For Amendment 7 to: RTOG 0813, Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT)
for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable
Patients

NCI/Local Protocol #: RTOG-0813/RTOG 0813

NCI Protocol Version Date: June 8, 2015 (Broadcast date: June 22, 2015)

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
</table>
| Title pages            | • Page 1, column 2, entry for Lech Papiez:  
  Line 2: “Former” was added in front of “Medical”  
  Lines 4-7 of his entry were deleted.  
  • On the 2nd title page, Dr. Hu’s office and contact information was updated.  
  • On the 2nd title page, this amendment was added to the Document History table. |
| 12.0                   | • On the 3rd line, office suite number was updated to 1720.                                                                               |
| 13.5.2.1               | • In first paragraph, line 5, “Time to” was deleted and “time” was inserted after “PFS”  
  This was a grammatical correction.  
  • In first paragraph, line 5, “randomization” was corrected to “start of SBRT”  
  This change is being made to have the definition of this secondary endpoint be  
  consistent with the definition of the primary endpoints which are both measured  
  from the start of SBRT.  
  • In first paragraph, line 7, “randomization” was corrected to “start of SBRT”  
  This change is being made to have the definition of this secondary endpoint be  
  consistent with the definition of the primary endpoints which are both measured  
  from the start of SBRT. |
| 13.5.2.2               | • In second paragraph, line 4, “metastases” was corrected to “metastasis”  
  • In second paragraph, line 6, “randomization” was corrected to “start of SBRT”                                                       |
| Informed Consent       | No changes                                                                                                                                 |


For Amendment 6 to: RTOG 0813, Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients

NCI/Local Protocol #: RTOG-0813/RTOG 0813

NCI Protocol Version Date: March 6, 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>
</tbody>
</table>
| Title pages   | • On the 1st title page as required by CTEP, “Radiation Therapy Oncology Group” was replaced with “NRG Oncology".  
• On the 1st title page, the affiliation and contact information for the Translational Research Co-Chair was updated.  
• On the 2nd title page, this amendment was added to the Document History table. |
| Schema page   | As required by CTEP, “Radiation Therapy Oncology Group” was replaced with “NRG Oncology”.                                               |
| 6.10.1        | In the 2nd paragraph, the date and link for the NCI Guidelines was updated.                                                              |
| Informed Consent | No changes                                                                                                                              |
RTOG 0813, Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients

Study Chair: Andrea Bezjak, MD, 416-946-2132, andrea.bezjak@rmp.uhn.on.ca

RTOG 0813 has been updated as follows:

2nd title page:
- The Senior Statistician has been updated from Dr. Dignam to Dr. Hu.
- This update was added to the Document History table.

Section 13.6: In the gender/minority table, the number of males who are not Hispanic or Latino was corrected from 60 to 61, and the total of females and males who are not Hispanic or Latino was corrected from 104 to 105.
SUMMARY OF CHANGES
Amendment 5, Version Date: July 23, 2012

RTOG 0813, “Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients”

Study Chair: Andrea Bezjak, MD; 416-946-2132; andrea.bezjak@rmp.uhn.on.ca

RTOG 0813 has been amended as follows:

The planned maximum sample size of 94 patients has been expanded to 110 patients. The current dose level (12.0 Gy/fx) began accruing as of February 20, 2012. Because of rapid accrual and necessary cautions warranted for further dose escalation before sufficient long-term observation on some patients was available, 78 patients had been enrolled at lower doses (dose levels 5 (10.0 Gy/fx) through 8 (11.5 Gy/fx), thus limiting the number of patients able to be enrolled at the presumed maximal tolerated dose (MTD) under the original design. The following sections have been amended for this change: Schema page; “Required Sample Size”; Sections 13.3 and 13.6, and Appendix I: “How many people will take part in the study?”.

Other Changes

1st title page: ”Study Chairs” was amended to the current RTOG standard text, “Study Team”.

2nd title page: The “Version Date” was deleted to amend the protocol to the current RTOG standard of bolding the version date of the protocol in the Document History table. In addition, this amendment was added to the Document History table.

Section 5.2.1: The link to the CTSU IRB/REB Certification Form was updated.

The following changes were made in Section 5.3:

- Section 5.3.1 was amended to the current RTOG standard text.
- Section 5.3.2: The last sentence was deleted to be consistent with current processes.
- Section 5.3.5: In the 2nd sentence, the phrase, “centrally at ITC”, was deleted to be consistent with current processes. In addition, a “note” was added as paragraph 2 to be consistent with changes in Section 6.0.

Section 6.0: The 2nd paragraph was added to instruct sites that rapid review for each case enrolled on dose level 9 (12 Gy/fx, 60 Gy) is required prior to treatment being delivered, as at the highest dose level, even greater attention must be paid to both target and normal tissue contouring. Even if the first case from the site passed review, there has been some variability in contouring; thus, the study team felt that real time review was advisable for patients on dose level 9.

Section 6.4.2.3: In “Note 1” below Table 1, the phrase, “dimension or”, was deleted prior to “volume” to amend the protocol to the current RTOG standard.

Section 6.10.1: In the 4th paragraph, the last sentence was added to amend the protocol to the current RTOG standard text.

Section 12.2: The reference to the “QA guidelines” in the table and the footnote to the table were deleted to amend the protocol to current RTOG standard text.

Section 13.6: In the heading of the table, the phrase, “Table 13.2”, was deleted to update the protocol to current RTOG standards.
RTOG 0813, Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients

Study Chair: Andrea Bezjak, MD, 416-946-2132, andrea.bezjak@rmp.uhn.on.ca

RTOG 0813 has been updated as follows:

Title pages:
- Contact information for Dr. Papiez was updated.
- Dr. Dignam is now the Senior Statistician for the study.
- The activation and update dates were deleted to update the title page to current RTOG standards. The version date was retained for clarity.
- This update was added to the Document History table.

Section 6.10.1: The adverse event reporting requirement table was updated as required by CTEP.

Sections 10.1.3, 10.3.3, and Appendix VI: The mailing and courier addresses for the RTOG Biospecimen Resource were updated.

Section 10.4: The first row was added to correct the Specimen Collection table.

Section 13.2: In the caption of Figure 13.2, the reference to Section 13.6.3 was corrected to Section 13.2.3.

Appendix I:
- Under “Will my medical information be kept private?”, the last 3 paragraphs were added to update the sample consent to current CTEP standard text.
- Under “About Using Tissue, Urine, and Blood for Research”, in the 4th paragraph, the web site link was updated.
- Under “Where can I get more information?”, the TTY number was deleted at CTEP’s request.
SUMMARY OF CHANGES
Amendment 4, Version Date: February 9, 2011
(Broadcast: 2/17/11)

RTOG 0813, “Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients”

Study Chair: Andrea Bezjak, MD; 416-946-2132; andrea.bezjak@rmp.uhn.on.ca

RTOG 0813 has been amended as follows:

Title page: On the second page, the “Document History” was added to update the protocol to current RTOG standards.

Section 1.1: In the 3rd paragraph, the second to last sentence regarding the University of Michigan study was updated by Dr. Kong.

Section 5.2.1.1, regarding translation of documents, was added to update the protocol to current RTOG standard text.

Section 6.10.3: This section was amended as required by CTEP to instruct sites to report AML or MDS via AdEERS.

Section 10.3.2 was amended to the RTOG Biospecimen Resource’s standard text.

Section 10.3.2.1: In the first sentence, the phrase, “frozen specimens”, was added to update the protocol to the RTOG Biospecimen Resource’s standard text.

Section 10.4: The second table, “Specimens for Translational Research”, was amended to the RTOG Biospecimen Resource’s standard text.

Section 11.2.1: The first bulleted item was corrected to be consistent with Section 10.3.1.

Appendix I: Under “About using tissue, urine, and blood for research”, the collection time points in the third paragraph were corrected to be consistent with Section 10.3.1.

Appendix VI was amended to the current RTOG Biospecimen Resource standard text.
RTOG 0813, "Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients"

Study Chair: Andrea Bezjak, MD; 416-946-2132; andrea.bezjak@rmp.uhn.on.ca

RTOG 0813 has been amended as follows:

In a review of the manuscript describing the conduct of RTOG 0236 (SBRT in medically inoperable lung cancer) by the Journal of the American Medical Association (JAMA), the editors correctly pointed out that unconventional definitions of local control were used, which described only recurrence of the primary treated tumor. The editors indicated that failure within the involved lobe (part of the T-stage for lung cancer in the TNM system) should be considered a component of local control. The editors indicated that recurrence definitions should reflect upon the site’s TNM staging. As such, a recurrence of the original primary tumor (originally characterized by the T of the TNM staging) is deemed a local recurrence. A recurrence in the primary tumor’s draining lymph nodes (hilar and mediastinal as originally characterized by the N of the TNM staging) is deemed a regional recurrence. Finally, a recurrence in distant sites (originally characterized by the M of the TNM staging) is deemed a disseminated recurrence. Fortunately, in 0236, the specific patterns of recurrence within the lungs were collected, and the oversight was corrected. In a re-analysis of 0236, 3 additional patients had new nodules within the same lobe and were included in the local recurrence definition. The primary endpoint was more correctly stated as “primary tumor control” (not local control), this nomenclature was corrected throughout the 0236 manuscript, and actuarial data on local control defined as primary tumor control plus control within the same (involved) lobe as well as local-regional control was added.

RTOG 0813 used the same unconventional recurrence definitions as RTOG 0236. Therefore, the protocol has been amended and patterns of recurrence have been reclassified appropriately. The terms “local control” and “local failure” as related to study procedures (not introduction) have been changed to “primary tumor control” and “primary tumor failure” throughout the protocol. The following sections were amended for this change: 1.2, 1.5, 2.1.2, 2.2.3, 2.3.1, 11.3.1, 11.3.3 (both tables revised), 13.1.2, 13.1.4.1, 13.2.3 (including Figure 13.2), 13.3, 13.5.1, 13.5.1.2, 13.5.8

Title page: Dr. Gaspar’s street and e-mail addresses were updated.

Eligibility Checklist, page 1, question 11: The timeframe for the pregnancy test was corrected to “within 72 hours prior to registration” to be consistent with Section 3.1.8.

Eligibility Checklist, page 2: Question 14 was amended to current RTOG standard text.

Section 3.1.7 was deleted because routine spirometry, lung volumes, diffusion capacity, and arterial blood gases are required prior to treatment (see Section 4.1.3), not to determine the patient’s eligibility for the study. Subsequent sections were appropriately renumbered. The corresponding question on page 1 of the Eligibility Checklist, #10, also was deleted (and subsequent questions were appropriately renumbered).

Continued on next page
Section 5.2.2 was deleted as the requirements in that section only pertain to studies involving drug treatment. The subsequent section was appropriately renumbered.

The following changes were made to Section 10.0:

- **Section 10.1**: The parenthetical phrase in the heading was amended to "(Optional and Highly Recommended)" for clarity, and the "Note" was added to instruct sites that lack of tissue submission should not exclude submission of urine.
- **Section 10.1.1.1** was amended to allow unstained slides if a tissue block or core cannot be submitted.
- **Section 10.1.1.2**: At the request of the RTOG Biospecimen Resource (BR), the phrase, "At least" was added prior to "10 ml of clean-catch urine".
- **Section 10.1.2** was amended for clarity.
- **Section 10.1.2.2**: The phrase, "or slides" was added to the first sentence to be consistent with changes made in Section 10.1.1.1.
- **Section 10.1.2.4**: At the request of the RTOG BR, the phrase, "and time" was added after "documenting the date".
- **Section 10.3**: The parenthetical phrase in the heading was amended to "(Optional and Highly Recommended)" for clarity, and the "Note" was added to instruct sites that lack of tissue submission should not exclude submission of blood samples.
- **Section 10.3.1**: In the 1st paragraph, at the request of the RTOG BR, "buffy coat" was replaced with "whole blood (for DNA)". In addition, in the 1st bulleted item, a "Note" was added regarding missed collection of whole blood within 3 days prior to the 1st dose of SBRT.
- **Section 10.3.2**: At the request of the RTOG BR, "buffy coat" was replaced with "whole blood".
- **Section 10.4**:  
  - In the 1st column of the 1st row, the phrase, "2 mm" was replaced with "1.5 mm" and the phrase, "skin punch" was replaced with "punch tool" to amend the protocol to current BR standard text.
  - In the 3rd column of the 1st row, a "note" was added regarding unstained slides to be consistent with changes made in Section 10.1.1.1.
  - In the 1st column of the 2nd row, the phrase, "A minimum of", was added prior to "10 ml of clean-catch urine" at the request of the BR.
  - In the 3rd column of the 2nd row, "in a sterile collection container" was replaced with "aliquotted into 2 sterile 15 ml polypropylene centrifuge tubes" at the request of the BR.
  - At the request of the BR, in the table, "Specimens for Translational Research", the original row was deleted and replaced by 3 rows for serum, plasma, and DNA.
- **Section 10.5**: The reimbursement schedule for this protocol was amended to be consistent with other similar RTOG studies.

Section 11.4.2 was deleted, as it was incorrect; the Division of Cancer Prevention did not approve cancer control credit for the submission of comorbidity data.

Appendix I: Under "About using tissue, urine, and blood for research", in the 3rd paragraph, the time points for collection of blood and urine was amended to be consistent with Sections 10.3.1 and 11.2.1

Appendix II: The timeframe for the pre-treatment pregnancy test was corrected to "Within 72 hours prior to registration" to be consistent with Section 3.1.8.

Appendix VI was amended to the current RTOG Biospecimen Resource standard text.
As mandated by CTEP, RTOG 0813 has been amended to require the use of CTCAE, version 4 for grading of all adverse events as of October 1, 2010.

The following sections were amended for this change: 2.2.1, 6.9.3, 6.9.5 (1st and 3rd paragraphs); 6.10.1 (under “AdEERS Reporting Requirements” and in the 2nd bulleted item below the 2nd table); 6.10.2, 13.1.1, 13.2, 13.5.1.1, 13.5.3.1, and 13.5.3.2.
SUMMARY OF CHANGES
Amendment 1, Version Date: February 16, 2010
(Broadcast 2/18/10)

RTOG 0813, “Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients”

Study Chair: Andrea Bezjak, MD; 416-946-2132; andrea.bezjak@rmp.uhn.on.ca

RTOG 0813 has been amended as follows:

**Title Page:** The Senior Statistician’s affiliation was amended to current RTOG standard text and her e-mail address was updated. The Consulting Statistician’s affiliation and contact information were updated.

**Eligibility Checklist,** page 3: Questions 18-20 were reformatted to current RTOG standard text. The corresponding questions in **Appendix I,** under “About Using Tissue, Urine, and Blood for Research”, were reformatted to be consistent.

**Section 3.1.5:** In the last sentence, the parenthetical phrase, “PTV touching the pleura”, was added for clarity. This phrase also was added to the corresponding question (number 8) on page 1 of the **Eligibility Checklist**.

**Section 3.1.9:** The timeframe for the required pregnancy test was corrected to “72 hours” to be consistent with question 12, page 1 of the Eligibility Checklist and with Appendix II.

**Section 4.1.6** was deleted as this information is provided in Section 10.0, as is current RTOG standard.

**Section 5.2.1** was amended to current RTOG standard text.

**Section 5.2.2** was amended and **Section 5.2.3** was added to amend “Regulatory Pre-Registration Requirements” to current RTOG standard text.

**Section 5.3.1:** The ITC’s e-mail address was updated. This change also was made in **Sections 5.3.3, 12.2, and 12.2.1.**

**Section 6.5:** Figure A was added below the 2nd paragraph (this figure was made available to sites on the RTOG web site at activation of the study). In addition, in the 1st paragraph, a reference to Figure 2 was added in a parenthetical phrase, “see Figure 2 below”.

In the heading of **Section 6.9,** the word, “Therapy”, was added to amend to the heading to current RTOG standard text.

**Section 10.0:** The phrase, “blood, urine, and tissue, if adequate tissue is available”, was added in parentheses for clarity.

**Section 10.3.2.1** was added to update the protocol to current Biospecimen Resource standards of storage of blood samples.

**Section 12.1:** The schedule for the Lung Adverse Event Form (AE) was revised to include a submission at 12 months after the start of SBRT.
Appendix II: Under “Pre-Treatment”, the last timeframe was amended from “Within 2 wks prior to registration” to “Within 2 wks prior to treatment”. In addition, the timeframes for evaluations required prior to treatment (versus prior to registration) were added for clarity and to be consistent with Section 4.1.

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.
SUMMARY OF CHANGES

Update: May 7, 2009
(Broadcast 5/7/09)

RTOG 0813, Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients

Study Chair: Andrea Bezjak, MD, 416-946-2132, andrea.bezjak@rmp.uhn.on.ca

At the request of the RTOG Biospecimen Resource and the Translational Research Co-Chair, Dr. Kong, the logistics for submission of specimens in RTOG 0813 have been updated as follows:

- **Section 10.0**: In the 3rd paragraph the location of the Biospecimen Resource was corrected to University of California San Francisco (vs. “in San Francisco”).
- **Section 10.1.1.1**: The word, “preferred”, was added after “tissue block of tumor” as information for sites.
- **Section 10.1.2.4**: In the “Note”, the temperature was corrected from -20° to -80° C.
- **Section 10.1.3**: “Mailing Address” was clarified to “U.S. Postal Service Mailing Address”, and “DHL” was updated to “UPS” in the Courier Address. These changes also were made in Appendix VI.
- **Section 10.3.1**: A note was added to inform sites that a blood collection kit can be obtained from the Biospecimen Resource. This information also was added in Appendix VI. In addition, the timeframe in the 1st bulleted item was clarified from “Within 3 days of…” to “Within 3 days before delivering the first dose of SBRT”.
- **Section 10.3.2** was updated to clarify that the Specimen Transmittal Form must document the date of collection of plasma and buffy coat, as well as serum.
- **Section 10.3.3**: Blood samples for translational research will be sent to the RTOG Biospecimen Resource rather than to Dr. Kong. The shipping address and contact information for questions were updated accordingly in this section and in Appendix VI.
- **Section 10.4**: In the 2nd column, “Specimens collected when”, the timeframes for collection of urine and blood were clarified from “Within 3 days of…” to “Within 3 days before the first dose of SBRT”. This clarification also was made in Appendix VI.
- **Section 10.5**: The last 3 paragraphs referring to submission of blood samples to Dr. Kong were deleted, and the remaining text regarding reimbursement and confirmation of appropriate materials was reorganized for clarity.
- **Appendix VI**:
  - The 2nd sentence regarding disposal of the Plug Kit was deleted to update the appendix to current Biospecimen Resource standard text.
  - In the 2nd paragraph under “Shipping instructions for urine specimens”, the 2nd sentence was corrected to “Specimens should be shipped only Monday through Wednesday…”
  - In the “Notes” under “Shipping instructions for urine specimens”, the phrase, “and there is sufficient ice for shipment” was added as an instruction to sites.
  - The mailing address under “Shipping instructions for urine specimens” was deleted as unnecessary.
SUMMARY OF CHANGES

Update: February 2, 2009
(Broadcast 2/2/09)

RTOG 0813, Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients

Study Chair: Andrea Bezjak, MD, 416-946-2132, andrea.bezjak@rmp.uhn.on.ca

RTOG 0813 has been updated as follows:

Section 5.2.2 was deleted as inclusion of this text in a non-drug trial is unnecessary. The former Section 5.2.2.2 was appropriately renumbered as Section 5.2.2.

The fax number for submission of the daily treatment record (T5) was updated on the Schema page under “All Sites Note: and in Sections 6.6 and 12.1.