For Amendment 9 to: RTOG 0234, A Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 (Cetuximab) For Advanced Squamous Cell Carcinoma of the Head and Neck

NCI/Local Protocol #: RTOG-0234/RTOG 0234

NCI Protocol Version Date: January 26, 2016

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title page</td>
<td>• The Senior Statistician’s street address and e-mail address were amended.</td>
</tr>
<tr>
<td></td>
<td>• The version date and amendment number were changed for this amendment.</td>
</tr>
<tr>
<td></td>
<td>• The text and textbox below the version date were amended to current NRG Oncology standard text.</td>
</tr>
<tr>
<td>Index page</td>
<td>Appendix V was deleted (and the subsequent appendix appropriate renumbered) to be consistent with the deletion of the former Appendix V (see below).</td>
</tr>
<tr>
<td>1.6 and 1.7</td>
<td>Throughout these sections, “acneform” was corrected to “acneiform”.</td>
</tr>
<tr>
<td>5.2.3</td>
<td>This section was deleted since it is no longer applicable. Patients have completed treatment, and ordering of cetuximab is no longer necessary.</td>
</tr>
<tr>
<td>5.3.1</td>
<td>In the 1st paragraph, the parenthetical phrase was deleted since ordering of cetuximab is no longer necessary.</td>
</tr>
<tr>
<td>5.4.1</td>
<td>In the last paragraph, “BMS” was replaced with “Eli Lilly and Company or its local affiliate”. Eli Lilly and Bristol-Myers Squibb have jointly decided that Lilly or its local affiliate will assume sole responsibility for commercialization and medical activities for cetuximab in the U.S., Canada, and Puerto Rico.</td>
</tr>
<tr>
<td>5.4.2</td>
<td>This section was deleted (and the subsequent section was appropriately renumbered) since it is no longer applicable. Patients have completed treatment, and ordering of cetuximab is no longer necessary.</td>
</tr>
<tr>
<td>5.5.1</td>
<td>In the 1st paragraph, “BMS” was replaced with “Eli Lilly and Company or its local affiliate”.</td>
</tr>
<tr>
<td>7.2.1</td>
<td>“Bristol-Myers Squibb” was replaced with “Eli Lilly and Company or its local affiliate”, and contact information for Eli Lilly was provided.</td>
</tr>
<tr>
<td>7.2.2</td>
<td>“Bristol-Myers Squibb” was replaced with “Eli Lilly and Company or its local affiliate”.</td>
</tr>
<tr>
<td>7.2.7</td>
<td>This section, “Drug Ordering”, was deleted (and the subsequent section was appropriately renumbered) since it is no longer applicable. Patients have completed treatment, and ordering of cetuximab is no longer necessary.</td>
</tr>
<tr>
<td>7.2.8</td>
<td>“BMS” was replaced with “Eli Lilly and Company or its local affiliate”, and contact information for Lilly was added.</td>
</tr>
<tr>
<td>Section</td>
<td>Change</td>
</tr>
<tr>
<td>---------</td>
<td>--------</td>
</tr>
</tbody>
</table>
| 7.7     | • Throughout this section, “RTOG Headquarters” and “RTOG” were replaced with “NRG Oncology” or deleted, as applicable.  
• In the last paragraph of Section 7.7.3, the last sentence was added concerning reporting of SAEs to Eli Lilly. |
| 10.1.2  | Appendix VI was amended to Appendix V to be consistent with the deletion of the former Appendix V (see below). |
| 12.0    | “RTOG Headquarters” was amended to “NRG Oncology” and the street address also was amended. |
| Appendix I, sample consent | • Under “What about Confidentiality?”, “the Radiation Therapy Oncology Group” was amended to NRG Oncology.  
• Under “What about Confidentiality?” and “What are the Costs?”, “Bristol-Myers Squibb” and “Imclone Systems Incorporated” were replaced with “Eli Lilly and Company or its local affiliate”.  
• Under “What Are My Rights as a Participant”, “RTOG” was replaced with “NRG Oncology” or deleted, as appropriate. |
| Appendix V | This appendix, “C225 (Cetuximab) Clinical Supply Shipment Request”, was deleted (and the subsequent appendix appropriately renumbered) since it is no longer applicable. Patients have completed treatment, and ordering of cetuximab is no longer necessary. |
For Amendment 8 to: RTOG 0234, A Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 (Cetuximab) For Advanced Squamous Cell Carcinoma of the Head and Neck

NCI/Local Protocol #: RTOG-0234/RTOG 0234

NCI Protocol Version Date: April 3, 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 page | • As required by CTEP, “Radiation Therapy Oncology Group” was replaced with “NRG Oncology”.
• Contact information for Drs. Harari, Kies, Myers, and Rosenthal was updated.
• It was noted that Dr. Ang is deceased, and the contact information for him was removed.
• The version date and amendment number were changed for this amendment. |
| Schema page | As required by CTEP, “Radiation Therapy Oncology Group” was replaced with “NRG Oncology”. |
| 6.9 and 7.7.1 | The link to CTCAE, v. 4 was updated. |
| 7.7.2 | The date and link to the NCI Guidelines were updated. |
| 7.7.3 | In the 2nd paragraph, the sentence below the bulleted items was deleted, as the correct information is provided in Section 7.7.2. |
| Sample Consent | No changes. |
SUMMARY OF CHANGES
Update: July 21, 2011
(Broadcast 7/21/11)

RTOG 0234, “A Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 (Cetuximab) For Advanced Squamous Cell Carcinoma of the Head and Neck”

Study Chair: Paul M. Harari, MD, 608-263-8500, FAX 608-263-9167, Harari@humonc.wisc.edu

RTOG 0234 has been updated as follows:

In amendment 6 (broadcast on 2/24/11), a note in Section 10.0 referring sites to RTOG 0514 was deleted as 0514 has been closed. Section 3.1.9, which also refers sites to RTOG 0514, has now been deleted (and the subsequent section was appropriately renumbered). This is a correction to make the protocol consistent with changes made in amendment 6, not a change to eligibility criteria.
RTOG 0234, "A Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 (Cetuximab) For Advanced Squamous Cell Carcinoma of the Head and Neck"

Study Chair: Paul M. Harari, MD, 608-263-8500, FAX 608-263-9167, Harari@humonc.wisc.edu

RTOG 0234 has been amended as follows:

As mandated by CTEP, Sections 6.9, 7.7, and 7.8 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 7.7.4: This section was amended as required by CTEP to instruct sites to report AML or MDS via AdEERS.
SUMMARY OF CHANGES
Update: March 2, 2011
(Broadcast 3/2/11)

RTOG 0234, “A Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 (Cetuximab) For Advanced Squamous Cell Carcinoma of the Head and Neck”

Study Chair: Paul M. Harari, MD, 608-263-8500, FAX 608-263-9167, Harari@humonc.wisc.edu

RTOG 0234 has been updated as follows:

Appendix I: Under “What is involved in the study?”, in the last table, the 1st column of the last row was corrected to be consistent with the changes made to long-term follow up in amendment 6 (from a total of 6 years to annual follow up for the patient’s lifetime).
RTOG 0234, “A Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 (Cetuximab) For Advanced Squamous Cell Carcinoma of the Head and Neck”

Study Chair: Paul M. Harari, MD, 608-263-8500, FAX 608-263-9167, Harari@humonc.wisc.edu

RTOG 0234 has been amended as follows:

Long-term follow up has been amended from a total of 6 years to annual follow up for the patient’s lifetime, the current RTOG standard. The following sections were changed: **Section 11.1**, footnote “i”, **Section 12.1**, and **Appendix I**, under “How long will I be in the study?”.

Other Changes

**Title page**: The Senior Statistician was added to update the protocol to current RTOG standards.

**Section 10.0**: The “note” referring sites to RTOG 0514 was deleted as that study has been closed.

**Section 12.1**: The Adverse Event Form (AE) was deleted, as adverse events are collected on the Follow-up Form (F1).
RTOG 0234, "A Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 (Cetuximab) For Advanced Squamous Cell Carcinoma of the Head and Neck"

Study Chair: Paul M. Harari, MD, 608-263-8500, FAX 608-263-9167, Harari@humonc.wisc.edu

RTOG 0234 has been updated as follows:

**Title page**: Dr. Hammond’s e-mail address was updated.

**Section 10.1**: The phrase, "tissue bank samples" was updated to "banked samples".

**Sections 10.1.2, 10.1.2.2, 10.1.2.6, 10.2, 10.3.1, and Appendix VI**: References to the RTOG Tissue Bank were updated to RTOG Biospecimen Resource.

**Section 10.1.3 and Appendix VI**: The shipping address and contact information was updated from LDS Hospital to the RTOG Biospecimen Resource.
RTOG 0234, “A Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 (Cetuximab) For Advanced Squamous Cell Carcinoma of the Head and Neck”

Study Chair: Paul M. Harari, MD, 608-263-8500, FAX 608-263-9167, Harari@humonc.wisc.edu

RTOG 0234 has been amended as follows:

Bristol-Myers Squibb (BMS) has requested that updated information be added to studies involving cetuximab and radiation treatment.

Information about cetuximab pharmacokinetics was added to Section 1.2 (two sentences at the end of the first paragraph).

In addition, information regarding clinical studies of cetuximab in head and neck cancer, safety of cetuximab in head and neck cancer clinical trials, and late radiation toxicity was added as Sections 1.5, 1.5.1, 1.5.2, 1.6, and 1.6.1. Subsequent sections were appropriately renumbered (as Sections 1.7, 1.8, 1.9, and 1.10.)

Other Changes
The e-mail address for the RTOG Tissue Bank was updated in Section 10.1.3 and Appendix VI.
SUMMARY OF CHANGES
Amendment 4, Version Date: March 27, 2006

RTOG 0234, “A Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 (Cetuximab) For Advanced Squamous Cell Carcinoma of the Head and Neck”

Study Chair: Paul M. Harari, MD, 608-263-8500, FAX 608-263-9167, Harari@humonc.wisc.edu

RTOG 0234 has been amended as follows:

**Title page:** Dr. Hammond’s e-mail address was updated.

**Index:** An entry was added for Appendix VI—Specimen Plug Kit and Instructions.

**Section 7.5.3:** The table of dose modifications for non-hematologic toxicity was revised as follows:
- The reference to footnote g after “Grade 4/Other” in the first column was deleted as was footnote g itself because this information is given in Section 7.5.4. The remaining footnotes and footnote references were renumbered accordingly.
- For clarity, under “Fatigue (Asthenia)” in the first column, “≥ Grade 3” was changed to “Grade 3-4.”
- The modification for Cetuximab Dose in the Fatigue (Asthenia) row was changed from “Maintain dose levels” to “Decrease by 1 dose level.” This is a practical necessity to avoid radiotherapy treatment breaks.
- For clarity, under “Neuropathy” in the first column, the ≥ symbol before “Grade 3-4” was deleted.
- Footnote l (lower case “ell”) after “Other non-hematologic Toxicities” in column 1 was deleted because this footnote does not exist.
- “See footnote J” in the Neuropathy row was changed to “See footnote i” in columns 2 and 3.
- The phrase “including mucocutaneous toxicity” was deleted after “Other: Mucositis in RT field” in column 1 because skin rash is discussed separately.

**Section 7.5.4:** The table was revised as follows:
- The sentence “Maintain the cetuximab dose and infusion rate” in the Grade 1 row and Cetuximab column was changed to “Maintain the cetuximab dose but slow the infusion rate by 50%.” The study chairs feel that this is better practice.
- For completeness, in the Grade 4 row for Docetaxel, “NO FURTHER STUDY DRUG THERAPY” and guidelines for appropriate medical therapy and observation were added.

**Section 10.1.2.2:** Under “NOTE”:
- A cross-reference to Section 10.13 was added.
- The sentence “An example of the kit and instructions may be found in Appendix VI” was added.
- The sentence “If both of these tissue types are unavailable, 15 stained slides may be submitted” was deleted.
- The sentence “Blocks, cores, or slides must be clearly labeled…” was changed to “Tissue blocks or cores must be clearly labeled…”

**Section 10.1.2.3:** The sentence “A Pathology Report documenting that the submitted blocks, cores, or slides contain tumor…” was changed to “A Pathology Report documenting that the submitted blocks or cores contain tumor…”

**Section 10.1.2.4:** A note was added instructing institutions to clearly indicate on the Specimen Transmittal Form the type of specimen being sent (pre-treatment or post-treatment) and the collection time frame (“Procedure Date”).
SUMMARY OF CHANGES
Amendment 4, Version Date: March 27, 2006
RTOG 0234 (Continued)

Section 10.1.2.6: For clarification, text was added regarding submission of tissue samples from tumors that recur after study treatment.

Section 10.1.3: The contact information for tissue submissions was updated.

Section 11.1: To improve patient safety, AST/ALT and creatinine were added to footnote e, the list of assessments to be done weekly during RT.

Appendix IA: Under “Why Is This Study Being Done,” the sentence “C225 was approved…, but is an experimental treatment for patients with head and neck cancer” was changed to “C225 was approved…, and when this study began, C225 was an experimental treatment for patients with head and neck cancer.” Following that sentence, a new sentence was added: “In 2006, the FDA approved C225 for the treatment of head and neck cancer.”

Appendix IB: Under “About Using Tissue for Research,” the sentence “If your tumor comes back after you complete study treatment, we would like to keep some of that tumor tissue as well” was added. The following sentence was changed from “If you agree, this tissue may be used…” to “If you agree to allow us to keep your tissue, it may be used…”

Appendix VI—Specimen Plug Kit and Instructions was added.

An amended protocol is available on the RTOG Web site, http://www.rtog.org
SUMMARY OF CHANGES
Update: February 2, 2006

RTOG 0234, “A Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 (Cetuximab) For Advanced Squamous Cell Carcinoma of the Head and Neck”

Study Chair: Paul M. Harari, MD, 608-263-8500, FAX 608-263-9167, Harari@humonc.wisc.edu

RTOG 0234 has been updated as follows:

Section 5.1 deleted from protocol; 3D-CRT credentialing was included in error and is not required for this study. Subsequent sections were appropriately renumbered. Section renumbering is also reflected on Schema Page, Section 5.2.3, and Appendix V.

Section 6.7.1: Added the phrase “IMRT RT Quality Assurance reviews will be remotely performed by the ITC (see section 12.2).”

Section 7.2.7: Changed initial drug shipment to 24 vials.

Section 12.2: Changed the “T2” form to “DDSI.”

An updated protocol is available (no password required) on the RTOG Web site, http://www.rtog.org
SUMMARY OF CHANGES
Amendment 3, Version Date: November 17, 2005

RTOG 0234, “A Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 (Cetuximab) For Advanced Squamous Cell Carcinoma of the Head and Neck”

Study Chair: Paul M. Harari, MD, 608-263-8500, FAX 608-263-9167, Harari@humonc.wisc.edu

RTOG 0234 has been amended as follows:

IMRT has been added as an optional radiation therapy technique, at the request of several RTOG sites and as this technique has become more standard in the treatment of head and neck cancer. The following changes were made for this addition:

- **Schema page:** “Use of IMRT” was added as a stratification variable. A footnote, “d”, was added next to “Randomize”, referring sites to Sections 5.1-5.3 for pre-registration requirements; the order of the other footnotes on this page was amended appropriately. A note was added below the footnotes requiring treating physicians to determine if IMRT will be used prior to the site registering the patient.
- **Eligibility Checklist:** On page 3, Question 23 was added to collect use of IMRT.
- **Section 1.8:** was added to provide rationale for permitting use of IMRT and to discuss the lack of enhancement on the primary endpoint.
- **Section 5.2:** Pre-registration requirements for IMRT were added. Subsequent sections were appropriately re-numbered, and references to those section numbers were amended throughout the protocol.
- **Section 6.0:**
  - The “Note” in Section 6.0 was amended to indicate that IMRT is permitted.
  - Section 6.1.1: The third through fifth paragraphs were added.
  - Section 6.1.2 was revised.
  - Sections 6.1.3 and 6.1.4: The last sentence, concerning a simultaneous boost, was added.
  - Section 6.2: In the first sentence of the first paragraph, the word “conventional” was added prior to “simulator”.
  - Sections 6.2.1, 6.2.2, and 6.2.3, describing volume definitions, were added.
  - Section 6.3: The phrase, “for 3D Radiotherapy”, was added to the heading.
  - Section 6.3.1: The last sentence, barring IMRT, was deleted.
  - Section 6.4: The heading was revised.
  - Section 6.5 was added, and subsequent sections were appropriately re-numbered.
  - Section 6.7.1: The table below the paragraph was revised.
- **Section 12.1:** The phrase, “for non-IMRT Approaches: (For IMRT, see Section 12.2)”, was added next to Preliminary and Final Dosimetry Information.
- **Section 12.2** was added, and the subsequent section was appropriately re-numbered.
- **Section 13.3:** The last paragraph was added describing the possible impact of IMRT on the primary endpoint and toxicity.
- **Section 13.4:** Use of IMRT was added as a stratification variable at the end of the last sentence.
- **Section 13.6.3:** A sentence was added at the end of the last paragraph describing toxicity reporting.
- **Appendix IA:** Under “What Is Involved in the Study?”, the duration of radiation therapy treatments was amended from “about 20 minutes” to “about 20-30 minutes”.

Other Changes

**Eligibility Checklist:**
- Page 1, Question 9: The word, “symptomatic”, was replaced with “active” to correctly correspond to Section 3.2.8.
- Page 2, Question 25: The response was corrected from “Y” to “Y/N”.
- Page 3: In the final paragraph, the phrase, “prior to calling RTOG”, was updated with the current standard, “prior to web registration”.
Section 3.1.1.1: In the “NOTE”, the phrase, “early stage” was deleted. The criteria in this section need to apply to all tonsillar cancer patients, to prevent patients from being over treated.

Section 3.1.5: The phrase, “AST and ALT”, was amended to “AST or ALT” to correspond to the table below.

Section 3.1.9, encouraging participation in RTOG 0514, was added, and the subsequent section was appropriately renumbered.

Section 5.1 was added to describe pre-registration requirements for a 3D CRT treatment approach. Subsequent sections were appropriately renumbered, and references to those section numbers were amended throughout the protocol.

Section 5.3: The phrase, “for Cetuximab” was added to the heading to differentiate it from Sections 5.1 and 5.2. Section 5.3.3 was updated to RTOG standard. These changes also were made in Section 7.2.7 and Appendix V.

Section 5.4.1: To update this section to RTOG standard, the sixth paragraph was added and two sentences were added to the last paragraph.

Section 6.6.1: In the first sentence, the last word, “mucositis”, was replaced by “in-field mucous and/or skin toxicity” to include skin toxicities. The last sentence, referring sites to Section 7.5.3 for information concerning resumption of cetuximab, was added.

Section 6.8, Radiation Toxicity Reporting, was amended, referring sites to Section 7.8 for adverse event reporting requirements.

Section 7.0: In the first sentence of the first paragraph, the parenthetical phrase was amended to “within seven weeks” for clarity. In the first sentence of the second paragraph, the phrase, “with C225 and chemotherapy” was added after “systemic therapy” for clarity.

Section 7.1.3: In the second bulleted item, the instructions concerning premedication with Decadron® were amended to more closely reflect standard practice.

Section 7.5: A note was added to provide instructions regarding adjustments in electrolyte therapy.

In the Section 7.5.2 table, footnote “f” was corrected to footnote “e”. The content of the table was not changed.

The following changes were made in the Section 7.5.3 table:

- The rows concerning "Renal Calculated Creatinine Clearance" were deleted, as the majority of treating physicians will use the serum creatinine levels to monitor cisplatin-related renal toxicity. In addition, there is an inconsistency in reducing the cisplatin dose based on a calculated clearance of < 50 mL/min (a dose reduction would be indicated in this circumstance, but if the clearance was very low, e.g., < 25 mL/min, then no further cisplatin should be given versus just one level dose reduction).
- In the first column, under “Other non-hematologic Toxicities”, the phrase, “Excluding Rash”, was deleted, as information concerning rash was added to the table.
- In the first column, under "Neuropathy", the phrase, “≥ grade 2” was corrected to “≤ grade 2”.
- Under “Other non-hematologic Toxicities”, the row, “Grade 4” was moved to the last row and was amended to read, "Grade 4/Other".
- Under “Other non-hematologic Toxicities”, the row, “Grades 2-4 (out of RT field that does not reverse to Grade 1 at time of treatment)”, was deleted, and was replaced with four
The following changes were made to the table in Section 7.5.4:

- Since the table is large and is, therefore, split between two pages, the section heading and the headings in the table were added at the top of the second page for clarity.
- In the table under the column, “CTCAE Grade”, the CTCAE v. 3.0 terminology for grades 1-4 infusion reactions was provided for clarity, and any descriptions of grades 1-4 were deleted under the column, “Cetuximab”.
- Under the column, “Cetuximab”:
  - The instructions for grade 1 reactions were rearranged for clarity, and the phrase, “or moderate”, was deleted to correctly differentiate grade 1 reactions from grade 2 reactions.
  - The first sentence of the instructions for grade 2 reactions was amended to specify that the rate of infusion be slowed by 50% and to make the medications given consistent with instructions in Section 7.1.3.
  - In the first sentence of the instructions of grade 4 reactions, the first word, “Severe”, was replaced with “Life-threatening” to correctly differentiate grade 4 reactions from grade 3 reactions.

Sections 7.5.5.1 and 7.5.5.2 were deleted as management of infusion reactions and treatment of drug fever are now addressed clearly in the Section 7.5.4 table. Subsequent sections were appropriately renumbered, as were references to those sections in the protocol text.

Section 7.5.5.2: Text for drug related rash management was added. The prior table, “Cetuximab Dose Modification Guidelines”, for acneform rash was deleted, as this information was added to the dose modification table for non-hematologic toxicity in Section 7.5.3.

Section 7.7 was amended from “Adverse Drug Reaction Reporting” to the RTOG standard description of “Adverse Events”, and the NCI mandated adverse event reporting requirements were added as Section 7.8.

Section 10.0: A note was added referring sites that also are participating in RTOG 0514, the Head and Neck Cancer Tissue/Specimen Bank, to that protocol for instructions.

Section 11.1: The row “Serum Chemistry Tests” and the row beginning “Electrolytes” were combined, and the row was amended to list all of the pretreatment laboratory studies (rather than refer sites to Section 3.1.4). Footnote “e” was amended to specify which lab studies are to be done “Weekly During RT”.

Section 11.2.1.4 was amended to clarify second primary neoplasms for sites. A reference (citation 43) was added; subsequent citations were re-numbered appropriately in the text, and the References section was amended accordingly.

Section 13.5: As recommended by the NCI (Larry Rubinstein, PhD), the threshold for early termination due to toxicity was raised from 12 (24%) to 14 (28%) among the first 50 patients “so as to more nearly achieve the stated statistical operating characteristics”.

Section 13.6: In the first sentence, the version of CDUS was updated from 1.1 to 3.0.

An amended protocol is available on the RTOG Web site, [http://www.rtog.org](http://www.rtog.org)
SUMMARY OF CHANGES
Update: April 5, 2005

RTOG 0234, “A Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 (Cetuximab) For Advanced Squamous Cell Carcinoma of the Head and Neck”

Study Chair: Paul M. Harari, MD, 608-263-8500, FAX 608-263-9167, Harari@humonc.wisc.edu

RTOG 0234 has been updated as follows:

Section 12.1: The “Surgical Consult Note” was deleted, as this information will be collected on the Operative Note (S2) and Surgical Path Report (S5) forms.

An updated protocol is available (no password required) on the RTOG Web site, http://www.rtog.org
RTOG 0234, “A Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 (Cetuximab) For Advanced Squamous Cell Carcinoma of the Head and Neck”

Study Chair: Paul M. Harari, MD, 608-263-8500, FAX 608-263-9167, Harari@humonc.wisc.edu

RTOG 0234 has been amended as follows:

In a recent Action Letter regarding the occurrence of hypomagnesemia in clinical trials with C225 (cetuximab), NCI mandated that serum magnesium monitoring be added to routine electrolyte monitoring. This monitoring was previously included in the protocol, but the table in Section 11.1 and footnote “e” were amended to ensure clarity. The study chairs reviewed the risks associated with cetuximab described in Appendix I, as mandated in NCI’s Action Letter, and determined that no additions/changes were necessary at this time.

Schema page: In the stratification factors, under “Risk Category”, footnote “d” was added next to “Positive margins”, referring to Section 3.1.1.1 for details about these margins.

Eligibility Checklist:
- Page 1: In question 13, the phrase, “over the past year” was added to correspond to Section 3.2.9. In question 22, the section referenced was amended to “Section 3.2.13” to correspond to changes made in Section 3.2.
- Page 2: Questions 24-26 were added to correspond to changes in Section 3.0, and the subsequent question was appropriately renumbered.

Section 1.1: In the second paragraph, the discussion of the results of RTOG 95-01 and EORTC 22931 was updated with current information.

Section 1.5 was amended by Bristol-Myers Squibb (BMS), supplier of cetuximab (C225), to be current with the Package Insert as follows:
- Section 1.5.1: In the third paragraph, “allergic reaction/hypersensitivity” was replaced with “infusion reaction”. In addition, the phrase, “as described in Section 10.3 of the Investigator Brochure” was deleted from the last sentence, as this may not be accurate if the brochure is updated. The two tables listing “Adverse Events in All Cetuximab Trials” were deleted and replaced with six paragraphs of text and a new table.
- Section 1.5.2 was amended.
- Section 1.5.4: In the heading, “Infusion” replaced “Allergic”, and the text in this section was amended.
- Section 1.5.5, “Pulmonary Toxicity”, was added.

Section 3.1: In Section 3.1.1.1, the last bullet, describing positive margins, was amended for clarity, and a note about the eligibility of early stage tonsil cancer patients was added. In Section 3.1.5, the heading, “AST or ALT” was added and “Alk Phos” was deleted as a row and added as a column for clarity.

Section 3.2: Sections 3.2.3 and 3.2.4 were added for clarity and to correspond to the prior advanced squamous head and neck study, RTOG 95-01, and subsequent sections were appropriately renumbered. At the request of BMS, Section 3.2.17 was added.

Section 5.1.3: At the request of BMS, a sentence was added to remind sites that regulatory documents must be received and approved by BMS before drug can be shipped. This sentence also was added to Section 7.2.7 and Appendix V.

(Continued on next page)
Section 7.0: In the second paragraph, the phrase, “loading dose” was replaced with “initial dose” at the request of BMS. In addition, two sentences were added at the end of the paragraph for clarity, and a reference to Section 9.0 was added.

Section 7.1.1:
- In the first paragraph: The phrase, “loading dose” was replaced with “initial dose” at the request of BMS. In addition, in the last sentence, the postoperative timeframe was amended.
- In the second paragraph: The first sentence was amended, deleting oral administration of cetuximab and replacing “allergic/hypersensitivity or cytokine reaction” with “infusion reaction”. In the second and third sentences, instructions were added about premedications.

Section 7.1.2:
- After “Weeks 2-7”, “IV” was added after the doses of C225 and cisplatin for clarity.
- In the second bullet, “Dexamethasone 20 mg IV” was deleted, “antibiotic” was corrected to “antiemetic”, and the last word, “only”, was deleted.
- In the third bullet, a phrase concerning chemotherapy administration was added.

Section 7.1.3:
- After “Weeks 2-7”, “IV” was added after the doses of C225 and cisplatin for clarity.
- Under “CAUTION”, “Allergic/hypersensitivity or cytokine release reactions” were replaced with “infusion reactions” at the request of BMS.

Section 7.2 was amended by Bristol-Myers Squibb (BMS), supplier of cetuximab (C225), to be current with the Package Insert as follows:
- In Section 7.2.1, the fourth sentence was added, and “or Package Insert” was added to the fifth sentence.
- Sections 7.2.2, 7.2.4, 7.2.5, and 7.2.7 were amended.
- The contact information for BMS was updated in Section 7.2.9.

Section 7.5.2:
- The instructions for the cetuximab dose for grades 3 and 4 neutropenia, for neutropenic fever, and for grades 3 and 4 thrombocytopenia were amended to “Maintain dose level”.
- In the instructions for docetaxel and cisplatin doses for grades 3 and 4 neutropenia and grades 2-4 thrombocytopenia, “continue” was replaced with “resume”.
- Footnotes “a” and “b” were deleted, and subsequent footnotes re-lettered appropriately.

Section 7.5.3:
- In the first column, a reference to footnote “a” was added after “NCI CTCAE Toxicity”.
- In the first column under “Renal-serum Creatinine”, the greater than or equal to symbol (≥) preceding “Grade 2” was deleted.
- In the first column, the asterisk (*) next to “Renal-serum Creatinine” and “Renal-Calculated Creatinine Clearance” was changed to a reference to footnote “b”. The sentence, “Choose one or the other study to assess renal function and base treatment decision”, previously indicated with an asterisk was made footnote “b”, and the prior footnote “b” text was deleted.
- In the first column, the phrase, “Excluding rash”, was added next to “Other non-hematologic Toxicities”.
- In the first column, instructions for ≥ grade 2 and ≥ grade 3-4 neuropathy were added.
- In the first column, the third row under “Other non-hematologic Toxicities”, (Grade 3-4 [out of RT field]), was deleted.
- In the second column, an instruction for the cetuximab dose for “Nausea/vomiting, ≥ Grade 3” was added, and the instruction for the cetuximab dose for “Other non-hematologic Toxicities, Grade 4” was amended.
- Footnotes “i” and “j” were added.  

(Continued on next page)
Section 7.5.4: In the heading, the table, and the text below the table, the phrases, “allergic reactions” or “hypersensitivity reactions”, were replaced with “infusion reactions”.

Section 7.5.5: At the request of BMS, the headings and text of Sections 7.5.5.1, 7.5.5.2, and 7.5.5.3 were amended. In addition, the diagram of Grade 3 skin toxicity was replaced with Section 7.5.5.4.

Section 7.5.6.3 (Stomatitis) was deleted, as stomatitis is an expected adverse event of chemoradiotherapy, and it would be inappropriate to interrupt therapy unless there are severe or life-threatening changes.

Section 7.5.6.4 (Peripheral Neuropathy) was deleted because grade 1-2 toxicity should not be an indication to discontinue chemotherapy. Guidelines for severe toxicity already are provided in Section 7.5.3.

Section 9.0: The Section 9.1 heading was deleted, and information regarding amifostine and pilocarpine was added.

Section 12.1: Two forms were added as due “Within 2 weeks of study entry”: the “Staging Diagrams (I6)” and the “Staging Diagram (nodes) [I7]”. “Surgical Consult Note” was added, due in the same timeframe as the Follow-up Form.

Section 13.2: The third paragraph was amended for clarity, and the fourth paragraph was amended to be consistent with Section 13.5.

Appendix IA:
- In the fifth paragraph under “Why Is This Study Being Done?”, the word, “tissue” was added after “your tumor” for clarity.
- In the third table under “What Is Involved In The Study?”:
  - Under “Weekly During Radiation Therapy”, “Physical exam” was replaced with “You will be seen by your doctor to monitor any side effects you may be having” to be more consistent with Section 11.1.
  - Under “Follow-up Visits”, “for three years” was replaced with “years 3 through 6” for clarity.

Appendix IB:
- To be consistent with the protocol text, the first paragraph under “About Using Tissue For Research” was amended and the second paragraph was deleted.
- In the first paragraph under “Things To Think About”, “left over tissue” was replaced with “tumor tissue”.
- Under “Risks”, the last sentence under “Physical Risks” was replaced with “Your doctor will discuss the risks of surgery with you” to be more consistent with the protocol text.

An amended protocol is available (no password required) on the RTOG Web site, http://www.rtog.org
RTOG 0234, “A Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 (Cetuximab) For Advanced Squamous Cell Carcinoma of the Head and Neck”

Study Chair: Paul M. Harari, MD, 608-263-8500, FAX 608-263-9167, Harari@humonc.wisc.edu

RTOG 0234 has been updated as follows:

- **Title Page** updated to reflect Dr. Ang’s new telephone and fax numbers.
- **Eligibility Checklist**, page 3, question 26 updated to include RTF number.
- **Section 12.1** - C3 form corrected to “Preoperative CT Scan Report”.

NOTE: This is an editorial/administrative change 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: http://www.rtog.org/
RTOG 0234, “A Phase II Randomized Trial of Surgery Followed by Chemoradiotherapy Plus C225 (Cetuximab) For Advanced Squamous Cell Carcinoma of the Head and Neck”

Study Chair: Paul M. Harari, MD, 608-263-8500, FAX 608-263-9167, Harari@humonc.wisc.edu

RTOG 0234 has been revised as follows:

The American College of Surgeons Oncology Group (ACOSOG) is participating in this study.

The following changes were made for ACOSOG participants:

- The ACOSOG Co-Chair was added to the title page;
- Question 26, page 3 of the Eligibility Checklist and Sections 3.3, 5.3, 5.4, 6.1.6, 7.1.4, and 12.2 were added;
- In Appendix IA, under “What About Confidentiality?”, ACOSOG was added to the organizations that may inspect and/or copy patient records.

Other changes:

Title page: The prior 800 number for RTOG Headquarters was deleted, as this number is no longer current. This number also was deleted from the table in Section 7.7.4. In addition, the address for RTOG Headquarters was updated in Sections 5.1.2 and 12.0.

The following changes were made to the Schema page:

- The symbols (+ and *) were re-formatted as footnotes (a-c);
- The timeframe for surgery, “within 7 weeks of randomization” was added as footnote a;
- Question 3, on page 1 of the Eligibility Checklist, and Sections 3.1.1.1 and 8.1 were revised to clarify this timeframe;
- The timeframe for radiation therapy (footnote c) was revised to “within 8 weeks after surgery”; Section 6.1.1 was revised to correspond and to clarify this timeframe.

Section 1.5.1: In the second paragraph, the reference to instructions for obtaining an Investigator's Brochure was corrected.

Section 5.1.1: The fax number for the CTSU Regulatory Office was corrected.

The email address for submission of the initial cetuximab shipment form was updated in Sections 5.1.3, 7.2.7, and in Appendix V.

Section 5.2.1: Instructions were added for obtaining a user name and password in order to register patients online.

Section 7.0 was revised to clarify the timeframe for C225 administration.

Section 7.5.3: The text in the table was revised for clarity.

Section 10.1.3: The email address for LDS Hospital was updated.

The following changes were made in the table in Section 11.1:

- The heading of the 5th column was corrected to “6 months from start of RT”;
- In the 2nd column, “Pre-Treatment”, the footnotes for CBC/Diff/PLT and Serum Chemistry Tests were corrected to “a”: Within 4 weeks prior to study entry;
- The dental evaluation during Follow Up was deleted, as this was inaccurate. This evaluation also was deleted from Appendix IA, under “What Is Involved In The Study?”.
Summary of Changes (Continued)

Appendix IA, under “How Long Will I Be In The Study?”, the timeframe for follow-up visits was revised to correspond to Sections 11.1 and 12.1.

Appendix V: The cetuximab shipment form was deleted and the web address for the updated form was provided.

A revised protocol is available (no password required) on the RTOG Web site, http://www.rtog.org