

For Amendment 10 to: RTOG 0522, A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) [Followed by Surgery for Selected Patients] for Stage III and IV Head and Neck Carcinomas

NCI/Local Protocol #: RTOG-0522/RTOG 0522

NCI Protocol Version Date: January 26, 2016

Section	Change
Title pages	<p>On the 2<sup>nd</sup> title page:</p> <ul style="list-style-type: none"> <li>The contact information for the Outcomes Co-Chair and the street address for the Senior Statistician were amended.</li> <li>This amendment was added to the Document History table.</li> <li>The text and textbox below the version date were amended to current NRG Oncology standard text.</li> </ul> <p>On the 3<sup>rd</sup> title page: In the text box, "RTOG Headquarters" and "the RTOG" were amended to "NRG Oncology".</p>
Index page	Appendix VIII was deleted (and the subsequent appendix appropriately renumbered) to be consistent with deletion of Appendix VIII (see below).
1.5	Throughout this section, "acneform" was corrected to "acneiform".
5.4.3	This section was deleted since it is no longer applicable. Patients have completed treatment, and ordering of cetuximab is no longer necessary.
7.3.6	"Bristol-Myers Squibb" 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.
7.3.7	This section, "Drug Ordering" was deleted (and subsequent sections appropriately renumbered) since it is no longer applicable. Patients have completed treatment, and ordering of cetuximab is no longer necessary.
7.3.8	The e-mail address for Bristol-Myers Squibb was replaced with Eli Lilly's contact information.
7.6 and 7.7	<ul style="list-style-type: none"> <li>Throughout these sections, "RTOG" was amended to "NRG Oncology" or deleted, as appropriate.</li> <li>Throughout these sections, all references to and discussion of "AdEERS" were amended to "CTEP-AERS".</li> </ul>
7.6.2	In the last paragraph, the last sentence was added concerning reporting of SAEs to Eli Lilly.
12.0	"RTOG Headquarters" was amended to "NRG Oncology" and the street address also was amended.
Appendix I, sample consent	<ul style="list-style-type: none"> <li>Under "Will my medical information be kept private?", "the Radiation Therapy Oncology Group" and "RTOG" were amended to "NRG Oncology". In addition, "The American College of Radiology Imaging Network" and "ACRIN" were amended to ECOG-ACRIN Medical Research Foundation, Inc.</li> <li>Under "Will my medical information be kept private?" and "What are the costs of taking part in this study?", "Bristol-Myers Squibb" was replaced with "Eli Lilly and Company or its local affiliate".</li> </ul>

Continued on next page

Appendix VIII	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
The former Appendix IX	In this appendix, amended to Appendix VIII: <ul data-bbox="560 378 1385 535" style="list-style-type: none"><li data-bbox="560 378 1385 441">• In the table, "RTOG "and "RTOG Headquarters were amended to "NRG Oncology" and the street address was amended.</li><li data-bbox="560 441 1385 535">• Under "Drug Procurement", the 2 bulleted items beneath item 4 were deleted since patients have completed treatment, and ordering of cetuximab is no longer necessary.</li></ul>

For Amendment 9 to: RTOG 0522, A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) [Followed by Surgery for Selected Patients] for Stage III and IV Head and Neck Carcinomas

NCI/Local Protocol #: RTOG-0522/RTOG 0522

NCI Protocol Version Date: January 14, 2014

Section	Change
1 <sup>st</sup> Title page	<ul style="list-style-type: none"><li>• As required by CTEP, the Principal Investigator has been changed. Since Dr. Ang is deceased, Dr. Rosenthal, the former Radiation Oncology Co-Chair for the U.S. now will serve as Principal Investigator/Radiation Oncology U.S.</li><li>• The affiliation and contact information for Dr. Schwartz was updated.</li><li>• “Study Chairs” was updated to the RTOG standard, “Study Team”.</li></ul>
2 <sup>nd</sup> Title page	“Study Chairs” was updated to the RTOG standard, “Study Team”.
1 <sup>st</sup> and 2 <sup>nd</sup> Title pages and Schema page	As required by CTEP, “Radiation Therapy Oncology Group” was replaced with “NRG Oncology”.

For Amendment 8 to: RTOG 0522, A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) [Followed by Surgery for Selected Patients] for Stage III and IV Head and Neck Carcinomas

NCI/Local Protocol #: RTOG-0522/RTOG 0522

NCI Protocol Version Date: 10/17/13

Section	Change
Title pages	<ul style="list-style-type: none"> <li>• 1<sup>st</sup> page: The dates of activation and closure and the update and version dates on the 1<sup>st</sup> page were deleted, and A Document History table was added to the 2<sup>nd</sup> title page to update the protocol to current RTOG standards.</li> <li>• 1<sup>st</sup> page: A note was added at the bottom of the page to direct queries to the Radiation Oncology Co-Chairs, as Dr. Ang is deceased.</li> <li>• This amendment was added to the Document History table.</li> </ul>
7.6, 7.6.1, 7.6.2	These sections were updated to current RTOG standard text.
7.6.3	This section was updated to current CTEP text.
7.7	<ul style="list-style-type: none"> <li>• The 2<sup>nd</sup> through 5<sup>th</sup> paragraphs and 3 bulleted items were added to update this section to current RTOG standard text.</li> <li>• The table was replaced with CTEP's current text.</li> </ul>
11.1	Footnote "L" was amended to limit the CT scan/MRI of the head and neck in follow up to 5 years, as there is no data to support this imaging beyond this timeframe.
Appendix I	Under "What will happen if I take part in this research study?" and "You will need these tests and procedures in follow-up visits, the timeframe for the CT scan or MRI of the head and neck was amended to be consistent with changes made in Section 11.1.

**SUMMARY OF CHANGES**  
**Amendment 7, Version Date: August 17, 2011**

**RTOG 0522**, “A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) [Followed by Surgery for Selected Patients] for Stage III and IV Head and Neck Carcinomas”

**Study Chair:** Kian Ang, MD, 713-563-2300, kianang@mdanderson.org

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**RTOG 0522** has been amended as follows:

**Title pages**, page 2: Dr. Zhang’s e-mail address was updated.

**Section 3.1.11** was deleted (and the subsequent section appropriately renumbered), as it referred to RTOG 0514, which has been closed.

**Section 5.5.1:** The link to the Password Authorization Form was updated.

**Section 7.6:** In the 3<sup>rd</sup> paragraph, the link to the definitions of SAEs was updated.

**Section 10.0:** The “Note” was deleted, as it referred to RTOG 0514, which has been closed. In addition, in the 1<sup>st</sup> paragraph, the word, “only”, was deleted to correspond to the deletion of information regarding RTOG 0514.

**Section 10.2.5** was amended to current RTOG Biospecimen Resource standard text.

**Section 10.2.8** was added (and the subsequent sections appropriately renumbered) to update the protocol to current RTOG Biospecimen Resource standard text.

**Section 10.2.9:** The summary table was amended to current RTOG Biospecimen Resource standards.

**Section 10.3** was amended to current RTOG standard text.

**Section 10.4:** The link to the tissue FAQs was updated.

**Section 11.3.7:** In the last sentence, the phrase, “patients that withdrawal consent”, was corrected to “patients that withdraw consent”.

**Section 12.1:** The schedule for the Follow-up Form (F1) was corrected to be consistent with Section 11.1.

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

- Under “How long will I be in the study?”: In the 2<sup>nd</sup> paragraph, the timeframe for follow up was corrected to be consistent with Sections 11.1 and 12.1.
- Under “About Using Tissue and Blood for Research”: In the 2<sup>nd</sup> paragraph, the title of and link to the information sheet were updated.

**Appendix VII** was amended to current RTOG Biospecimen Resource standard text.

**SUMMARY OF CHANGES**  
**Amendment 6, Version Date: February 23, 2011**  
(Broadcast: 3/2/11)

**RTOG 0522**, “A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) [Followed by Surgery for Selected Patients] for Stage III and IV Head and Neck Carcinomas”

**Study Chair:** Kian Ang, MD, 713-563-2300, kianang@mdanderson.org

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**RTOG 0522** has been amended as follows:

Details regarding biomarker studies were added to **Section 10.1**, as follows:

- **Section 10.1.2:** The last sentence was added, specifying that the assays will be performed at M.D. Anderson Cancer Center.
- **Section 10.2.7:** In the 1<sup>st</sup> paragraph, the phrase, “to Johns Hopkins”, was deleted. In addition, the 2<sup>nd</sup> paragraph was added to provide details of the assay to be completed and at what site. A reference to Ang 2010 included in the 2<sup>nd</sup> paragraph was added as citation 68 in “**References**”.

**SUMMARY OF CHANGES**  
**Amendment 5, Version Date: December 9, 2010**  
(Broadcast: 12/23/10)

**RTOG 0522**, “A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) [Followed by Surgery for Selected Patients] for Stage III and IV Head and Neck Carcinomas”

**Study Chair:** Kian Ang, MD, 713-563-2300, kianang@mdanderson.org

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**RTOG 0522** has been amended as follows:

As mandated by CTEP, **Sections 6.9 and 7.6** have been amended to require the use of CTCAE, version 4 for grading of all adverse events as of January 1, 2011.

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

Other Changes

**Section 7.6.3:** This section was amended as required by CTEP to instruct sites to report AML or MDS via AdEERS. In Appendix IX, CTSU logistics, under “Serious Adverse Event (AE) Reporting”, item 4 was amended to be consistent with this change.

**SUMMARY OF CHANGES**  
**Update: September 1, 2009**  
(Broadcast 9/1/09)

**RTOG 0522**, “A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) [Followed by Surgery for Selected Patients] for Stage III and IV Head and Neck Carcinomas”

**Study Chair:** Kian Ang, MD, 713-563-2300, [kianang@mdanderson.org](mailto:kianang@mdanderson.org)

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**RTOG 0522** has been updated as follows:

**Title page** (page 2): The contact information for the Outcomes Co-Chair, Dr. Konski, was updated. The Senior Statistician’s name and contact information were updated.

**Section 7.3.1** was updated to refer institutions to the RTOG web site for the investigator’s brochure for cetuximab.



## SUMMARY OF CHANGES

### Amendment 4, Version Date: August 25, 2008

(Amendment 4 broadcast on 10/23/08; Corrected Summary broadcast on 11/21/08)

**RTOG 0522**, “A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) [Followed by Surgery for Selected Patients] for Stage III and IV Head and Neck Carcinomas”

**Study Chair:** Kian Ang, MD, 713-563-2300, kianang@mdanderson.org

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**RTOG 0522** has been amended as follows:

The primary endpoint was amended from disease-free survival (DFS) to progression-free survival (PFS) to allow the results from this study to be compared with results reported by the French Meta-Analysis Group and with other multi-institutional studies. The sample size was increased to reduce the time interval to analysis of efficacy data. The following sections were amended:

- **Schema page:** The required sample size was amended to be consistent with changes made in Section 13.2.1.
- **Sections 2.1 and 2.2.3:** Disease-free survival was amended to progression-free survival to be consistent with changes made in Section 13.1.
- **Section 11.3.1:** The 1<sup>st</sup> sentence of the 1<sup>st</sup> paragraph and the last sentence of the 2<sup>nd</sup> paragraph were deleted and in the 2<sup>nd</sup> paragraph, disease-free survival was amended to progression-free survival to make the section consistent with changes made in Section 13.1.
- **Section 13.1.1:** Disease-free survival was amended to progression-free survival, and the definition of “Failure” was deleted, as this information is now provided in Section 13.7.1.
- **Sections 13.1.2.1 and 13.1.2.2:** The definition of “Failure” in these sections was deleted, as this information is now provided in Section 13.7.1.
- **Sections 13.1.2.9 and 13.1.2.10:** Disease-free survival was amended to progression-free survival.
- **Section 13.2.1** was added to provide the rationale for changing the primary endpoint and increasing the sample size.
- **Section 13.3:** A sentence was added at the end of the 2<sup>nd</sup> paragraph concerning the revised sample size.
- **Section 13.4.1:** In the 3<sup>rd</sup> paragraph and in the heading for Table 4, “DFS” was amended to “PFS”.
- **Section 13.5:** The 2<sup>nd</sup> paragraph was added providing details of the average monthly accrual.
- **Section 13.7.1:** In the 1<sup>st</sup> sentence of the 1<sup>st</sup> paragraph, disease-free survival was amended to progression-free survival. The 2<sup>nd</sup>, 3<sup>rd</sup>, and 4<sup>th</sup> paragraphs were replaced by a paragraph beginning, “All failure times” and a table, to provide information regarding failure.
- **Section 13.7.4:** “DFS” was amended to “PFS” throughout the section. In addition, the number of failures in the 1<sup>st</sup> sentence was amended.
- **Section 13.7.5:** In the 1<sup>st</sup> sentence, the number of failures was amended. “DFS” was amended to “PFS” in the 1<sup>st</sup> and 3<sup>rd</sup> paragraphs. In the 4<sup>th</sup> paragraph, “this analysis” was amended to “treatment analysis”. The 5<sup>th</sup> paragraph concerning subset analyses was added.

## RTOG 0522, Amendment 4, Page 2

- **Section 13.8:** In the paragraph, the hypothesized treatment differences for males and whites were amended. The projected distribution of gender and minorities in the table was amended to be consistent with the increased sample size.
- **References:** Citation number 55 was added, and subsequent citations were appropriately renumbered.
- **Appendix I:** The sample size under “How many people will take part in the study?” was amended to be consistent with changes made in Section 13.2.1.

At the request of Bristol-Myers Squibb (BMS) updated information has been added regarding cetuximab (**Section 1.3**); clinical studies of cetuximab in head and neck and colorectal cancer (**Section 1.4**); and safety of cetuximab in clinical studies (**Section 1.5**). Subsequent sections were appropriately renumbered (as Sections 1.6, 1.7 and 1.8).

### Other Changes

**Title page:** The contact information for Drs. Axelrod and Sherman was updated. Dr. El-Naggar has replaced Dr. Hammond as the Translational Research Co-Chair. The name and contact information of the study Senior Statistician was added to update the protocol to current RTOG standard.

### **Eligibility Checklist:**

- Page 3, question 19: The reference to Section 3.2.6 was amended to Section 3.2.8 to be consistent with renumbering of subsections in Section 3.2.
- Page 4: A subquestion was added to question 26 to update it to current RTOG standard text.
- Page 4: Question 27 was deleted, as the RTOG Health Services Research and Outcomes (HSRO) Committee has decided not to routinely collect social security numbers for Medicare patients for the EQ-5D. Cost utility analysis will be done by means of modeling costs.

**Section 3.1.1:** The phrase, “Histologically proven”, was amended to “Pathologically (histologically or cytologically) proven” for clarity. The change also was made in the corresponding question on the **Eligibility Checklist**, page 1, question 1.

**Section 3.1.2:** A note was added at the end of the section to clarify that patients with T1, any N, or T2N1 tumors are not eligible. The change also was made in the corresponding question on the **Eligibility Checklist**, page 1, question 2.

### **Section 3.1.3.3:**

- The CT scan or MRI of the head and neck was clarified with a parenthetical phrase, “of the primary tumor and neck nodes”. This phrase also was added to the corresponding question on the **Eligibility Checklist**, page 1, question 5.
- A note was added to clarify that a PET/CT can only be used in place of a CT scan or MRI if the CT is a high quality scan with contrast. This information also was added as a subquestion on the **Eligibility Checklist**, page 1, question 5.

### **Section 3.2:**

- **Section 3.2.2** was added specifying that patients with simultaneous primaries or bilateral tumors are not eligible (subsequent sections were appropriately renumbered).
- **Section 3.2.3** was added excluding patients who have had gross total excisions of the primary tumor (subsequent sections were appropriately renumbered).
- **Section 3.2.8.1**, concerning cardiac disease, was revised at the request of BMS.

## RTOG 0522, Amendment 4, Page 3

- **Section 3.2.12** was added at the request of BMS, excluding patients who have had prior severe infusion reactions to a monoclonal antibody.

Questions 13, 14, and 22 on pages 1 and 2 of the **Eligibility Checklist** were added to correspond to Sections 3.2.2, 3.2.3, and 3.2.11.

**Section 4.2.1:** The reference to details of PET/CT scans was corrected from Section 11.4 to Section 6.11. This reference also was corrected in the first paragraph of **Section 13.4.2**.

**Section 5.3.3:** Contact information for the PET Core Laboratory was updated.

**Section 5.4:** The prior text, "Preregistration Requirements for Cetuximab", was replaced with the current RTOG standard, "Regulatory Pre-Registration Requirements".

**Section 6.0:** The second paragraph was added to provide instructions regarding missed treatments.

**Section 6.7:** Instructions regarding missed treatments were added to the first paragraph. In addition, the second paragraph was amended for clarity.

**Section 6.11.7** was amended for clarity and to update instructions to the current PET Core Laboratory standard.

**Section 7.1.1.1:** A parenthetical note was added after the 1<sup>st</sup> sentence to instruct sites that cisplatin given within 24 hours of days 1 and 22 (due to holidays, etc.) is acceptable. At the end of the section, the instructions for BSA were revised for clarity and bolded for emphasis.

**Section 7.1.2.1:** The CTCAE, v. 3.0 definition of neutropenic fever was added for clarity.

**Section 7.1.2.7:** An Instruction to modify the cisplatin dose for weight changes  $\geq 10\%$  was added.

**Section 7.1.3.1:**

- In the first paragraph, instructions were added to begin radiation treatment no later than 7 days after the first dose of cetuximab.
- Instructions concerning actual body weight and BSA were added at the end of the first paragraph and bolded for emphasis.
- The second paragraph was revised to provide detailed instructions regarding the timing of cisplatin, cetuximab, and radiation therapy.

**Section 7.3:** The following changes were made at the request of BMS:

- Section 7.3.1: The contact information for BMS was amended.
- Section 7.3.7: In the last paragraph, the phone number for BMS was replaced with an e-mail address.
- Section 7.3.9 was amended to instruct sites to dispose of opened vials at the site rather than return them to BMS for disposal and the phone number for BMS was replaced with an e-mail address.

**Section 7.4.1:** Under the table, an Instruction to modify the cetuximab dose for weight changes  $\geq 10\%$  was added.

## RTOG 0522, Amendment 4, Page 4

### Section 7.4.3:

- In the table, the instruction for  $\geq$  grade 3 nausea/vomiting was changed from “Hold drug until  $\leq$  grade 2” to “Maintain dose levels”.
- In footnote “a”, the last sentence was amended for clarity to read, “‘Held’ C225 doses will be made up at the assigned dose level, although no cetuximab doses should be given more than 4 weeks after the completion of radiation therapy”.

**Section 7.6**, “Adverse Events”, was amended to current RTOG standard.

### Section 10.0:

- In the first paragraph, the title of RTOG 0514 was changed from “the Head and Neck Cancer Tissue/Specimen Bank” to “Tissue/Specimen Repository” to be consistent with the current title of that study.
- In the third paragraph the name of and location for the prior RTOG tissue bank was amended to the new name and location.
- In the fourth paragraph and throughout the text of Sections 10.1-10.4 “RTOG Tissue Bank” was replaced with “RTOG Biospecimen Resource”.
- Section 10.2.7 was added to describe the HPV analysis of oropharyngeal carcinoma specimens. Subsequent sections were appropriately renumbered.
- Section 10.2.9 was amended with the contact information of the Biospecimen Resource.
- Section 10.3 was amended with the current RTOG standard text.

### Section 11.1:

- The lab assessments, calcium, glucose, potassium, and sodium, were added to the “Pre-Study Entry” column to be consistent with Section 3.2.7.8.
- In addition, at the request of Health Canada, these assessments were added to be done every 3 weeks, prior to chemotherapy (cisplatin) cycle to periodically monitor for hypocalcemia and/or hypokalemia. The timing of these blood tests was added in **Appendix I**, the sample consent, under tests and procedures during the study.
- **Footnote “i”** was amended to require that assessments be done “no later than 72 hours” prior to the chemotherapy (cisplatin) cycle and “within 48 hours of cetuximab”.
- In **footnote “j”**, the phrase, “24 hours of receiving chemotherapy” was clarified to “24 hours prior to chemotherapy” and to require that the assessments be done “within 48 hours of cetuximab”.
- **Footnote “L”**: The 2<sup>nd</sup> sentence was amended for clarity. In addition, a note was added at the end of the footnote instructing sites that the scan at 8-9 weeks for patients with N0 disease is not necessary but all other scans must be done as specified.

### Section 12.1:

- The Adverse Event Forms (at the completion or discontinuation of systemic treatment and as needed) were deleted, as this information is collected on the Treatment Form (TF) and the Follow-up Form (F1).
- The schedule for submission of the PSS-HN and EQ-5D was amended to be consistent with Section 11.1.

**Section 12.2:** The instruction, “copy to HQ and ITC” was added next to the Daily Treatment Record (T5); this is now required for quality assurance.

**Section 12.3:** Contact information for the PET Core Laboratory was updated.

**Section 13.2.2**, providing details of HPV determination and analysis, was added, as were 3 new references (subsequent citations were appropriately renumbered in the text and in **References**).

## RTOG 0522, Amendment 4, Page 5

**Section 13.4.1:** The 1<sup>st</sup>, 2<sup>nd</sup>, and last paragraphs were amended, as were Tables 4-6, to discuss data and analysis of PET/CT scans.

**Section 13.4.2:** The 2<sup>nd</sup> paragraph was added to discuss lower-than-projected participation in the post-treatment PET/CT scans.

**Appendix I**, the sample consent:

Under “Risks Associated with Cetuximab”,

- Under the “Less Likely, But Serious” risks, “reduced white blood cell counts” was corrected to “reduced blood counts”.
- Under the heading, “Rare”, at the request of the Central IRB, the risk of elevated liver function tests was added (in plain language for patients).
- The heading “Rare, But Serious” was added and at the request of the Central IRB, the following risks were added:
  - Heart attack;
  - Blood clots outside of the lungs, legs, and pelvis.

In addition, the risk, “Scarring of lung tissue, which could be life threatening or lead to death”, was reclassified from “Rare” to “Rare, But Serious”.

Under “Will my medical information be kept private?”, the 3<sup>rd</sup> bulleted item was amended to read, “Qualified representatives of ImClone, makers of cetuximab” and the 4<sup>th</sup> bulleted item was added, “Qualified representatives of Bristol-Myers Squibb, marketer and distributor of cetuximab”. These changes were made to clarify the roles of Imclone and Bristol-Myers Squibb.

In addition, under “Quality of Life Study”, the paragraph describing the need for the social security number of patients for whom health care is covered at least in part by Medicare was deleted as the RTOG Health Services Research and Outcomes (HSRO) Committee has decided not to routinely collect social security numbers for Medicare patients for the EQ-5D. Cost utility analysis will be done by means of modeling costs.

**Appendix IV**, Surgical Management of the Neck: Instructions for N1, N2A, N2B, and N2C were amended to be more consistent with Section 8.0 of the protocol.

**Appendix VII:** “RTOG Tissue Bank” was replaced with “RTOG Biospecimen Resource” as appropriate throughout the text and the contact information of the Biospecimen Resource was added.

**Appendix IX:** At the request of CTSU, the hours of operation under “For patient enrollments” was amended to 9:00 AM-5:30 PM.

**SUMMARY OF CHANGES**  
**Amendment 3, Version Date: February 14, 2007**

**RTOG 0522**, “A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) [Followed by Surgery for Selected Patients] for Stage III and IV Head and Neck Carcinomas”

**Study Chair:** Kian Ang, MD, 713-563-2300, kianang@mdanderson.org

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At the request of the Cancer Trials Support Unit (CTSU), **RTOG 0522** has been amended as follows:

**Title page:** The statement at the bottom of the first title page regarding patient enrollments from institutions not aligned with RTOG was deleted and replaced with text on the page prior to “Index”.

**Appendix IX:** The prior CTSU logistics were deleted and replaced with CTSU’s new text.

**SUMMARY OF CHANGES**  
**Amendment 2, Version Date: January 8, 2007**

**RTOG 0522**, “A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) [Followed by Surgery for Selected Patients] for Stage III and IV Head and Neck Carcinomas”

**Study Chair:** Kian Ang, MD, 713-563-2300, kianang@mdanderson.org

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**RTOG 0522** has been amended as follows:

The eligibility criterion of pre-treatment electrolyte levels (including magnesium and serum calcium) within normal range has been deleted. This criterion was included in the study as a precaution, given two deaths (one due to pneumonia and one of unknown cause) observed in a prior Memorial Sloan-Kettering Cancer Center trial. Since similar serious adverse events have not been observed on 0522, this stringent requirement has been deleted so that eligibility criteria are consistent with prior RTOG trials. To continue to provide safety precautions, patients with a co-morbidity of CTCAE, v. 3.0 grade 3-4 electrolyte abnormalities (as defined in Section 3.2.6.8) have been excluded. The following sections were amended for this change: **Eligibility Checklist**, page 1, question 9 and page 2, question 17; **Section 3.2.6.8**; **Section 11.1** under “Assessments” and in footnote “e”. In addition, **Sections 3.1.9 and 3.1.10** were deleted, and subsequent sections were appropriately renumbered.

Other Changes

**Section 5.3.1:** The first sentence, specifying the population for which the PET Core Laboratory will collect scans, was added for clarity and for consistency with Section 6.11.5.

**Section 5.3.4:** At the request of Health Canada, instructions were added for Canadian sites participating in FDG-PET in studies. The instructions also were added in **Section 6.11**.

**Sections 5.4.1 and 5.4.2:** The phrase, “IRB assurance number”, was replaced with “Federalwide Assurance (FWA) number” for clarity.

**Section 6.11:** The parenthetical phrase in the second sentence, “in addition to the required CT scan or MRI”, was deleted, and a note was added at the end of the paragraph to provide detailed instructions about diagnostic imaging. These changes also were made in **Sections 6.11.5 and 8.1**.

**Section 7.6:** The text in this section, defining adverse events and serious adverse events, was updated to the current RTOG standard.

**Section 11.1**, footnote “h”: The phrase, “If the patient consents to participate in the quality of life component of the study”, was added to clarify that this component of the study is optional, not required.

**Section 11.3.1:** The second paragraph was revised to clarify that the PET portion of a PET/CT scan should not be used in determining response to treatment, as it is investigational and to provide details instructions about diagnostic imaging.

**Section 11.3.6:** This section was updated to current RTOG standard.

**Section 12.2.1:** The zip code for the Image-Guided Therapy Center (ITC) was corrected.

**RTOG 0522, Amendment 2, page 2**

**Appendix I**, the sample consent: Under “What are the costs of taking part in this study?”, the third paragraph regarding potential cost if cetuximab becomes approved for treatment of head and neck cancer was deleted. Cetuximab is now approved for this treatment, and Bristol-Myers Squibb is providing cetuximab at no cost to patients on study.



**SUMMARY OF CHANGES**  
**Amendment 1, Version Date: June 1, 2006**

**RTOG 0522**, “A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) [Followed by Surgery for Selected Patients] for Stage III and IV Head and Neck Carcinomas”

**Study Chair:** Kian Ang, MD, 713-563-2300, kianang@mdanderson.org

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**RTOG 0522** has been amended as follows:

Throughout the protocol, “toxicity” was replaced with “adverse event” as appropriate to update the protocol to current RTOG standard.

**Title page:** Dr. Rosenthal’s email address was corrected and Dr. Hammond’s email address was updated.

**Index page:** Section 6.0 and Appendix VII were retitled to be consistent with changes in those sections.

The following changes were made to the demographic/operational portion of the **Eligibility Checklist, pages 2 and 3** to be consistent with web registration. Eligibility criteria were not changed.

- On page 2 under “The following questions will be asked at Study Registration”, two sentences concerning required IMRT and PET credentialing were added. In addition, two items requesting information about use of IMRT and PET credentialing through the PET Core Laboratory were added.
- On page 3:
  - Question 16 was amended to “Randomization date”.
  - Question 17 was amended to “Medical Oncologist’s Name”.
  - Question 24 was deleted, as this information is now collected on page 2, and subsequent questions were appropriately renumbered.
  - Question 25 and a subquestion were added concerning submission of PET/CT scans and confirmation of N stage.
  - Questions 26 and 27 were added regarding use of Medicare data for health utility research.

**Section 5.2**, “Pre-Registration Requirements for IMRT Treatment Approach”: The second paragraph was amended for clarity.

**Section 5.3:** The PET credentialing text from Section 11.4.1 was moved to this section, to emphasize that this credentialing is a pre-registration requirement for institutions participating in the PET component of the study. In addition, the text was amended for clarity. The subsequent section, “Pre-registration Requirements for Cetuximab”, was renumbered appropriately, and references to that section on the **Schema page**, in **Section 7.3.7**, and in **Appendix VIII** were updated accordingly.

The following changes were made in **Section 6.0**:

- The heading of the section was amended to “Radiation Therapy/Functional Imaging”.
- In Sections 6.1.1.1, 6.1.1.2, 6.1.2.1, 6.1.2.4, 6.4.4, and 6.7, “PVT<sub>1</sub>” was amended to “PVT<sub>HD</sub>” (PVT high dose) and “PVT<sub>2</sub>” was amended to “PVT<sub>LD</sub>” (PVT low dose) or PVT<sub>ED</sub> (PVT elected dose), as appropriate. The subscript “int” (intermediate) in Sections 6.1.1.2 and 6.1.2.2 (e.g., “PVT<sub>int</sub>”) was capitalized to “INT” to be consistent with the new subscripts. These changes were made for clarity and for consistency across RTOG head and neck trials.

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## RTOG 0522: Summary of Changes, Amendment 1, page 2

### Section 6.0 changes continued

- Section 6.5.1, “Spinal Cord”, was amended for clarity and for consistency across RTOG head and neck trials.
- Section 6.11: Text concerning PET/CT imaging, previously in Section 11.4, was moved to this section to update the protocol to current RTOG standard (and the subsequent text in Section 11, Quality of Life Assessments, was appropriately renumbered). References in **Sections 3.1.3.2 and 3.1.3.3** to the PET/CT text were amended to refer sites to Section 6.11 versus 11.4.
- Sections 6.11.8 and 6.11.9, concerning adverse events and reporting of adverse events, were added to update the protocol to current RTOG standard.

**Section 7.1.1.2:** In the first numbered item, in the second sentence was amended to correct the dose of dexamethasone to “up to 8 mg total daily for up to 4 days total”. In the second numbered item, the last sentence was added to modify the dose of dexamethasone for patients who have received aprepitant.

**Section 7.1.2.4:** In the “Note”, the first phrase was corrected to “If creatinine is > 1.2 mg/dl...”.

**Section 7.1.3.1:** In the fifth paragraph, the parenthetical phrase following the first sentence was amended to direct sites to Section 7.4.4 for management of infusion reactions.

**Section 7.2.1:** The last sentence was amended to provide information about cisplatin in aqueous solution.

**Section 7.4:** The table was reformatted so that dose levels -1 and -2 appear on the same line as the 250 mg/m<sup>2</sup> dose of cetuximab.

**Section 7.4.4:** Descriptions were added under each CTCAE grade for clarity, and treatment guidelines were amended to reflect current practice.

**Section 7.4.5.1:** In the first sentence, the phrase “or life threatening” was added to correctly describe grade 4 reactions.

**Section 7.4.5.3:** Under “Acute Skin Changes” and “Late Skin Changes”, the timeframe definitions in parentheses were deleted; under CTCAE 3.0 criteria, these timeframes no longer apply. In addition, in the last table in this section, the grade of adverse event at which the dose modifications should be initiated, “≥ Grade 3”, was added.

The following changes were made to **Section 10.2:**

- Section 10.2.2: The third sentence concerning unstained slides was deleted to be consistent with current RTOG Tissue Bank practices.
- Section 10.2.5 was amended to be consistent with current RTOG Tissue Bank practices and to provide sites with instructions for processing blood specimens.
- Section 10.2.6 was added to request specimens from patients who manifest tumor recurrence post protocol treatment. This request was added in plain language in **Appendix I**, the sample consent, in the second paragraph under “About Using Tissue and Blood for Research”.
- Section 10.2.7 was added to provide concise directions to sites for submission and shipment of specimens, and the subsequent section was renumbered appropriately.
- Section 10.2.8: Contact information for the RTOG Tissue Bank was updated.

**Section 10.3:** In the first sentence, “per case” was replaced with “per time point” and reimbursement information was added for “buffy coat cells” and “plasma collection” (replacing prior “leukocyte collection”).

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### **RTOG 0522: Summary of Changes, Amendment 1, page 3**

**Section 11.1:** A “complete history/physical” was added at 8-9 weeks, and at 6, 9, and 12 months, as this is standard care and is necessary to assess adverse events. In addition, in footnote “c”, the phrase, “and Appendix VI”, was added to direct sites to the text for management of dental problems.

**Section 11.2.1, table:**

- Under “During treatment on TF form”, the following AE terms were added to be consistent with the TF data form: pruritis/itching, rash: acne/acneiform, nail changes, and rash: dermatitis.
- Under “During follow-up on F1 form”, the following changes were made to be consistent with the F1 data form: The category, “Pain”, was added and its accompanying AE term was amended; the category, “Auditory”, and its accompanying AE term were added; the page number for “Pulmonary/Upper Respiratory” was corrected; and the AE terms “Induration/fibrosis” and “Osteonecrosis” were moved from “Musculoskeletal/Soft Tissue” to “Dermatology/Skin”.

**Section 12.3:** A “note” was added to provide sites with information concerning PET data submission. In addition, the pre- and post-treatment PET scan (C4 and C5) were added as items due.

**Section 13.7.5:** A sentence was added to the third paragraph addressing analysis of patients with laryngeal primaries.

**Section 13.8:** The title of the table was updated to current RTOG standard, “Projected Distribution of Gender and Minorities”.

The following changes were made to **Appendix I**, sample consent:

- Under “Why Is This Study Being Done,” in the second paragraph, the sentence “C225 was approved..., but is an experimental treatment for patients with head and neck cancer” was amended 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.”
- Under “What will happen if I take part in this research study, the bulleted item, “Tests of heart function” was amended at the request of the Central IRB to specify and describe the tests used. In addition, “a physical examination” was added at 8-9 weeks, and at 6, 9, and 12 months to correspond with changes in Section 11.1.
- The “Re-evaluation” text of the “Study Plan” was amended to clarify that all patients are re-evaluated at 8-9 weeks. In addition, at the request of the Central IRB, the text regarding surgery was amended to clarify that patients with evidence of disease after treatment will have surgery and that patients with no evidence of disease after treatment will seen in follow-up visits.
- Under “Risks Associated with cisplatin”, the following changes were made at the request of the Central IRB:
  - Under “Very Likely”, “Low magnesium in the body” was amended to read, “Low magnesium in the blood, which could result in muscle cramps and/or weakness”;
  - Under “Very Likely”, “Low calcium in the body” was amended to “Low calcium in the blood”;
  - “Low potassium in the body” was moved from “Very Likely” to “Less Likely, But Serious” and amended to “Calcium or potassium levels so low that it may affect heart function”.

### **RTOG 0522: Summary of Changes, Amendment 1, page 3**

Changes to **Appendix I**, sample consent (Continued)

- Under “Risks Associated with Cetuximab (C225), the following changes were made at the request of the Central IRB:
  - Under “Very Likely”, “Low calcium in the blood” was added;
  - Under “Less Likely, But Serious”, “Calcium or potassium levels so low that it may affect heart function” was added.
- Under “What other choices do I have if I do not take part in this study?”, the second bullet, “Receiving cetuximab without being in a study” was added at the request of the Central IRB.
- Under “What are my rights if I take part in this study?”, the second paragraph concerning monitoring by the Data Safety Monitoring Board was added to update the protocol to current RTOG standard.
- Under “Quality of Life Study”, the third paragraph was added to explain the collection of social security numbers of Medicare patients for health utility research.

**Appendix VII** was updated to reflect current RTOG Tissue Bank practice and to provide the current contact information for the RTOG Tissue Bank.

**Appendix IX:** At the request of the CTSU, two changes were made under the “Special Materials or Substudies” section to be consistent with the protocol text. The heading was amended to “Radiation Therapy/Functional Imaging”, and the designation for the Digital Data Submission Form was changed from “T2” to “DDSI”. In addition, in the “Quality of Life” heading, the reference to the protocol section was amended from 11.5 to 11.4 to be consistent with changes in the protocol.

**An amended protocol and a protocol with all changes tracked are attached.**

**SUMMARY OF CHANGES**  
**Update: February 2, 2006**

**RTOG 0522**, “A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) [Followed by Surgery for Selected Patients] for Stage III and IV Head and Neck Carcinomas”

**Study Chair:** Kian Ang, MD, 713-563-2300, [kianang@mdanderson.org](mailto:kianang@mdanderson.org)

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**RTOG 0522** has been updated as follows:

**Title page:** Corrected contact information for Doctors Axelrod and Sherman

**Section 6.8:** Corrected to indicate that RT Quality Assurance reviews will be performed remotely once cases are received by the ITC.

**Section 7.3.7:** Changed initial drug shipment to 24 vials. This change is also reflected in Appendix VIII (Initial Drug and Re-supply Shipment forms)

**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**  
**Update: November 23, 2005**

**RTOG 0522**, “A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) [Followed by Surgery for Selected Patients] for Stage III and IV Head and Neck Carcinomas”

**Study Chair:** Kian Ang, MD, 713-563-2300, [kianang@mdanderson.org](mailto:kianang@mdanderson.org)

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**RTOG 0522** has been updated as follows:

**Title page:** The phone numbers for Drs. Ang and Rosenthal were corrected.

**An updated protocol is available (no password required) on the RTOG Web site, <http://www.rtog.org>**

**SUMMARY OF CHANGES**  
**Update: November 22, 2005**

**RTOG 0522**, “A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) [Followed by Surgery for Selected Patients] for Stage III and IV Head and Neck Carcinomas”

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**RTOG 0522** has been updated as follows:

**Title page:** The contact information for Eric Sherman, MD, was updated.

**Section 5.1**, “Pre-Registration Requirements for 3D-CRT Treatment Approach”, was added. These requirements also were added to the CTSU logistics in **Appendix IX**. Subsequent sections and references to these sections throughout the protocol were appropriately renumbered.

**Section 6.4.4:** In the second sentence, “0.5 mm” was corrected to “0.5 cm”.

**Section 7.7.1:** In footnote 1 below the table, the phrase, “via AdEERS for CTEP IND agents” was corrected to “via AdEERS for non-CTEP IND agents”.

**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 12.3:** The timeframe for the first submission of images and the Technical Assessment Form was corrected to “Within 14 days of registration”.

**An updated protocol is available (no password required) on the RTOG Web site, <http://www.rtog.org>**