For Amendment 8 to: RTOG 0129, A Phase III Trial of Concurrent Radiation and Chemotherapy (Followed by Surgery for Residual Primary/N2-3 Nodal Disease) for Advanced Head and Neck Carcinomas

NCI/Local Protocol #: RTOG-0129/RTOG 0129

NCI Protocol Version Date: July 16, 2014

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Title page</td>
<td>• The Principal Investigator has been changed, as Dr. Ang is deceased. Phuc Felix Nguyen-Tân, MD, now will serve as Principal Investigator/Radiation Oncology.</td>
</tr>
<tr>
<td></td>
<td>• Dr. Zhang’s contact information was updated.</td>
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<tr>
<td></td>
<td>• The version date was changed for this amendment, and the number of amendments was changed to 1-8.</td>
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SUMMARY OF CHANGES
Update: June 5, 2012
(Broadcast 6/5/12)

RTOG 0129, “A Phase III Trial Of Concurrent Radiation and Chemotherapy (Followed By Surgery for Residual Primary/N2-3 Nodal Disease) for Advanced Head and Neck Carcinoma”

Study Chair: Kian Ang, MD, 713-563-2323, FAX 713-563-2331, kianang@mdanderson.org

RTOG 0129 has been updated as follows:

Title page: Dr. Zhang has replaced Dr. Pajak as the Senior Statistician for the study.
SUMMARY OF CHANGES
Amendment 7, Version Date: March 24, 2010
(Broadcast 4/1/10)

RTOG 0129, "A Phase III Trial Of Concurrent Radiation and Chemotherapy (Followed By Surgery for Residual Primary/N2-3 Nodal Disease) for Advanced Head and Neck Carcinoma"

Study Chair: Kian Ang, MD, 713-563-2323, FAX 713-563-2331, kianang@mdanderson.org

As mandated by CTEP, RTOG 0129 has been amended to replace CTC version 2.0 with the CTEP Active Version of CTCAE. Changes were made to the following sections:

- Section 7.4.1
- Appendix V: Sections "B", "D", and "E"
RTOG 0129, "A Phase III Trial Of Concurrent Radiation and Chemotherapy (Followed By Surgery for Residual Primary/N2-3 Nodal Disease) for Advanced Head and Neck Carcinoma"

Study Chair: Kian Ang, MD, 713-563-2323, FAX 713-563-2331, kianang@mdanderson.org

RTOG 0129 has been amended as follows:

The estimated 2-year survival rate for the control arm of this study has significantly exceeded the projected rate; therefore the statistical analysis, planned to be done after a specified number of deaths, has been significantly delayed. In order to provide efficacy results to investigators and patients in a reasonable timeframe, the statistical analysis plan has been amended. Section 13.5.2.1 was added to provide a detailed rationale for amending the planned analysis and to provide specifics of the revised analysis plan. Sections 13.5.3.2 and 13.5.4.2 were added to clarify that there will be no second interim treatment comparison and to provide the timeframe for the final analysis.

Other Changes

The title page was amended to current RTOG standard with full contact information provided for all Study Chairs and the name of and contact information provided for the study Senior Statistician.

Section 8.6, Surgical Quality Assurance Reviews: The Study Chairs determined that since surgery was not a major aspect of care in this study, surgical quality assurance reviews were not needed; therefore, this section was deleted.

Section 10.1: The phrase, "RTOG Tissue Bank", was replaced with "RTOG Biospecimen Resource" throughout this section.

Sections 10.1.3 and 10.2.2: References to LDS Hospital were replaced with the current name, location, and contact information of the RTOG Biospecimen Resource.

Section 10.2.3 was amended to the current RTOG standard text for specimen reimbursement.
RTOG 0129, “A Phase III Trial Of Concurrent Radiation and Chemotherapy (Followed By Surgery for Residual Primary/N2-3 Nodal Disease) for Advanced Head and Neck Carcinoma”

Study Chair: K. Kian Ang, M.D., (713) 792-3409, FAX # (713) 794-5573, kianang@mdanderson.org

RTOG 0129 has been updated as follows:

Section 11 — For clarification, the phrase "nurse participant" was changed to "nurse".

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”.

An updated protocol is available (no password required) on the RTOG website: http://www.rtog.org/
SUMMARY OF CHANGES
Amendment 5, Version Date: January 31, 2005

RTOG 0129, “A Phase III Trial Of Concurrent Radiation and Chemotherapy (Followed By Surgery for Residual Primary/N2-3 Nodal Disease) for Advanced Head and Neck Carcinoma”

Study Chair: Kian Ang, MD, 713-563-2323, FAX 713-563-2331, kianang@mdanderson.org

RTOG 0129 has been amended as follows:

Title page: Dr. Ang’s phone and fax numbers were updated.

Section 3.1.5: The formula for calculating the corrected calcium was corrected.

Section 7.2.1.1: The instructions concerning BSA were revised for clarity.

Section 7.4: A reference to Appendix V was added to Section 7.4.2.1, and the address for RTOG Headquarters was updated in Sections 7.4.2.4 and 7.4.4.

The following changes were made in Section 10.0:

- Section 10.1.1 was revised for clarity, and Section 10.1.2 was deleted (and the subsequent sections appropriately renumbered);
- Section 10.1.3 was deleted (and the subsequent sections appropriately renumbered), and Section 10.2.3 was revised with the current process for reimbursement of tissue and serum specimens;
- Section 10.1.5: The email address for LDS Hospital was updated; this change also was made in Section 10.2.2.

Section 11.1: The table was corrected with an addition of a column for follow up at 9 months post all treatment.

Section 11.8: In the first sentence, the phrase “nurse participant” was amended to “nurse” for clarity.

Section 12.0: The address for RTOG Headquarters was updated.

Section 12.1: The timeframe for the Follow-up Form (F1) was revised to correspond to Section 11.1, and the Long Term Follow-up Form (FF) was deleted, as it is unnecessary.

Section 13.7: The Gender and Minority Accrual table was revised to NCI standard, deleting the row, “More than one race”, and the Racial Category estimates were corrected for Black/African American and for White patients.
The following changes were made in Appendix IA, the sample consent:

- In the last paragraph under “What Is Involved In The Study?”, the first sentence was revised to “…you will have a biopsy” (versus “you may have”), and the second sentence was revised to “…your doctor will recommend” (versus “your doctor may”). In addition, in the table under “Standard procedures being done because you are in the study”, the timeframes were amended for physical examination, evaluation for side effects, blood tests, and chest x-ray/CT scan to correspond to Section 11.1;
- The timeframe of follow-up visits was corrected under “How Long Will I Be In The Study?” to correspond to Section 11.1.

An amended protocol is available (no password required) on the RTOG Web site, http://www.rtog.org
SUMMARY OF CHANGES
Revision 4, Version Date: May 11, 2004

RTOG 0129, “A Phase III Trial Of Concurrent Radiation and Chemotherapy (Followed By Surgery for Residual Primary/N2-3 Nodal Disease) for Advanced Head and Neck Carcinoma”

Study Chair: Kian Ang, MD, 713-792-3409, FAX 713-794-5573, kianang@mdanderson.org

IRB Review Requirements:
( X ) Full board review required
(   ) Expedited review allowed; however, site IRB requirements take precedence.
(   ) No review required

RTOG 0129 has been revised as follows:

The sample size of the study has been increased. The following sections have been added for this change: Sections 13.3.1, 13.5.3.1, 13.5.4, 13.5.4.1, and Section 13.6 was revised. In addition, the sample size was revised on the Schema page, in Section 13.7, and in Appendix I, the sample consent.

The protocol was revised to clarify that selected patients will have surgery following completion of radiation and chemotherapy. The title was revised throughout the protocol, and the following sections were revised to reflect this: The Schema, Section 1.5, Section 12.1, and Appendix I, under “What Is Involved In The Study?”. Section 8.5.1 was added.

Other Changes:
Section 8.6, describing Surgical Quality Assurance Reviews, was added.

Section 11.1: The column, “At 4 weeks post-XRT”, was replaced by the column, “6-8 weeks post all tx”. All of the assessments previously done at 4 weeks will now be done at 6-8 weeks, and a CT/MRI of tumor was added at this time period; footnote “m” was added. Corresponding changes were made in Appendix I in the procedures under “What Is Involved In The Study?”.

Sections 13.1.2.1 and 13.1.2.2 were revised to more clearly define these secondary endpoints.

References: The EGFR results of RTOG 90-03, unpublished when the protocol opened, have been published. The publication was referenced in the first paragraph of Section 13.6, and the citation was added as number 63.

A revised protocol is available (no password required) on the RTOG Web site,
http://www.rtog.org
SUMMARY OF CHANGES
Revision 3, Version Date: February 24, 2004

**RTOG 0129**, “A Phase III Trial Of Concurrent Radiation and Chemotherapy for Advanced Head and Neck Carcinoma”

**Study Chair**: Kian Ang, MD, 713-792-3409, FAX 713-794-5573, kianang@mdanderson.org

**IRB Review Requirements:**
( ) Full board review required
( ) Expedited review allowed; however, site IRB requirements take precedence.
(X) No review required

The protocol has been re-designated RTOG 0129 (formerly RTOG H-0129). The letter “H” (for Head & Neck) that preceded the protocol number was deleted throughout the protocol to make the protocol designation consistent with current RTOG standards.

**A revised protocol is available (no password required) on the RTOG Web site, http://www.rtog.org**
RTOG H-0129, “A Phase III Trial Of Concurrent Radiation and Chemotherapy for Advanced Head and Neck Carcinoma”

Study Chair: Kian Ang, MD, 713-792-3409, FAX 713-794-5573, kianang@mdanderson.org

IRB Review Requirements:
(  ) Full board review required
( X ) Expedited review allowed; however, site IRB requirements take precedence.
(  ) No review required

RTOG H-0129 has been revised as follows:

Eligibility checklist: Add to # 17: Is the serum calcium (or corrected serum calcium) within normal range (see Section 3.1.5)? Change made to match Section 3.1.5.

Section 3.1.5: Complete formula for corrected calcium put back in (this appears to have been an inadvertent omission in the 1st revision):

\[
\text{Corrected Calcium (mg/dl)} = 4 - [\text{patient albumin (g/dl)}] \times 0.8 + \text{patient calcium (mg/dl)}
\]

Also, in the first sentence of this section, add (or normal corrected serum calcium) to the end of the sentence for clarity.

Section 4.6.3: Change "greater than or equal to 2" to "greater than or equal to 1.5." The revised wording would then be: Abdominal CT if abnormal LFTs are noted (must be done in the presence of elevation greater than or equal to 1.5 x ULN of alkaline phosphatase, SGOT, bilirubin, or other clinical indicator).

Section 7.1.1.1: The sentences say: "One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5." The following sentence has been added because cisplatin comes ready-to-use now: Reconstituted drug is now available from the manufacturer.

Section 7.2.1.4.4: For accuracy, add the following sentence to the footnote: If the calculated nomogram is 50 mL/min or above, a 24-hour urine collection is not needed, but if the nomogram calculation is less than 50 mL/min, a 24-hour urine collection is mandated.

Section 11.1 Study Parameters: The previous wording in column one, line six, has been changed from SMA-12 (per 4.4.2) to SMA-12 (per 4.5.2).

Section 11.0, Study Parameters, footnote b: Change 2 x ULN to 1.5 x ULN to match
the change in Section 4.6.3; **footnote f**: Because the wrong footnote wording was used, change the current wording (Prior to dose of cisplatin) to the following: *As applicable (creatinine clearance should be done as indicated in Section 7.2.1.4.4)*; **footnote l**: In order to make sure that the risk of hematologic toxicity is not underestimated, add a footnote with the following wording: *CBC should be done 3 weeks post last dose of chemotherapy*.

A revised protocol is available (no password required) on the RTOG web site, [http://www.rtog.org](http://www.rtog.org)
SUMMARY OF CHANGES
Update Date: December 16, 2003

RTOG H-0129, “A Phase III Trial Of Concurrent Radiation And Chemotherapy For Advanced Head and Neck Carcinomas”

Study Chair: K. Kian Ang, M.D., (713) 792-3409, FAX # (713) 794-5573, kianang@mdanderson.org

RTOG H-0129 has been updated as follows:

Appendix IB — In Tissue Consent under “Things To Think About”, 3rd paragraph: Change phone number to 801-408-5626. This change is being made to make this section of the protocol consistent with the section 10.2.2 change made in a previous update.

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”.

An updated protocol is available (no password required) on the RTOG website: http://www.rtog.org/
SUMMARY OF CHANGES
Revision 1, Version Date: September 30, 2003

RTOG H-0129, “A Phase III Trial Of Concurrent Radiation And Chemotherapy For Advanced Head and Neck Carcinomas”

Study Chair: K. Kian Ang, M.D., (713) 792-3409, FAX (713) 794-5573, kianang@mdanderson.org

IRB Review Requirements:
( ) Full board review required
(X) Expedited review allowed, but site IRB requirements take precedence.
( ) No review required

RTOG H-0129 has been revised as follows:

Title Page — Dr. Weber’s contact information was updated.

Section 3.1.5 — The phrase, “ionized serum calcium or corrected” was deleted; many sites have difficulty obtaining an ionized calcium. Corresponding changes were made in the Eligibility list on the Schema and in question 17, page 1 of the Eligibility Checklist. In addition, the phrase, “if albumin value is below normal range,” was deleted, and the phrase, “[patient albumin (g/dl) x 0.8 + patient calcium (mg/dl),” was deleted from the formula for corrected calcium.

Section 3.1.7 was revised to clarify that patients with symptomatic angina, who are subsequently determined to be disease free, are eligible for the study; Corresponding changes were made in question 5, page 1 of the Eligibility Checklist.

Section 3.2.5 was revised to allow “nodal sampling of neck” and exclude “radical or modified neck dissection.” Corresponding changes were made in question 8, page 1 of the Eligibility Checklist.

Section 4.6.3 — The parenthetical phrase, “must be done in the presence of elevation > 2 x ULN of alkaline phosphatase, SGOT, bilirubin, or other clinical indicator,” was added for clarity; this phrase also was added in Section 11.1, to footnote “b.”

The following changes were made to Section 7.2.1:

- Section 7.2.1.1 — The first sentence was revised to read, “…on days 1, 22, and 43 of the treatment course, i.e., weekends count as days.” (a corresponding change also was made in Section 7.2.2.1). The last two sentences of Section 7.2.1.1, concerning body surface area, were added;
- Section 7.2.1.4.1 — The phrase, “hold treatment until ANC > 2000,” was corrected to “hold treatment until ANC ≥ 2000;”
- **Section 7.2.1.4.5**, “Other Toxicities,” was added with dose modifications for mucositis and ototoxicity;
- **Section 7.2.1.4.6** was revised for clarity.

**Section 11.2** — The section previously numbered 11.2 was deleted, and the subsequent section was renumbered appropriately as Section 11.2. The remaining section adequately defines response.

**Section 12.0** — The data submission address and information was updated to RTOG standard.

**Section 12.1** — One of the Tumor and Nodal Diagrams, the I6, was deleted, as this form is not being collected. The schedule for the Operative Report (S2) and the Surgical Pathology Report (S5) was clarified.

**A revised protocol is available (no password required) on the RTOG web site**, [http://www.rtog.org](http://www.rtog.org)
SUMMARY OF CHANGES
Update Date: May 13, 2003

RTOG H-0129, “A Phase III Trial Of Concurrent Radiation And Chemotherapy For Advanced Head and Neck Carcinomas”

Study Chair: K. Kian Ang, M.D., (713) 792-3409, FAX # (713) 794-5573, kianang@mdanderson.org

RTOG H-0129 has been updated as follows:

**Title Page** — Changed Medical Oncologist to Dr. Wheeler; corresponding changes were made to Sections 7.0, 7.2 and 7.2.1.4.4.

**Section 10.2.2** — Changed blood shipment location to LDS Hospital in Salt Lake City, Utah.

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”.

An updated protocol is available (no password required) on the RTOG website: http://www.rtog.org/