For Protocol Amendment 6 of RTOG 0517, Randomized Phase III Trial To Evaluate Radiopharmaceuticals And Zoledronic Acid In The Palliation Of OsteoBlastic Metastases From Lung, Breast, And Prostate Cancer

NCI/Local Protocol #: RTOG-0517/RTOG 0517

NCI Protocol Version Date: December 22, 2014 (Broadcast Date: January 20, 2015)

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
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</table>
| 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. Pugh.  
  • This amendment was added to the Document History Table. |
| Appendix I/ Sample Consent | No changes                                                                                                                               |
For **Protocol** Administrative Update of **RTOG 0517**, “Randomized Phase III Trial to Evaluate Radiopharmaceuticals and Zoledronic Acid in the Palliation of Osteoblastic Metastases from Lung, Breast, and Prostate Cancer”

NCI/Local Protocol #: RTOG-0517/RTOG 0517

NCI Protocol Version Date: May 19, 2011   **Update Broadcast Date: April 30, 2014**

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
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<tbody>
<tr>
<td>7.2.7</td>
<td>The details for the I.V. Solutions contact were updated.</td>
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<tr>
<td>7.7</td>
<td></td>
</tr>
<tr>
<td>7.8</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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<tr>
<td>Appendix V (CTSU)</td>
<td></td>
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<tr>
<td>Title page</td>
<td>This update was added to the Document History table.</td>
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RTOG 0517, “Randomized Phase III Trial to Evaluate Radiopharmaceuticals and Zoledronic Acid in the Palliation of Osteoblastic Metastases from Lung, Breast, and Prostate Cancer”

Study Chair: Michael J. Seider, PhD, MD; 330-375-3557; seiderm@summa-health.org

RTOG 0517 has been amended as follows:
As mandated by NCI, beginning July 1, 2011, this study will utilize CTCAE version 4 for reporting of all adverse events. Related changes were made to the first paragraph of Section 7.7.

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

Other Changes
Global: All web links and related descriptions to sub-pages of the RTOG web site were updated.

Title Page: Dr. Langer’s telephone and fax numbers were updated. The contact information for Dr. Shook, the senior statistician for the study, was added, and a document history table was added per current RTOG standard.

Section 5.2.1: The RTOG web support e-mail address in the next to the last paragraph was updated.

Section 7.7.3: Updated per current NCI reporting requirements for acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).
RTOG 0517, "Randomized Phase III Trial to Evaluate Radiopharmaceuticals and Zoledronic Acid in the Palliation of Osteoblastic Metastases from Lung, Breast, and Prostate Cancer"

Study Chair: Michael J. Seider, PhD, MD; 330-375-3557; seiderm@summa-health.org

RTOG 0517 has been amended as follows:

Title Page:
- Dr. Langer's contact information was updated.
- CTSU participation procedures were added for non-RTOG institutions.

Eligibility Checklist:
- Page 3, Question 20: Follow-up statements were added to allow institutions to specify the reason for patient refusal to participate in the Quality of Life component of the study.
- Page 3, Question 21 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. Cost utility analysis will be done by means of modeling costs.

Section 3.1.2.2: The word "only" was added to clarify to institutions that bone scans are required; other modalities are to be used only to confirm bone scan results.

Section 7.1.1: In the first paragraph, "a minimum of" was added before "500 mg of calcium" to allow for a range of calcium dosage, at the discretion of the physician. Also, the second paragraph was revised to clarify that chemotherapy and/or hormonal therapy should not be changed within 14 days prior to or 14 days after the start of protocol treatment.

Section 7.1.2: In the second paragraph, "a minimum of" was added before "500 mg of calcium" to allow for a range of calcium dosage, at the discretion of the physician. Also, the third paragraph was revised to clarify that chemotherapy and/or hormonal therapy should not be changed within 14 days prior to or 14 days after the start of protocol treatment.

Section 7.2.7: Was revised slightly to clarify shipping details. Additionally, the
information for the I.V. Solutions contact person was updated.

**Section 7.4.2:** "A minimum of" was added before "500 mg of calcium" to allow for a range of calcium dosage, at the discretion of the physician.

**Section 7.5:** A typo was corrected in the last row of the zoledronic acid dose determination table: 30-39 mg/min was changed to 30-39 ml/min.

**Section 7.7, "Adverse Events":** Was updated to current RTOG standard.

**Appendix I (sample consent):**

- Under "Will my medical information be kept private?", the Cancer Trials Support Unit was added to the list of organizations that may look at and/or copy patient medical records for research, quality assurance, and data analysis.
- Under "Quality of Life Study", the paragraph describing the need for the social security number of patients for whom health care is covered at least in part by Medicare 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. Cost utility analysis will be done by means of modeling costs.

**Appendix V:** Was added to include the CTSU logistics.
SUMMARY OF CHANGES
Amendment 3, Version Date: September 28, 2007

RTOG 0517, "Randomized Phase III Trial to Evaluate Radiopharmaceuticals and Zoledronic Acid in the Palliation of Osteoblastic Metastases from Lung, Breast, and Prostate Cancer"

Study Chair: Michael J. Seider, PhD, MD; 330-375-3557; seiderm@summa-health.org

RTOG 0517 has been amended as follows:

Section 3.2.3: Patients who have undergone prior treatment with Strontium-89 or Samarium-153 for bone metastases are not eligible for this study.

Eligibility Checklist, pp. 1-2:

- For consistency with Section 3.2.3, a new question 13 was inserted regarding prior Strontium-89 or Samarium-153 treatment; the original question 13 is now question 14 and the following questions were renumbered.
- Question 17 (originally question 16): The incorrect reference to Appendix V was deleted.

Section 1.4.2: Second paragraph, last sentence: The incorrect reference to Appendix IV was deleted.

Section 6.3.4: A typo under the gastrointestinal, CNS, and cardiovascular adverse events was corrected: less than 1% of patients experience the adverse events listed.
SUMMARY OF CHANGES
Amendment 2, Version Date: July 25, 2007

RTOG 0517, "Randomized Phase III Trial to Evaluate Radiopharmaceuticals and Zoledronic Acid in the Palliation of Osteoblastic Metastases from Lung, Breast, and Prostate Cancer"

Study Chair: Michael J. Seider, PhD, MD; 330-375-3557; seiderm@summa-health.org

RTOG 0517 has been amended as follows:

Eligibility Checklist, pp. 1-2: For consistency with Section 3.1.5, a new question 11 was inserted regarding CyberKnife treatment; the original question 11 is now question 12 and the following questions were renumbered.

Section 3.0

- 3.1.5: The sentence, "If patients have undergone CyberKnife treatment, treatment must be completed ≥ 14 days prior to registration" was added for clarity.
- 3.2.1: A "note" was added regarding the eligibility of patients with no evidence of disease in the brain after treatment for brain metastases.

Section 7.2.5: The typo at the end of the first sentence was corrected to "a temperature between 2-8ºC".

Consent, Appendix I: Under "During the Study", the blood tests for red and white blood cell levels will be conducted every week for 8 weeks instead of every other week.

Appendix II: Under "During Treatment", the blood tests for red and white blood cell levels will be conducted every week for 8 weeks instead of every other week.
RTOG 0517, "Randomized Phase III Trial to Evaluate Radiopharmaceuticals and Zoledronic Acid in the Palliation of Osteoblastic Metastases from Lung, Breast, and Prostate Cancer"

Study Chair: Michael J. Seider, PhD, MD; 330-375-3557; seiderm@summa-health.org

RTOG 0517 has been amended as follows:

Appendix I, sample consent, "Risks Related to Zoledronic Acid": At the recommendation of Novartis, maker of Zometa®, a paragraph was added (below the bulleted risks) concerning the risk of atrial fibrillation experienced by post-menopausal women with osteoporosis who received zoledronic acid in a recent study. In addition, the following changes were made:

- Under "Likely", the risk of low calcium levels in the blood was added to be consistent with adverse events associated with zoledronic acid provided in Section 7.2.4.
- Under "Less Likely", the following risks were added to be consistent with Section 7.2.4: weakness; increased sweating; redness of the skin and/or itching.
- Under "Rare, but serious", the risks of "nerve damage" and "too much calcium in the blood" were deleted as incorrect. In addition, the risk of "swelling of the skin, the lining of the mouth and throat, and/or organs" was added to be consistent with Section 7.2.4.

Other Changes

Title page: The phrase, "Radiation Oncology Alliance", was added to the contact information for Dr. Wyatt, the Quality of Life Co-Chair.

Eligibility Checklist, Page 1: The subquestion below question 16 was amended for clarity.

Section 5.1 was updated to reflect current RTOG standard for study agent shipment. Corresponding changes were made in Section 7.2.7 and Appendix IV.

Section 7.2.2: The fifth sentence of the first paragraph was corrected to read, "The necessary infusion bags containing 100 mL calcium free 0.9% sodium chloride will be provided." In addition, the first sentence of the second paragraph was corrected to read, "A peripheral or central intravenous line…".

Section 11.3.3 and 11.3.4 were deleted as this text is no longer RTOG standard. The subsequent section was appropriately renumbered.
Appendix I, under "During the Study" and Appendix II, under "During Treatment": The CBC with differential and ANC will be done every other week instead of every week.

Appendix IV, "Opioid Analgesic Documentation", and Appendix V, "Brief Pain Inventory", were deleted, as this information is provided in the study case report forms. The subsequent appendix was appropriately renumbered. These appendices also were deleted from the Index page.