RTOG 0123, “A Phase II Randomized Trial With Captopril In Patients Who Have Received Radiation Therapy +/- Chemotherapy For Stage II-IIIB Non-Small Cell Lung Cancer, Stage I Central Non-Small Cell Lung Cancer, Or Limited-Stage Small-Cell Lung Cancer ”

Study Chair: William Small, Jr. M.D., (312) 926-6810; w-small@northwestern.edu

RTOG 0123 has been amended as follows:

As mandated by NCI, Sections 7.5 and 7.6 have been amended to require the use of CTCAE, version 4 for grading of all adverse events as of July 1, 2011.

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

Other Changes
Section 7.5.4: This section was amended as required by CTEP to instruct sites to report AML or MDS via AdEERS.

Section 11.1.2 was amended to clarify that adverse events will be reported on case report forms using CTCAE, v. 3.0.
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Cancer, Stage I Central Non-Small Cell Lung Cancer, Or Limited-Stage Small-Cell Lung
Cancer

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RTOG 0123 has been amended as follows:

In order to make the study available to more patients, the required timeframe for
registering patients and the timeframe for pre-randomization evaluations were amended.
Patients can now be registered during radiation therapy up to 48 hours prior to
randomization, as well as within 7 days prior to the start of radiation therapy. Pre-
randomization evaluations can now be done within 2 weeks prior to randomization, rather
than within 48 hours prior to randomization. The following sections were amended for
this change: the Schema page, Sections 3.1.10 and 3.1.11, Sections 5.1 and 5.2,
Appendix IA, under "What Is Involved In The Study?" and Appendix IB, under "About
Using Blood For Research".

Other Changes

Title page: Full contact information has been provided for all Study Co-Chairs to update
this page to current RTOG standard.

Schema page:

- Under the first stratification variable, "Amount of Lung Irradiated", a third option,
"< 25%", was added, based on data suggesting increased pulmonary toxicity for
this cohort of patients receiving concurrent chemoradiotherapy. This option also
was added to the demographic оперational portion of the Eligibility Checklist,
Step 2, page 1, question 7.
- Patient Population" was updated to current RTOG standard and amended to be
consistent with Section 3.1.

Section 1.6: The heading was amended to "Dose Volume Relationship to Pulmonary
Toxicity" to be consistent with content and changes in this section. The first column of
the embedded table was amended to "Total Lung Volume > 20 Gy (%)" for clarity. The
second paragraph was amended to include recent research results regarding the
relationship of dose volume to pulmonary toxicity. In REFERENCES, four citations
were added for this section, and subsequent citations were appropriately renumbered in
REFERENCES and in the protocol text.
Section 3.1:

- In **Section 3.1.4**, the phrase, "if receiving radiotherapy alone" was added at the end of the section based on the reduced pulmonary toxicity in radiotherapy-alone patients as compared to chemoradiotherapy patients; this necessitates a larger volume of lung irradiated to demonstrate a statistically significant reduction in pulmonary toxicity with the addition of captopril. This change also was made to the **Eligibility Checklist**, Step 1, page 1, question 4.

- **Section 3.1.7**: The phrase, "either during radiotherapy or during therapy with captopril", was added after "allowed" for clarity.

- **Section 3.1.8**, requiring patients to have a life expectancy of at least six months was deleted. Institutions and investigators rarely define or document a patient's life expectancy, and cases may be made ineligible if there was no documentation to verify this eligibility item; therefore, it is the current RTOG standard not to require a defined life expectancy. The required CT planning scan was added as the new Section 3.1.8, as pre-treatment requirements in Section 3.0 and 4.0 were re-organized.

- **Section 3.1.11**:
  - In the second bullet, the absolute granulocyte count was amended from to "greater than or equal to 1,000/mm³" and the platelet count was amended "greater than or equal to 75,000/mm³" to be allow for patients with cytopenias thought to be related to chemotherapy.
  - The required serum Na⁺ and K⁺ parameters were amended to "within institutional normal" to be consistent with clinical practice.

**Sections 3.1.11, 4.1, and 4.2**: The prior text in these sections was re-organized to current RTOG standard and amended to clarify evaluations required within 2 weeks prior to patient registration and within 2 weeks of randomization and to clarify the evaluations that are "Highly Recommended" but not required. Corresponding changes were made in **Section 11.1** and in **Appendix I** under "What Is Involved In The Study?".

**Section 5.1.1** was amended to the current RTOG standard for online registration. A corresponding change was made to the **Eligibility Checklist**, Step 1, page 3, in the paragraph under the questions: The phrase, "prior to calling RTOG" was replaced with "prior to web registration".

**Section 6.2** was deleted, as it was inconsistent with changes in other sections and as it does reflect current RTOG standard.

**Section 7.3**, "Treatment Plan": In the second paragraph, "Day (-)1", the instruction to check for adequate resting blood pressure and pulse prior to administration of the test dose was added for patient safety. This instruction also was added in the fourth, fifth, and sixth paragraphs, "Day 1", "Day 15", and "Day 29".

**Sections 7.5 and 7.6** were added to update the protocol to current RTOG standards and
NCI requirements regarding adverse events and reporting of these events. The prior text was deleted.

Section 10.0: The heading was updated to RTOG standard, "Tissue/Specimen Submission". This change also was made on the Index page.

Section 10.2, "Serum Collection", was updated for current RTOG Tissue Bank procedures and contact information, and to refer sites to Appendix IV, which was added to provide details of the collection kit and details instructions. The new appendix also was added to the Index page.

Section 10.3, "Reimbursement", was amended to reflect current per case reimbursement for buffy coat and for serum/plasma.

Section 13.5: A statement was added concerning monitoring of the study by the Clinical Data Update System (CDUS).

Appendix IA: The text under "Whom Do I Call If I Have Questions or Problems?" and "Where Can I Get More Information?" was updated to the current NCI consent template.

An amended protocol is available on the RTOG Web site, www.rtog.org
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RTOG 0123 has been amended as follows:

Title page: Contact information was updated for Dr. Movsas, Outcomes Co-Chair.

Schema page:

- Patients can be registered “Within 7 days prior to or within 14 days after the start of radiation therapy” (versus only prior to the start of radiation). Section 3.1.10 was added to correspond (and subsequent sections were appropriately renumbered), and this change also was made in Section 5.1.
- The timeframe for randomization was amended to “48 hours prior to captopril/observation” for clarity. This change also was made in Section 5.2.

Section 3.1.11: The timeframes for laboratory evaluations were amended to “14 days prior to registration” and “within 48 hours prior to captopril/observation” for clarity. These changes also were made in Sections 4.2, 4.3, and 11.1.

Section 3.2.1, excluding patients from being on other cooperative or single institution studies, was deleted, and subsequent sections were appropriately renumbered. This change also was made in “Eligibility” on the Schema page, and Question 14 on page 1 of the Eligibility Checklist was deleted. In addition, Section 9.1.1 was added under “Permitted Therapy”.

Section 4.0 was reorganized into three sections for clarity.

Section 6.0: A note that IMRT is not allowed was added to the heading for clarity. In Section 6.1, a sentence defining total lung volume was added for clarity.

Section 7.3: Instructions regarding hypotensive episodes were added to Day (-)1, Day 1, and beneath Day 29.

Section 7.5.3.6: The address for RTOG Headquarters was updated. This change also was made in Sections 7.5.5 and 12.0.

Sections 9.1.2 and 9.1.3 were added under Permitted Therapy.
Section 10.2.7: The email address for LDS Hospital was updated.

Section 11.1: Footnote “a” was amended for clarity and footnote “g” was amended to correspond to Section 4.1.

Section 12.1 was corrected to include a Quality of Life (QL) form “Within 2 weeks of completion of RT”.

Appendix IA:

- A phrase, “and will be receiving radiation therapy”, was added to the second paragraph for clarity;
- Under “What Is Involved In The Study?”, the timeframes for evaluations were corrected to correspond to Section 11.1. This change also was made in Appendix IB, under “About Using Blood For Research”;
- Under “What Are My Rights As A Participant”, the group of experts reviewing the study data was corrected to “experts from the Symptom Management Committee”.

An amended protocol is available (no password required) on the RTOG Web site, www.rtog.org
SUMMARY OF CHANGES
Revision 1, Version Date: December 16, 2003

RTOG 0123, “A Phase II Randomized Trial With Captopril In Patients Who Have Received Radiation Therapy +/- Chemotherapy For Stage II-IIIB Non-Small Cell Lung Cancer, Stage I Central Non-Small Cell Lung Cancer, Or Limited-Stage Small-Cell Lung Cancer

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IRB Review Requirements:
( ) Full board review required
(X) Expedited review allowed, but site IRB requirements take precedence.
( ) No review required

RTOG 0123 has been revised as follows:

Schema Page — The phrase, “Prior to Initiation of Lung Cancer Therapy”, was revised to “Prior to initiation of Radiation Therapy”.

Eligibility Checklist — Question 5 on page 2 of Step 1 and question 2 on page 1 of Step 2 were updated to RTOG standard.

Section 3.1.1 — A parenthetical phrase was added to further describe “limited-stage small-cell lung cancer”; this change also was made in the Eligibility list on the Schema page.

Section 3.2.1 was revised to exclude patients on other “cooperative group or single institution” (versus “RTOG”) lung treatment trials using radiation +/- chemotherapy; this change also was made in the Eligibility list on the Schema page and on the Eligibility Checklist, question 14 on page 1 of Step 1.

Section 7.4.2 — Instructions for discontinuing captopril for ≥ Grade 2 pulmonary toxicity were added below the bullet points.

Section 11.1:

- The title of the second column, “Pre Lung Cancer Therapy”, was revised to “Pre Initiation of Radiation Therapy”;
- A toxicity evaluation was added at 4.5 months;
- Footnote “a” was revised to indicate that the assessments referenced are only “for patients randomized to captopril arm”, and that footnote was added appropriately to the CBC, urinalysis, and serum chemistry assessments;
- Footnote “f” was deleted, and subsequent footnotes were appropriately redesignated.
Section 12.0 — The data submission instructions were updated to RTOG standard.

Section 12.1 — The schedule of the Follow-Up Form (F1) was revised for clarity.

The following changes were made in Appendix I, the sample consent:

- The schedule of assessments for Treatments 1 and 2 in Appendix I, under “What Is Involved In The Study?”, were revised to correspond to Section 11.1;
- Under “What About Confidentiality?”, RTOG was added to the groups that may inspect and/or copy patients’ records;
- Under “Where Can I Get More Information?”, the second paragraph was updated.

A revised protocol is available (no password required) on the RTOG Web site, www.rtog.org
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RTOG 0123 has been updated as follows:

Eligibility Checklist, Step 1, page 2 — The following changes were made to this operational/demographic portion of the checklist:

- Question 5 was updated to RTOG standard (The initials required are now first middle last);
- Questions 16-18 were deleted from this page (and added to Eligibility Checklist, Step 2, page 1); subsequent questions were appropriately renumbered.

Eligibility Checklist, Step 2, page 1 — The following changes were made to this operational/demographic portion of the checklist:

- Question 2 was updated to RTOG standard;
- Question 5 was revised to “protocol treatment” for clarity;
- As noted above, the stratification questions were added as numbers 7-9.

Section 12.1 — The schedule for the Radiotherapy Form (T1) and the Dose Volume Histograms (DV) has been corrected to accommodate the two-step registration procedures; the note at the bottom of the section, referring to submission of Dose Volume Histograms was clarified.

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 a revision.

An updated protocol is available (no password required) on the RTOG website: www.rtog.org