 10.4.2**: In the last sentence, the example of a storage method was corrected from -20°C to -80°C.

**Section 10.5**: In the last row of the table, the name, phone number, and e-mail address was updated for the RTOG Biospecimen Resource (replacing the RTOG Tissue Bank).
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Study Chair: Dian Wang, MD, PhD; 414-805-4496; dwang@radonc.mcw.edu

RTOG 0630 has been amended as follows:

**Title page:** The Senior Statistician's name and contact information were added to update the page to current RTOG standard.

**Eligibility Checklist, page 3:** Question 25, asking if the patient agreed to participate in the quality of life component and asking the site to specify the reason if the patient did not agree, was added to update this demographic portion of the checklist to current RTOG standard.

**Section 5.4, "Regulatory Pre-Registration Requirements",** was added to update Section 5.0 to current RTOG standard (and the subsequent section was appropriately renumbered).

**Section 6.6:** In the 2nd sentence of the 1st paragraph, "RTOG" was corrected to "the ITC".

**Section 7.1:** In the 2nd sentence, the word, "and", was added after "dimension" to clarify that chemotherapy is allowed for patients with deep, large, and intermediate-to-high grade soft tissue sarcomas.

**Sections 7.2.1, 7.2.2, and 7.3** were updated to current RTOG standard, as follows:

- The last sentence was added to the 2nd paragraph of Section 7.2.1.
- The last sentence was added to the 3rd paragraph of Section 7.2.2
- The 1st paragraph was added to Section 7.3.

**Section 10.3.1.2:** The 1st sentence was amended to 2 sentences to clarify that if submission of fresh tissue is not possible, fixed tissue may be submitted as a tissue block or a 2 mm diameter core of tissue.

**Section 10.3.1.3:** The heading was amended to "Fresh or Fixed" to be consistent with the changes made in Section 10.3.1.2.

**Section 10.8:** The web address in the 1st paragraph was updated.

**Section 11.5.2:** In Table 1, definitions of grade 4 toxicity, inadvertently omitted, were
Appendix II: The note for Adverse Event evaluations at the bottom of the table, "**And as needed based on reporting requirements**, was deleted, as sites are directed when to submit adverse events in Sections 7.2 and 12.0.
RTOG 0630, "A Phase II Trial of Image Guided Preoperative Radiotherapy for Primary Soft Tissue Sarcomas of the Extremity"

Study Chair: Dian Wang, MD, PhD; 414-805-4496; dwang@radonc.mcw.edu

RTOG 0630 has been updated as follows:

Section 12.2, IGRT Submission:

- The form designation, "IG", was added following "IGRT Images obtained on the first day of treatment" and "One IGRT image data set per week of treatment".
- The IGRT final spreadsheet was re-titled "IGRT Data Collection Spreadsheet on Daily Variances (Final)" and the form designation, "SG", was added following the title.

Note: These are editorial/administrative changes to the protocol. NCI requires that these changes be documented on the protocol title page as "Update Date".
RTOG 0630, "A Phase II Trial of Image Guided Preoperative Radiotherapy for Primary Soft Tissue Sarcomas of the Extremity"

Study Chair: Dian Wang, MD, PhD; 414-805-4496; dwang@radonc.mcw.edu

RTOG 0630 has been updated as follows:

Eligibility Checklist, page 3: Questions 22 and 23 were added to this demographic portion of the checklist to gather data regarding the patient's consent for the quality of life component and whether or not the patient will receive chemotherapy. The subsequent question was appropriately renumbered. No changes to eligibility criteria were made.

Note: This is an editorial/administrative change to the protocol. NCI requires that these changes