RTOG 0518, “A Phase III Randomized Trial to Evaluate the Efficacy of Zometa® for the Prevention of Osteoporosis and Associated Fractures in Patients Receiving Radiation Therapy and Long Term LHRH Agonists for High-Grade and/or Locally Advanced Prostate Cancer”

Study Chair: Colleen Lawton, MD; 414-805-4472; clawton@mcw.edu

RTOG 0518 has been amended as follows:

As mandated by NCI, Section 7.9 (first paragraph) has been amended to require the use of CTCAE version 4 for grading of all adverse events reported via AdEERS as of October 1, 2011. All AE reporting on the study case report forms (CRFs) should follow grading criteria instructions on the specific CRF.

Other Changes
Title Page: Dr. Shook is now the senior statistician for this trial; Dr. Shook’s contact information was added to the title page.

Section 7.9: The RTOG web address in the third paragraph was updated.

Section 7.9.3: Amended as required per current NCI-CTEP reporting requirements for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) via AdEERS.
SUMMARY OF CHANGES

Update: June 26, 2008
(Broadcast Date: June 26, 2008)

RTOG 0518, A Phase III Randomized Trial To Evaluate The Efficacy Of Zometa® For The Prevention Of Osteoporosis And Associated Fractures In Patients Receiving Radiation Therapy And Long Term LHRH Agonists For High-Grade And/Or Locally Advanced Prostate Cancer

Study Chair: Colleen Lawton, MD; 414-805-4472; clawton@radonc.mcw.edu

RTOG 0518 has been updated as follows:

Section 7.3.7, “Drug Ordering and Accountability”: The first and second paragraphs were revised to clarify frequency and amount of drug shipments.

An updated protocol is available on the RTOG website, http://www.rtog.org/.
SUMMARY OF CHANGES
Amendment 5: June 17, 2008
(Broadcast Date: June 26, 2008)

RTOG 0518, A Phase III Randomized Trial to Evaluate the Efficacy of Zometa® for the Prevention of Osteoporosis and Associated Fractures in Patients Receiving Radiation Therapy and Long Term LHRH Agonists For High-Grade and/or Locally Advanced Prostate Cancer

Study Chair: Colleen Lawton, MD; 414-805-4472; clawton@mcw.edu

RTOG 0518 has been amended as follows:

Section 7.0:
- **Section 7.2**: Was revised to include information regarding the treatment assignment unbinding and re-assignment of cases on study.
- **Section 7.7**: Revised to include information regarding treatment assignment unbinding notification to institutions.

Other changes

Schema page: The timing for zoledronic acid administration was added to the schema.

Section 7.3.7: The contact information for the I.V. Solutions contact was updated.

Section 11.1: For clarity of presentation, the following changes were made:
- The superscript “h” was removed from next to the “X” in the fourth column of the table, and added to the first column, next to the “FACT-G” and the “EQ-5D” in the last two rows of the table.
- In the sixth column, next to “Follow Up”, the superscript “i” was added in place of the “h”.
- An “X” was placed in the last two rows of columns 3, 5, and 6.
- The superscript “l” was added for consistency with the unbinding/reassignment changes made in other areas of the protocol.

Section 13.0:
- **Section 13.2.2**: A typo in the second paragraph was corrected (“in” was changed to “of”).
- **Section 13.2.3.1**: A typo in the first paragraph was corrected (“placebo” was changed to “control”).
- **Section 13.4.1**: An extra word, “any” was removed from the second sentence.
- **Section 13.4.3**: In the first paragraph, FABFPlacebo was corrected to FABFControl for consistency with the equation.

Appendix I (Consent):
- Under “What will happen if I take part in this research study?”, beneath the bulleted text, the paragraphs were revised slightly for clarity; the content was not changed.
- Under “Study Plan” the last box for “All patients” was revised slightly for clarity.
- Under “How long will I be in the study?” 3 months was revised to 6 months, for consistency with the protocol.
- Under “Risks and Side Effects Related to External RT/Less Likely, But Serious” and “Risks and Side Effects Related to Internal RT/Less Likely, But Serious”, “Blockage of the intestinal or urinary tract” was revised to “Blockage of the intestinal or urinary tract”.
- Under “Other Medicine” a typo in the third bullet was corrected (“are” was changed to “at”).

An updated protocol is available on the RTOG website, [http://www.rtog.org/](http://www.rtog.org/).
RTOG 0518, A Phase III Randomized Trial to Evaluate the Efficacy of Zometa® for the Prevention of Osteoporosis and Associated Fractures in Patients Receiving Radiation Therapy and Long Term LHRH Agonists For High-Grade and/or Locally Advanced Prostate Cancer

Study Chair: Colleen Lawton, MD; 414-805-4472; clawton@mcw.edu

RTOG 0518 has been updated as follows:

Title page: Study chair contact information format was made consistent with RTOG standard.

Section 5.1: Regulatory preregistration requirements for international sites were added to meet RTOG standard.

Note: These are editorial/administrative changes to the protocol. NCI requires that these changes be documented on the protocol title page as "Update Date."
SUMMARY OF CHANGES
Amendment 4: March 13, 2008
(broadcast April 24, 2008)

RTOG 0518, A Phase III Randomized Trial to Evaluate the Efficacy of Zometa® for the Prevention of Osteoporosis and Associated Fractures in Patients Receiving Radiation Therapy and Long Term LHRH Agonists For High-Grade and/or Locally Advanced Prostate Cancer

Study Chair: Colleen Lawton, MD; 414-805-4472; clawton@mcw.edu

In response to feedback from multiple RTOG sites with interest in this study regarding placebo cost and patients’ reluctance to take part in the study due to the placebo injection, the study has been amended to compare the experiment arm, zoledronic acid plus vitamin D and calcium supplement, to standard therapy with vitamin D and calcium supplement (no placebo).

In addition, frequency of treatment was reduced to decrease risk from potential zoledronic acid toxicities. Two studies published since the opening of this trial have shown that decreasing the frequency of zoledronic acid does not change its effectiveness.

Accordingly, the following changes were made in the protocol:

Title page: The title was amended to “Randomized Trial” to reflect the protocol’s design.

Schema page: The title was amended to “Randomized Trial” and the word “placebo” was deleted from the schema (Arm 2).

Eligibility Checklist, page 3 of 3: Question #16 was amended to eliminate “placebo” and correspond to Section 7.2.

Section 2.2.2: Revised to reflect specific changes, e.g., the phrase “versus placebo” was deleted.

Section 7.2: All references to Arm 2 placebo were removed; “on Arm 1” was inserted for clarity. Treatment frequency was amended to every 6 months and 6 infusions over 3 years.

Sections 7.3, 7.6, and 7.10: All references to placebo and/or placebo infusion kit and notes describing the placebo kit were removed; “zoledronic acid/placebo” was deleted in Section 7.8.

Section 7.6.1: Treatment frequency was amended to every 6 months.

Section 11.0: Column heads and a footnote were amended to remove “placebo” and change the treatment frequency to every 6 months.

Section 12.1: Due dates for treatment forms were amended to every 6 months.

Sections 13.2 and 13.4: References to placebo were amended to “observational control” or “control”; “either” was inserted for clarity in Section 13.2.1; the first sentence of Section 13.2.2 was rewritten to accurately describe the study arms; “placebo” was amended to “standard treatment” in 13.4.5.

Appendix I: The subsections Why is this study being done, What will happen if I take part in this research study, Study Plan, Can I stop being in the study, and What are the costs of taking part in this study were amended and clarified to remove “placebo” and change the treatment frequency to every 6 months and 6 infusions over 3 years. Risks Related to Placebo was deleted.

Other Changes
Summary of Changes, RTOG 0518, Amendment 4 (Continued)

Title page: The e-mail address for the principal investigator, Dr Lawton, was corrected.

Schema page: Schema note was made consistent with note in Section 7.1.

Eligibility Checklist, page 1 of 3, Question #2, and corresponding Section 3.1.1: Time to registration from date of biopsy was changed to 12 months to help postop patients meet the registration timeline.

Eligibility Checklist, page 1 of 3, Question #5, and corresponding Section 3.1.5: Time to registration from start of LHRH (hormone therapy) was changed to 6 months to help hormone therapy patients meet the registration timeline. Question #5 was also made consistent with note in Section 7.1.

Section 3.1.4: A clarification was inserted to make Section 3.1 consistent with note in Section 7.1.

Section 3.1.13: An item was added clarifying that postprostatectomy patients are eligible.

Section 5.2.1: The URL was revised to RTOG standard.

Section 7.3.7: Drug company contact information was amended to reflect new personnel.
RTOG 0518, “A Phase III, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy of Zometa® for the Prevention of Osteoporosis and Associated Fractures in Patients Receiving Radiation Therapy and Long Term LHRH Agonists for High-Grade and/or Locally Advanced Prostate Cancer”

Study Chair: Colleen Lawton, MD; 414-805-4472; clawton@radonc.mcw.edu

RTOG 0518 has been amended as follows:

Eligibility Checklist: Page 1, question 11, “within 16 weeks prior to registration” was added for clarity; this change was also made in Section 3.1.6.

Section 3.1.8: “Serum creatinine within 4 weeks prior to registration” was added for consistency with Section 11.1

Sections 3.1.9 to 3.1.12: Were renumbered.

Section 11.1: Notation “a” under the Study Parameters table was changed to “within 16 weeks of registration”; Notation “b” was changed to “within 8 weeks of registration”; the original notation “b” is now notation “c” and the subsequent notation letters were revised. Also, in notation “h” (originally notation “g”), the timing of the QOL assessments was changed to “every 6 months for 3 years”.

Section 12.1: The timing for submission of the DXA Scan Report and DXA Scan Data Form was revised to “within 16 weeks of registration…”

Consent, Appendix I: Under “What will happen if I take part in this research study?” in the paragraph beginning, “All patients in this study will receive radiation therapy while they receive zoledronic acid or placebo”, the fifth sentence was revised to “Internal radiation therapy involves the insertion of a temporary or permanent implant into your body…”
SUMMARY OF CHANGES  
Amendment 2, Version Date: March 22, 2007

RTOG 0518, “A Phase III, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy of Zometa® for the Prevention of Osteoporosis and Associated Fractures in Patients Receiving Radiation Therapy and Long Term LHRH Agonists for High-Grade and/or Locally Advanced Prostate Cancer”

Study Chair: Colleen Lawton, MD; 414-805-4472; clawton@radonc.mcw.edu

RTOG 0518 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 concerning the risk of atrial fibrillation experienced by post-menopausal women with osteoporosis who received zoledronic acid in a recent study.

Other Changes

Section 3.1.4: Based on feedback from participating RTOG sites, the timeframe for pre-treatment LHRH therapy was amended from 12 weeks to 20 weeks prior to registration. In addition, instructions were added for patients who have started pelvic RT for their current prostate cancer: that RT must have begun ≤ 8 weeks prior to registration.

- The following changes were made to page 1 of the Eligibility Checklist to be consistent with the amendments to Section 3.1.4: Question 1 was added (and subsequent questions were appropriately renumbered), and the timeframe in Question 5 was amended.

Section 3.1.5: Based on feedback from participating RTOG sites, the timeframe for the diagnostic workup was amended from 12 weeks to 16 weeks prior to registration.

- The following changes were made to page 1 of the Eligibility Checklist to be consistent with the amendment of Section 3.1.5: Timeframes in Questions 6, 7, 8, 9, and 10 were amended.

Section 3.1.8 was amended to provide further instructions to sites regarding corrected serum calcium.

Section 3.2.5: The exclusion of “Prior pelvic radiation” was clarified with a parenthetical phrase, “other than for current prostate cancer”.

- The following change was made to page 2 of the Eligibility Checklist to be consistent with the amendment of Section 3.2.5: In question 19, the parenthetical phrase, “other than for current prostate cancer” was added after “prior pelvic radiation”.

Section 7.0: The reference to Section 3.2.3 was corrected to Section 3.2.6.

Section 7.2.1: The first paragraph was amended to clarify the timing of the first dose of zoledronic acid/placebo.

- The following change was made to page 3 of the Eligibility Checklist to be consistent with the amendment of Section 7.2.1: The calendar base date in question 16 was clarified with the parenthetical phrase, “scheduled date of first zoledronic acid/placebo”.

Section 7.3.5: In the first sentence, the storage temperature was corrected to “2-8° C”.

Section 7.6: A “note” was added to the third paragraph instructing sites to use the patients’ actual (vs. ideal) weight to calculate creatinine clearance.
RTOG 0518, “A Phase III, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy of Zometa® for the Prevention of Osteoporosis and Associated Fractures in Patients Receiving Radiation Therapy and Long Term LHRH Agonists for High-Grade and/or Locally Advanced Prostate Cancer”

Study Chair: Colleen Lawton, MD; 414-805-4472; clawton@radonc.mcw.edu

RTOG 0518 has been updated as follows:

Section 7.3.2, “Preparation”: The fifth sentence of the first paragraph and the first sentence of the second paragraph were corrected. In addition, clarification regarding the placebo “kit” provided for patients randomized to placebo was added to the “Note” at the end of the section.

Section 7.3.6, “Supply”: Clarification was added regarding the placebo “kit” provided for patients randomized to placebo. In addition, a “Note” was added at the end of the section clarifying that the person receiving and preparing the study agent should not unblind the treatment to the administrator of the study agent.

Section 7.3.7, “Drug Ordering and Accountability”: The first sentence was made consistent with Sections 7.3.2 and 7.3.6.

An updated protocol is available on the RTOG website, http://www.rtog.org/.
SUMMARY OF CHANGES
Amendment 1, Version Date: November 17, 2006

RTOG 0518, “A Phase III, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy of Zometa® for the Prevention of Osteoporosis and Associated Fractures in Patients Receiving Radiation Therapy and Long Term LHRH Agonists for High-Grade and/or Locally Advanced Prostate Cancer”

Study Chair: Colleen Lawton, MD; 414-805-4472; clawton@radonc.mcw.edu

RTOG 0518 has been amended as follows:

The following changes were made to the Eligibility Checklist, page 1:

- Question 1: The phrase, “within 6 months of registration”, was added for consistency with Section 3.1.1.
- Question 4 was amended to include a subquestion, for consistency with Section 3.1.4.
- Question 9 was simplified to one question.
- Question 11 was clarified to “Is the patient ≥ 18 years of age?”
- Question 12: The phrase, “serum calcium”, was replaced with “corrected serum calcium” to be consistent with Section 3.1.8. In addition, “serum creatinine” was replaced with “calculated creatinine clearance” and a reference to Section 3.2 was added at the end of the question to be consistent with Section 3.2.3.
- Question 13 was added to be consistent with Section 3.1.10, and subsequent questions were appropriately renumbered.

Section 3.1.2: The clinical stages (e.g., “≥ T3 disease, any N stage, M0 with any Gleason score and any PSA”) were amended so that they are exclusive versus overlapping. This change also was made under “Patient Population” on the Schema page and on page 1 of the Eligibility Checklist, question 2.

Section 3.1.9 was deleted (and subsequent sections appropriately renumbered) and Section 3.2.3 was amended, excluding patients with a baseline calculated creatinine clearance < 30 mL/min (versus a baseline calculated creatinine clearance ≥ 60 mL/min), and providing the Cockcroft-Gault formula. These changes were made to be consistent with Sections 7.6 and 7.6.1.

Section 4.2: In the last sentence, the phrase, “please contact RTOG HQ immediately” was corrected to “sites should document it on the appropriate case report form”.

Section 7.2.1: The second sentence of the fourth paragraph was amended for clarity: “calculated serum creatinine clearance” was replaced with “calculated creatinine clearance at baseline”. In addition, two sentences were added to the section to provide more detailed instructions regarding the doses of zoledronic acid/placebo during the study. These changes also were made in Sections 7.3.3 and 7.6.

Section 7.3.3: In the second sentence the phrase, “is to be measured” was replaced with “will be measured” for clarity. In addition, in the second and third sentences, “study drug” and “Zometa®” were replaced with “zoledronic acid/placebo” for clarity and consistency.

Sections 7.4.2 and 7.4.3: The phrase, “for 3 years” was added at the end of each section for clarity and to be consistent with Section 7.2.1.

Sections 7.9, 7.9.1, and 7.9.2 defining Adverse Events and Serious Adverse Events, were updated to current RTOG standard.
Summary of Changes, RTOG 0518, Amendment 1 (Continued)

Section 11.1:
- Albumin was added to the assessments, following “Serum calcium” to be consistent with the formula for corrected serum calcium in Section 3.1.8, which refers to albumin.
- In the last column of the table, “Follow Up”, the “X” for the FACT-G and EQ-5D was deleted, as the time frame for these assessments is specified in the third column, footnote “g”.
- Footnote “d” was amended for clarity.
- Footnote “f” was added for the quality of life (QOL) assessments, FACT-G and EQ-5D, to clarify that if the patient consents to participate in the QOL component of the study, sites are required to administer baseline assessments. This footnote is consistent with Section 4.1.1.
- Subsequent footnotes were appropriately re-lettered, and the phrase, “If the patient consents to participate in the quality of life component of the study”, was added to footnote “g” for clarity. In addition, reference to the assessment, “OQOL”, was deleted from this footnote as only the FACT-G and EQ-5D will be administered.

Section 11.2:
- Sections 11.2.1 and 11.2.2 were amended for clarity.
- Section 11.2.3 was amended from “may withdraw the patient from protocol treatment” to “may discontinue protocol treatment”, to update the text to RTOG standard. In addition, the subsequent and corresponding phrase, “Reasons for withdrawing”, was amended to “Reasons for discontinuing treatment”.
- Sections 11.2.4 and 11.2.5 were deleted to update this section to current RTOG standard, and subsequent sections were appropriately renumbered.

Section 12.1: The Adverse Event (AE) forms were deleted, as this information will be collected on the Follow-up Form (F1).

In Appendix I, the sample consent:
The “Study Plan” was amended for clarity: the text concerning all patients receiving radiation and hormone therapies was moved from the top to the bottom, and the phrase, “while they receive zoledronic acid or placebo, Vitamin D, and a calcium supplement” was added.

The following changes were made to the risks related to zoledronic acid (Zometa®):
- 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 7.3.4.
- Under “Less Likely”, the following risks were added to be consistent with Section 7.3.4: 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 7.3.4.
- Under “Quality of Life Study”, in the sixth paragraph, the reference to “three questionnaires”, was corrected to “2 questionnaires”.

An amended protocol and a protocol with all changes tracked are attached.
SUMMARY OF CHANGES
Update: March 28, 2006

RTOG 0518, “A Phase III, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy of Zometa® for the Prevention of Osteoporosis and Associated Fractures in Patients Receiving Radiation Therapy and Long Term LHRH Agonists for High-Grade and/or Locally Advanced Prostate Cancer”

Study Chair: Colleen Lawton, MD; 414-805-4472; clawton@radonc.mcw.edu

RTOG 0518 has been updated as follows:

Eligibility Checklist, page 3: Questions 21 and 22, regarding use of Medicare data for health utility research, were added to this operational/demographic portion of the checklist. Eligibility criteria were not changed.

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