SUMMARY OF CHANGES
Amendment 4, Version Date: September 19, 2012

RTOG 1008, A Randomized Phase II Study of Adjuvant Concurrent Radiation and Chemotherapy Versus Radiation Alone in Resected High-Risk Malignant Salivary Gland Tumors

Co-Principal Investigators: Cristina Rodriguez, MD, 503-494-8535, rodrigcr@ohsu.edu
David J. Adelstein, MD, 216-444-9310, adelstd@ccf.org

RTOG 1008 has amended as follows:

The Medical Oncology evaluation, previously required within 4 weeks prior to *treatment* was amended to "within 4 weeks of *registration*". The following sections were amended for this change:

- **Eligibility Checklist**, page 1: Question 12 was added (and subsequent questions were appropriately renumbered).
- **Section 3.1.10** was added (and subsequent sections were appropriately renumbered).
- **Section 4.1.2** was deleted (and subsequent sections were appropriately renumbered).
- **Section 11.1.4** was added.
- **Appendix II**: The timeframe for this evaluation was amended to within 4 weeks prior to registration.

Other Changes

1st 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.

2nd Title page: This amendment was added to the Document History table.

Schema page: The 2nd "note" under the table was amended to clarify the basis for the stratification variable, "Nodal Status", in patients who have or don't have a neck dissection.

Section 5.1.2: The phrase, "or RTOG 1016", was added to the "note" to update this section with another active head and neck trial for which sites already may be credentialed.

Section 5.1.2.2 was amended to reflect that Dr. Kim (rather than Dr. Le) is now the Radiation Oncology Co-Chair.

Section 6.8 was amended to reflect that Dr. Kim is the Co-Chair responsible for RT Quality Assurance reviews.

Section 7.1.1: In paragraph 1, a sentence was added to provide instructions to sites regarding doses of cisplatin that are not given or which are held.

Section 7.3.1: In the 2nd and 3rd paragraphs, greater than (>) 1000/mm^3 was corrected to greater than or equal to (≥) 1000/mm^3.

Section 7.3.8: The phrase, "With the exception of grade 4 lymphopenia", was added to clarify that it is not necessary to discontinue cisplatin for this toxicity.

Section 7.4: The scoring mechanism (Per Protocol, Acceptable Variation, etc.) was amended to current RTOG standard text.

Section 7.5.2: In the 4th paragraph, the sentence beginning "Any pregnancy…" was amended to current RTOG standard text.

Section 11.1.3: The phrase, "or an MRI", was added to allow that imaging for tumor evaluation. This addition also was made in **Appendix I**, under "When you have finished radiation therapy" and in **Appendix II**, under "Assessments".

SUMMARY OF CHANGES
Update: March 6, 2012
(Broadcast 3/6/12)

RTOG 1008, A Randomized Phase II Study of Adjuvant Concurrent Radiation and Chemotherapy Versus Radiation Alone in Resected High-Risk Malignant Salivary Gland Tumors

Co-Principal Investigators: Cristina Rodriguez, MD, 216-445-8688, rodrigc@ccf.org
David J. Adelstein, MD, 216-444-9310, adelstd@ccf.org

RTOG 1008 was updated as follows:

Schema page: Text from the 2nd paragraph of Section 3.1.1 regarding pathologic interpretation of salivary gland malignancies was added below the table as a "note" for emphasis and clarity.

SUMMARY OF CHANGES
Amendment 3, Version Date: February 27, 2012

RTOG 1008, A Randomized Phase II Study of Adjuvant Concurrent Radiation and Chemotherapy Versus Radiation Alone in Resected High-Risk Malignant Salivary Gland Tumors

Co-Principal Investigators: Cristina Rodriguez, MD, 503-494-8535, rodrigcr@ohsu.edu
David J. Adelstein, MD, 216-444-9310, adelstd@ccf.org

RTOG 1008 has amended as follows:

Eligibility has been expanded to include patients with salivary gland carcinomas involving the major (parotid, submandibular, or sublingual glands) and minor salivary glands of the head and neck with the following histologies: intermediate or high-grade mucoepidermoid carcinoma; intermediate or high-grade adenocarcinoma or salivary duct carcinoma; high-grade acinic cell carcinoma or high-grade (>30% solid component) adenoid cystic carcinoma.

The expansion of eligibility was done in recognition that these additional histologic subtypes, originating in both major and minor salivary gland cancers also have a very significant risk for disease recurrence after surgery. Inclusion of these patients will serve to increase accrual and will make this trial available to additional groups of patients who might potentially benefit.

The protocol was amended as follows for this change:

- **Schema page**: The "Histology" stratification variable was amended in the table, and "Patient Population" was amended to correspond to the table.
- **Eligibility Checklist, page 1**: Question 1 was amended, and Question 15 was deleted (and subsequent questions were appropriately renumbered).
- **Eligibility Checklist, page 3**: Question 25 was amended.
- **Section 1.1**, 3rd paragraph: The last sentence was deleted.
- **Section 3.1.1** was amended.
- **Section 3.2.2** was deleted (and subsequent sections were appropriately renumbered).
- **Sections 6.4.1.1 and 6.4.1.2**: In the 1st paragraph, the 1st sentence was amended. In the 2nd paragraph, the last sentence was added.
- **Section 6.4.1.3**, "Minor Salivary Gland Cancer", was added (and subsequent sections were appropriately renumbered).
- **Section 8.1**: The 3rd paragraph was added.
- **Section 13.3**: The variables for histology were amended.
- **Section 13.4**: In the 3rd sentence, the word, "major" was deleted prior to "salivary gland tumor".
- **Appendix IV**: A "note" was added under "Major Salivary Glands" regarding staging of minor salivary gland cancers.

<u>Other changes</u>:
1st Title page: Dr. Kim was added as Radiation Oncology Co-Chair. Dr. Le will serve as the Correlative Studies Co-Chair (she will no longer also serve as Radiation Oncology Co-Chair).

2nd Title page: The Document History table was updated for this amendment, and the version date was updated.

Section 3.2.3 was deleted as it was unnecessarily redundant, and the corresponding question (#16) on page 1 of the **Eligibility Checklist** also was deleted (and subsequent questions were appropriately renumbered).

Appendix I: Under "Where can I get more information", the TTY was deleted at CTEP's request.

SUMMARY OF CHANGES
Amendment 2, Version Date: October 26, 2011

RTOG 1008, A Randomized Phase II Study of Adjuvant Concurrent Radiation and Chemotherapy Versus Radiation Alone in Resected High-Risk Malignant Salivary Gland Tumors

Co-Principal Investigators: Cristina Rodriguez, MD, 503-494-8535, rodrigcr@ohsu.edu
David J. Adelstein, MD, 216-444-9310, adelstd@ccf.org

RTOG 1008 has amended as follows:

The **1st title page** was amended to reflect the change in affiliation of the Co-Principal Investigator, Cristina Rodriguez, MD. On the **2nd title page**, the "Activation Date" and "Update Date" were removed, as this information is provided in the Document History table. The "Version Date" remains for clarity.

Section 4.1.6 was revised to indicate that the pretreatment audiogram only is required for patients randomized to Arm 1, radiation therapy and cisplatin. This change also was made in **Appendix I**, under "Before you begin the study" and in **Appendix II**.

Section 7.2: A reference to the package insert was added to amend this section to current RTOG standard. In addition, the subsections, 7.2.1, "Formulation", and 7.2.4, "Storage and Stability", were updated.

Section 7.6: The table heading and table were replaced with those currently required by CTEP.

Section 10.7: The street address for the Biospecimen Resource was updated. This change also was made in **Appendices V and VI**.

Section 11.1.3: The CT scan of the neck at 6 months from the start of radiation therapy is unnecessary and was deleted. This change also was made in **Appendix I** under "When you have finished radiation therapy".

The following changes were made in **Appendix I:**

- Under "Will my medical information be kept private?", the last 3 paragraphs were added to update the consent form to current NCI standards.
- Under "About Using Tissue and Blood for Research", in the 3rd paragraph, the title of and link to the information sheet were updated.

Appendix II: The timeframe for the "Surgical Eval" was corrected from 4 to 6 weeks prior to treatment to be consistent with changes made to Section 4.1.3 in Amendment 1.

SUMMARY OF CHANGES
Update: August 5, 2011
(Broadcast 8/5/11)

RTOG 1008, A Randomized Phase II Study of Adjuvant Concurrent Radiation and Chemotherapy Versus Radiation Alone in Resected High-Risk Malignant Salivary Gland Tumors

Co-Principal Investigators: Cristina Rodriguez, MD, 216-445-8688, rodrigc@ccf.org
David J. Adelstein, MD, 216-444-9310, adelstd@ccf.org

RTOG 1008 will be included on CTSU's menu of studies as of August 8, 2011 and has been updated for implementation of CTSU's Oncology Patient Enrollment Network (OPEN). The following changes were made:

- **Title pages**: CTSU's logistics and contact information were added in 2 text boxes on the 2nd and 3rd pages.
- **Eligibility Checklist**, page 3: Questions 24, 25, 26, and 27 were updated to be CDE compliant for database purposes.
- **Section 5.4**, "Regulatory Pre-Registration Requirements", was updated.
- **Section 5.4.1.1** was added.
- **Section 5.5**, "Registration", was updated;
- **Appendix I**, under "Will my medical information be kept private?": CTSU was added as an organization that may look at and/or copy the patient's medical records.

SUMMARY OF CHANGES
Amendment 1, Version Date: May 4, 2011
(Broadcast 5/12/11)

RTOG 1008, A Randomized Phase II Study of Adjuvant Concurrent Radiation and Chemotherapy Versus Radiation Alone in Resected High-Risk Malignant Salivary Gland Tumors

Co-Principal Investigators: Cristina Rodriguez, MD, 216-445-8688, rodrigc@ccf.org
David J. Adelstein, MD, 216-444-9310, adelstd@ccf.org

RTOG 1008 has amended as follows:

Urine will not be collected for banking. The following sections have been amended for this change: **Index page** (Appendix VII deleted); **Eligibility Checklist**, page 3 (questions 21 and 24 were deleted); **Sections 10.3.3, 10.3.3.1** (deleted); **10.3.5, 10.4, 10.6**, **Appendix I** (under "Consent Form for Use of Tissue and Blood for Research"), **Appendix II**, and **Appendix VII** (deleted).

Title page: Dr. Dignam's e-mail address was updated. In addition, a Document History table was added on the 2nd title page to amend the protocol to current RTOG standards.

Section 4.1.3: The timeframe for the surgical evaluation was amended from 4 to 6 weeks to provide investigators with more time to complete this assessment.

Section 5.4.1: The link to the CTSU-IRB/REB Certification Form was updated.

Section 5.4.3.1: The link to information for international sites was updated.

Section 5.5.1: The link to the Password Authorization Form (2nd paragraph) and the e-mail address for web support (6th paragraph) were updated.

Section 6.3.2: In the last sentence, the symbol for less than (<) prior to "3 mm slice thickness" was corrected to the phrase, "less than or equal to".

Section 6.5: The 1st paragraph concerning mandatory critical structures was added to provide information to site investigators.

Section 6.5.2: The 1st sentence was added to refer investigators to Sections 6.1.1 and 6.1.2 for detailed dose specifications. In addition, in the 3rd sentence, the word, "sequential", was added prior to "boost" for clarity.

The following changes were made in **Section 6.5.3**:

- A "note" was added as the 1st sentence referring investigators to Section 6.5 for mandatory normal tissue constraints.
- Section 6.5.3.8: The word, "Dmean", was added after < 35 Gy for clarity.
- Section 6.5.3.13: The word, "keel", was corrected to "keep".
- Section 6.5.3.16: In the last sentence, the word, "dose", was corrected to "volume".

Section 7.3.2: In the 4th paragraph, greater than 75,000/mm^3 was corrected to greater than or equal to 75,000/mm^3.

Section 7.5: The link to SAE definitions on the RTOG web site was updated.

Section 7.5.3: This section was amended as required by CTEP to instruct sites to report AML or MDS via AdEERS.

Section 10.2.2: In the "note", the phrase, "a 2 mm core of the block" was amended to "two 2 mm cores of the block" in order to collect sufficient tissue specimens.

Section 10.3.2.1: In item "c", the centrifuge speed was amended from "3000g" to "~2500g" and the word, "preferred", was added after "Celsius" at the request of the RTOG Biospecimen Resource. These changes also were made in Section 10.3.2.3.

Section 10.5: The phrase, "frozen specimens", was added to the 1st sentence to amend it to current RTOG Biospecimen Resource standard text.

Section 10.6: The text in the "Submitted as" column for serum, plasma, and DNA was amended to current RTOG Biospecimen Resource standard text.

Section 10.8: The link to the reimbursement and case credit schedule was updated.

Section 10.9: The link to the Tissue Consent FAQs was updated.

Section 11.4.1.1: The link to the FACT web site was corrected.

The following changes were made in **Appendix I**:

- Under "During the study", the paragraph and the 2 bulleted items were amended to indicate that weekly blood tests are required for Group 1 (Arm 1, radiation and cisplatin) patients only and that evaluation of adverse events is required for both groups (arms).
- Under "When you have finished radiation therapy":
  - The heading, "At 3 months from the end of treatment and at 6, 9, 12, and 24 months from the start of treatment", was corrected to include 18 months to be consistent with Appendix II.
  - The heading, "At 3 months from the end of treatment and at 6, 12, and 24 months from the start of treatment, then as your doctor recommends", was corrected to include 9 months to be consistent with Appendix II.
  - The heading, "Once a year during years 3-4", was corrected to "Twice a year during years 3-4", to be consistent with Appendix II.
- Under "Study Plan", the description of treatment for Group 1 was amended to clarify that patients receive radiation therapy for 6-7 weeks and cisplatin for 7 weeks.
- Under "How long will I be in the study?", in the 2nd sentence, the phrase, "at the end of radiation therapy", was deleted and in the 3rd sentence, "18", was added to correct the follow-up schedule to be consistent with Section 12.0
- Under the risks associated with radiation therapy, the last 2 risks under "Less Likely, but serious" were moved to a "Rare, but serious" category.
- Under "About Using Tissue, Blood, and Urine for Research": In the 2nd paragraph, the title of and the link to the information sheet were updated.

The following changes were made in **Appendix II**:

- Under "Weekly", the requirement for the CBC and creatinine were amended to "For Arm 1" only.
- Under "Follow Up", the column titled, "6, 9, 12 mos. from start of RT" was corrected to "6, 9, 12 & 18 mos. from the start of RT".
- Under "During Treatment", an "X" was added to indicate that QOL/PROs should be administered "At end of RT" to be consistent with Section 11.4.

SUMMARY OF CHANGES
Update: November 3, 2010
(Broadcast: 11/3/10)

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Co-Principal Investigators: Cristina Rodriguez, MD, 216-445-8688, rodrigc@ccf.org
David J. Adelstein, MD, 216-444-9310, adelstd@ccf.org

RTOG 1008 has been updated as follows:

Section 6.6.1, "Additional Documentation Requirements for IGRT Treatment Approach", was deleted, as it was included in error and is not necessary for this trial.

Section 8.0: The timeframe for the start of treatment after surgery was corrected from 8 weeks to 10 weeks to be consistent with the timeframes for start of treatment in Sections 6.0 and 7.0.

Section 12.1: The schedules for the Treatment Form (TF) and the Follow-up Form (F1) were updated. In addition, the schedule for the quality of life forms below the F1 was updated.

Section 13.2.8: The schedule for the quality of life forms was updated to correspond to changes made in Section 12.1.