For **Protocol and Consent Amendment** 4 to: RTOG 0539, Phase II Trial of Observation for Low-Risk Meningiomas and of Radiotherapy for Intermediate- and High-Risk Meningiomas

NCI/Local Protocol #: RTOG 0539

NCI Protocol Version Date: September 11, 2014 (Broadcast October 27, 2014)

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
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</thead>
<tbody>
<tr>
<td><strong>Cover pages</strong></td>
<td>This amendment was added to the document history table. Formatting for the study chair list was adjusted for space considerations. Contact information was updated for Dr. Rogers, Dr. Modi, and Dr. Tsien.</td>
</tr>
<tr>
<td><strong>Global</strong></td>
<td>Due to the transition to the NCTN, RTOG terminology was revised to NRG Oncology terminology or deleted as applicable to studies closed to accrual. The protocol was repaginated per current CTEP requirements.</td>
</tr>
</tbody>
</table>
| **Informed Consent (Appendix I)**  
Will my medical information be kept private? | The Radiation Oncology Therapy Group (RTOG) was changed to NRG Oncology. |
For **Protocol** Update to: RTOG 0539, Phase II Trial of Observation for Low-Risk Meningiomas and of Radiotherapy for Intermediate- and High-Risk Meningiomas

NCI/Local Protocol #: RTOG 0539

NCI Protocol Version Date: December 5, 2011  
**Update Date:** May 1, 2014 (Broadcast May 1, 2014)

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
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<tbody>
<tr>
<td>Cover pages</td>
<td>This update was added to the document history table. Peixin Zhang has replaced Minhee Won as the Statistician.</td>
</tr>
<tr>
<td>Global</td>
<td>As required by CTEP, references to the &quot;Adverse Event Reporting System (AdEERS)&quot; have been changed to &quot;CTEP Adverse Event Reporting System (CTEP-AERS)&quot; throughout the protocol.</td>
</tr>
<tr>
<td>Informed Consent</td>
<td>No changes</td>
</tr>
</tbody>
</table>
For **Protocol** Update to: RTOG 0539, Phase II Trial of Observation for Low-Risk Meningiomas and of Radiotherapy for Intermediate- and High-Risk Meningiomas

NCI/Local Protocol #: RTOG 0539

NCI Protocol Version Date: December 5, 2011  
**Update Date: February 26, 2013 (Broadcast February 26, 2013)**

<table>
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<tr>
<th>Section</th>
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<tbody>
<tr>
<td>Cover pages</td>
<td>The document history table was updated to include Update 2/26/13.</td>
</tr>
<tr>
<td></td>
<td>Ms. Won has replaced Dr. Wang as the Statistician.</td>
</tr>
<tr>
<td>Cover pages, 6.7, 11.5</td>
<td>Dr. Modi and Dr. Alleman have replaced Dr. Dean as the Neuroradiologist Co-Chairs.</td>
</tr>
</tbody>
</table>
RTOG 0539, Phase II Trial of Observation for Low-Risk Meningiomas and of Radiotherapy for Intermediate- and High-Risk Meningiomas

Study Chair: C. Leland Rogers, MD; (801) 350-8400; leland@gammawest.com

RTOG 0539 has been amended as follows:

Hyperostosis can occur in association with meningiomas [Cushing H, Eisenhardt L. Chapter III: Serial enumeration of meningiomas. In: Meningiomas. Their classification, regional behaviour, life history, and surgical end results. Springfield, IL: Charles C. Thomas, 1938, p56-73 and Pieper DR, Al-Mefty O, Hanada Y, Buechner D. Hyperostosis associated with meningioma of the cranial base: secondary changes or tumor invasion. Neurosurgery 1999;44:742-747], and hyperostotic bone frequently contains tumor. Pieper and co-authors correlated imaging with histopathology findings in 51 cranial base meningioma patients. Surgery included biopsies of adjacent hyperostotic and radiographically normal bone. Twenty-six patients had hyperostosis on pre-operative imaging, and among these tumor invasion was present in all but one. Nine of 25 patients without hyperostosis were also found to have tumor invasion of bone. Resection of abnormal bone is required in order to achieve a thorough, Simpson grade 1 resection [Simpson D. The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry 1957; 20:22-39], and the location of hyperostosis would often have limited impact on normal tissues, excepting hyperostosis near the anterior visual pathway or the petrous ridge near the facial and acoustic nerves. Until further research illuminates this matter, it appears sensible to include hyperostotic bone within radiation therapy portals when this can be accomplished safely.

The sections below were accordingly amended:

**Section 6.4.2.1:** The following statement was added: “However, this will not be permissible with hyperostotic or directly invaded bone, in which settings the involved bone must be fully included within the GTV, and thus within its attendant CTV54.”

**Section 6.4.2.2:** The following statement was added: “As mentioned in section 6.4.2.1 above, target reduction will not be permissible with hyperostotic or directly invaded bone, in which settings the involved bone must be fully included within the GTV, and thus within its attendant CTVs.”

**Other Changes**

**Section 5.2.2:** The section was removed; it is not applicable to protocols without drug therapy. Subsequent sections were renumbered accordingly.

**Section 10.4 and Appendices VI, VII, and VIII:** The mailing address for the RTOG Biospecimen Resource was updated.
RTOG 0539, Phase II Trial of Observation for Low-Risk Meningiomas and of Radiotherapy for Intermediate- and High-Risk Meningiomas

Study Chair: C. Leland Rogers, MD; (801) 350-8400; leland@gammawest.com

RTOG 0539 was updated as follows:

Appendix I, Sample Consent, About Using Tissue/Blood/Urine for Research: In the 2nd-to-last paragraph, the title of the information sheet and the weblink were corrected.
SUMMARY OF CHANGES
Amendment #2: March 8, 2011
(Broadcast: March 15, 2011)

RTOG 0539, Phase II Trial of Observation for Low-Risk Meningiomas and of Radiotherapy for Intermediate- and High-Risk Meningiomas

Study Chair: C. Leland Rogers, MD; (801) 350-8400; leland@gammawest.com

RTOG 0539 has been amended as follows:
As mandated by CTEP, beginning April 1, 2011, this study will utilize CTCAE version 4.0 for AdEERS reporting of adverse events. Related changes were made to Section 6.9, 9th paragraph.

NOTE: All AE reporting on the study case report forms will continue to use CTCAE version 3.0.

Administrative/Editorial Changes
Cover Page: A document version history was added to the Cover Page per current RTOG standard.

Global: All weblinks to sub-pages of RTOG website, plus related explanatory text, were updated.

Section 5.2: Instructions were updated per current process.

Section 6.9, 5th to last paragraph: The paragraph beginning “AdEERS provides a radiation therapy (RT)-only pathway…” was deleted because it already is included earlier in the same section.

Section 10.9: In the H&E stained slide row, “per paraffin block” was added for consistency with Section 10.2.

Appendix II
- Due to table formatting errors, the time points for urine banking and serum/plasma banking were misaligned and rendered inconsistent with Section 10 and Appendix I/informed consent. The time points were realigned as originally intended as follows:
  - The time points for urine banking were corrected from pre-treatment, 1 month after the completion of RT, and 3 months after the completion of RT to pre-treatment, on the last day of RT, and 1 month after the completion of RT.
The time points for serum/plasma were corrected from pre-treatment, 3 months after the completion of RT, and at failure to pre-treatment, 1 month after the completion of RT, and at failure.

- An asterisk was added before “see Sections 11.2, 11.3, & 11.5 for details” to correlate with the asterisk listed after Brain MRI.
RTOG 0539, Phase II Trial of Observation for Low-Risk Meningiomas and of Radiotherapy for Intermediate- and High-Risk Meningiomas

Study Chair: C. Leland Rogers, MD; (801) 350-8400; leland@gammawest.com

RTOG 0539 has been updated as follows:

Sections 5.1, 6.3.2, and 13.4.2: Subsection numbering was corrected.
RTOG 0539, Phase II Trial of Observation for Low-Risk Meningiomas and of Radiotherapy for Intermediate- and High-Risk Meningiomas

Study Chair: C. Leland Rogers, MD; (801) 350-8400; leland@gammawest.com

RTOG 0539 has been amended as follows:

Cover Pages

- "Co-Chair" has been added after each Study Chair for clarity per current RTOG standard.
- Contact information was updated for Dr. Perry; related changes were made to the last paragraph of Section 10.2.
- Contact information was updated for Dr. Vogelbaum.
- Dr. Tsien has replaced Dr. Michalski as the Image-Guided Radiation Therapy Chair.
- The Physics Co-Chair designation was corrected to Medical Physicist.
- Dr. Lu was added as the Proton Therapy Physics Co-Chair.
- Dr. Shih was added as the Proton Radiation Oncology Co-Chair.

Schema Page: "Or Proton" added to Group II.

Eligibility Checklist, Step 1, page 1, question 18: Wording revised to include proton use due to database needs.

Section 1.9, last paragraph, 2nd sentence: Serum collection on the last day of radiotherapy (Groups II and III) and every 6 months post-radiation (all groups) was removed because it was included in error. The serum collection schedule in Section 1.9 is now consistent with the serum collection timeline provided in Section 10 and Appendices I and II.

Section 3.1.5: 2nd-to-last sentence revised for clarity and accuracy.

Section 3.2.8: Added because patients must be able to receive gadolinium.

Section 5.1.1.1.4: Statement concerning proton credentialing added.

Section 6.0

- The formatting/capitalization of the first 2 sentences was revised for consistency.
"Within 1 month of protocol enrollment" was clarified as "within 1 month of Step 2 registration" in the following places:
- Section 6.1.1.2, 3rd sentence
- Section 6.1.1.3, last sentence

Information concerning use of photons and RBEs was added in the following places:
- Section 6.0, 1st sentence, 1st paragraph, last sentence; 2nd paragraph
- Section 6.1.1.2, 1st, 2nd, and 4th sentences
- Section 6.2, 1st and 3rd sentences
- Section 6.4.1
- Section 6.4.2.1, last sentence
- Section 6.4.2.1.1

Section 6.4.2.2, 5th-to-last sentence: "below" changed to "Section 6.5" for clarity
Section 6.4.2.2, 2nd-to-last last sentence: "respective PTV" changed to "PTV_{54}" for clarity

Section 10.2, 1st bullet: For clarity and emphasis, the formatting was modified and last 2 sentences were added.

Section 12.1
- Surgical Report (S2) and Surgical Pathology Report (S5) added because they were unintentionally omitted
- In section on "Scan data to be collected at RTOG HQ"
  - "Within 2 weeks of registration" was changed to "within 2 weeks of Step 2 registration" for clarity
  - Under "subgroup of recurrent disease without further surgery for recurrence," the first bullet was added due to collection needs
- Statement, "for proton submission; information available on the ATC website, added

Section 12.2
- Preliminary Dosimetry Information: Planning MRI SCAN added
- Web address for ITC updated

Appendix I/Sample Consent: In the Reproductive Risks section, the statement "Some methods [of birth control] might not be approved for use in this study" was deleted. Any standard method birth control is acceptable in this study.

Appendix II/Study Parameter Table
- Pre-Treatment section: "to" added in heading "Within 12 weeks prior to Step 2 Registration"
- Pre-Treatment section: "Registration" capitalized in headings throughout for consistency
• Follow-Up section: heading "3 months after the completion of RT (Groups II & III)" added; corresponding Brain MRI added to this column and deleted from "1 month after the completion of RT (Groups II & III)" column due to inadvertent error
• Follow-Up section: MMSE added to "1 month after the completion of RT (Groups II & III)" column due to inadvertent error
RTOG 0539, Phase II Trial of Observation for Low-Risk Meningiomas and of Radiotherapy for Intermediate- and High-Risk Meningiomas

Study Chair: C. Leland Rogers, MD; (801) 350-8400; leland@gammawest.com

RTOG 0539 has been updated as follows:

Cover Page: Phone number for RTOG Headquarters updated

Eligibility Checklist, Step 1, page 1: Question 18 moved from Eligibility Checklist, Step 2, page 4

Eligibility Checklist, Step 2, page 3: Sub-questions for Question 2 corrected to be protocol specific

Section 12.1 and Appendix II: Mini mental status exam added due to inadvertent omission

Sections 13.2.6-13.1.2.8: Numbering corrected

Sections 13.2.9: "Overall survival" changed to "survival rate at 3 years" for consistency with Section 2

Appendix II: Pre-treatment timeframes clarified as occurring prior to Step 2 registration

REFERENCES: Styled according to current RTOG standard