SUMMARY OF CHANGES
Update: April 27, 2012
(Broadcast: April 27, 2012)

RTOG 1010, "A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2-Overexpressing Esophageal Adenocarcinoma"

Study Chair: Howard Safran, MD; 401-444-6217; hsafran@lifespan.org

RTOG 1010 has been updated as follows:

Section 3.1.1: The header ***"Prior to Step 1 Registration But within 56 Days prior to Step 2 Registration"*** was moved farther down in the section to be consistent with the changes made with the current Amendment 2 (removal of the 56 day time frame from the pathological diagnosis but still required to be within the time frame for all staging/laboratory studies) **Corresponding Change** made to **Appendix II**

SUMMARY OF CHANGES
Amendment 2, Version Date: February 22, 2012
(Broadcast: April 10, 2012)

RTOG 1010, "A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2-Overexpressing Esophageal Adenocarcinoma"

Study Chair: Howard Safran, MD; 401-444-6217; hsafran@lifespan.org

---

RTOG 1010 has been amended as follows:

At CTEP's request the CAEPR for trastuzumab (Section 7.3.1.6) and the risks related to trastuzumab (Appendix I) have been amended.

Per CTEP, the following specific changes were made to the CAEPR:

- The Agent Specific Adverse Event List (ASAEL) is now termed the Specific Protocol Exceptions to Expedited Reporting (SPEER) and includes grades for adverse events found on the SPEER that are used to determine if expedited reporting is required.
- Added New Risk:
  - Also Reported on Trastuzumab Trials But With the Relationship to Trastuzumab Still Undetermined: Acute coronary syndrome; Atrial fibrillation
- Decrease in Risk Attribution:
  - Changed to Rare but Serious from Less Likely: Adult respiratory distress syndrome; Bronchospasm; Pneumonitis
  - Changed to Reported But Undetermined from Less Likely: Cardiac arrest; Cardiac troponin I increased; Pleural effusion
- Provided Further Clarification:
  - The footnote has been deleted from Pleural effusion.
  - The footnote for Urticaria has been deleted.
- Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
  - Added: Back pain; Bone pain; Flu like symptoms; Pain; Rash acneiform
  - Deleted: Allergic reaction; Bronchospasm
- Deleted Risk:
  - Less Likely: White blood cell decreased

Per CTEP, the following specific changes were made to the risks related to trastuzumab in the sample consent (Appendix I):

- Decrease in Risk Attribution:
  - Changed to Rare but Serious from Less Likely: Inflammation of the lungs that may cause difficulty breathing and can be life-threatening; Severe potentially life-threatening damage to the lungs which can lead to fluid in the lungs; Sudden constriction of the small airways of the lung that can cause wheezing and shortness of breath
  - Changed to Reported But Undetermined from Less Likely (i.e., Removed from the Risk Profile): Build up of a large amount of fluid between the layers of tissue that line the lungs and chest cavity; Increased blood level of a heart muscle protein (troponin I) indicating damage to the heart muscle; The heart stops pumping blood
- Deleted Risk:
  - Less Likely: Decrease in the total number of white blood cells (leukocytes)

Per CTEP: The potential risks listed in the CAEPR whose relationship to trastuzumab is still undetermined are not required by CTEP to be described in the sample consent; however, they may be communicated to patients according to local IRB requirements.

Continued on next page

Other Changes

The protocol has been amended to allow Intensity Modulated RT (IMRT). The following sections were amended for this change: The **Schema page** ("note" added below the Schema); **Eligibility Checklist for Step 1** (page 2: "and IMRT" added to 1st sentence below "The following questions will be asked at Study Registration"; page 3: addition of question 25); **Sections 5.1, 6.0, 6.4, 6.5, and 6.7**. In addition, the text in Section 6.9 was moved to Section 6.7, and subsequent sections were appropriately renumbered.

Title page: Amendment 2 was added to and the protocol version date was amended in the Document History table.

Schema page: "Patient Population" was amended to be consistent with changes made in Sections 3.1.1.1 and 3.1.2.1.

Sections 3.1.1.1 and 3.1.2.1: The required timeframe for pathologic confirmation of diagnosis (56 days prior to Step 2 registration) was deleted as it was unnecessarily restrictive. Patients are still required to have a biopsy to confirm diagnosis and all staging/laboratory studies must be completed within the timeframes specified in Section 3.0.

Section 3.1.1.3: The reference to Section 10.2.3 was corrected to Sections 10.2.2 and 10.2.3.

Section 4.1.2: The required timeframe for Na, K, BUN, and glucose was amended to within 14 days prior to Step 1 registration; these tests no longer have to be repeated 14 days prior to Step 2 registration.

Section 7.1: A "note" was added to require that chemotherapy be administered within 48 hours of the scheduled date for this treatment, to reduce protocol violations.

Section 7.6.1: The phrase, "within 72 hours of" was added to the 1st sentence to expand the timeframe for blood counts. The expanded timeframe will provide flexibility for patients and sites.

Section 8.1: In the 1st sentence, the phrase, "imaging and", was deleted to remove the requirement that imaging must be done prior to the placement of a stent. EUS can provide the local T stage. A "note" was added to instruct sites that if imaging demonstrates adenopathy, then an EUS is not required, to make this section consistent with Appendix II.

Appendix I:

- On the 1st page, NCI's template date was amended to August 12, 2011, to update the appendix to the current NCI consent template.
- Under "Before you begin the study", in the 3rd bulleted item of the 2nd paragraph, the phrase, "If your doctor recommends", was added prior to "endoscopic ultrasound" to be consistent with Section 8.1 and Appendix II.
- Under "Will my medical information be kept private?", the last 3 paragraphs were added to update the appendix to the current NCI consent template language.
- Under "Where can I get more information?", at NCI's request, the TTY number for the NCI's Cancer Information Servide was deleted.

Continued on next page

Appendix II:

- The pre-treatment timeframe for Na, K, BUN, and glucose was clarified to “Within 14 days prior to Step 1 registration”, as is consistent with changes made in Section 4.1.2.
- The assessment, creatinine, was moved from “Na, K, BUN, and glucose” to a separate row and the required timeframes for this assessment were added to be consistent with Sections 3.0 and 4.0.
- The assessments in the column, “Within 14 days prior to Step 2 registration” were corrected to indicate that Na, K, BUN, glucose, bilirubin, and AST are not required in this timeframe.

SUMMARY OF CHANGES
Update: December 20, 2011
(Broadcast: December 20, 2011)

RTOG 1010, "A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2-Overexpressing Esophageal Adenocarcinoma"

Study Chair: Howard Safran, MD; 401-444-6217; hsafran@lifespan.org

---

RTOG 1010 has been updated for implementation of CTSU's Oncology Patient Enrollment Network (OPEN). The following changes were made:

- **Title pages**: CTSU's contact information (2nd text box) was updated on the 3rd page.
- **Index page**: Reference to "Appendix VII, CTSU Logistics", was deleted.
- **Section 5.2**, "Regulatory Pre-Registration Requirements", was updated.
- **Section 5.4**, " Registration", was updated.
- **Appendix VII**, "CTSU Logistics", was deleted.

Other Changes:
Section 10.3.4 and Appendix VI: The street address of the RTOG Biospecimen Resource was updated.

SUMMARY OF CHANGES
Update: August 16, 2011
(Broadcast: August 16, 2011)

RTOG 1010, "A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2-Overexpressing Esophageal Adenocarcinoma"

Study Chair: Howard Safran, MD; 401-444-6217; hsafran@lifespan.org

RTOG 1010 has been updated as follows:

Title page: Updated to include information for SWOG Endorsement Plus of RTOG 1010

Section 7.2: The timeframe for administration of chemotherapy was clarified in the 2nd and 3rd sentences of the 1st paragraph

Section 7.2.2: Clarifying text for the use of an equivalent agent for dexamethasone administration was added to the 1st sentence of the 2nd paragraph.

SUMMARY OF CHANGES
Amendment 1: July 26, 2011
(Broadcast: August 16, 2011)

RTOG 1010, "A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2-Overexpressing Esophageal Adenocarcinoma"

Study Chair: Howard Safran, MD; 401-444-6217; hsafran@lifespan.org

RTOG 1010 has been amended as follows:

Section 3.1.1.1: The time frame for confirmation of primary adenocarcinoma of the esophagus was added for clarity

Section 3.1.1.4: A clarifying note about the requirement for the endoscopic ultrasound was added; a corresponding change was made to **question #4** of the **Eligibility Checklist (Step 2);** a corresponding change and additional clarifying text was added to the 2nd and 3rd bullets of **Section 10.2.1**

Section 7.1.1: Text clarifying the administration of chemotherapy and trastuzumab with radiation along with text clarifying the recalculation of doses for body weight in Arm 1 was added.

Section 7.1.2: Text clarifying the administration of chemotherapy with radiation along with text clarifying the recalculation of doses for body weight in Arm 2 was added.

Section 7.2.1: The duration of administration for trastuzumab on day 57 was added to the 3rd sentence.

Section 7.6: Text stating that chemotherapy doses that are missed for toxicity are not made up was added as the last sentence.

Section 7.6.1: The blood count for ANC in the 1st row, 1st column was modified from ">1,000 mcL" to "≥ 1,000 mcL"

Section 7.6.2: Clarifying text for treatment related toxicities was added to the "Nonhematologic Adverse Events"

Section 7.9: The AE reporting table was revised per the current NCI reporting guidelines

Section 10.2.2: Instructions for submitting the Specimen Form (SP) and the Specimen Transmittal Form (ST) form have been revised in the 4th and 5th bullet

Section 10.3.3: the 2nd row, 2nd column was revised to clarify that the a 2nd biopsy from the endoscopic ultrasound is highly recommended, but not required for patients in whom HER 2 status has already been determined.

Section 13.5.4.3: Treatment Arms 1 and 2 which were inadvertently reversed in the 2nd paragraph have been corrected; The futility rule has been corrected to reflect the critical values for comparison with the interim analysis Z-scores.

Appendix I (Informed Consent):

- **"**Before you begin the study"…the Endoscopic Ultrasound was removed from the 3rd paragraph, 7th bullet and added as a procedure in the 2nd paragraph 3rd bullet for clarity;

The Pulmonary Function tests was added as a 7th bullet in the 3rd paragraph to correspond with the timeframes indicated in Appendix II

- "Risks and side effects related to radiation…", Under "Rare but Serious", "for" was corrected to "from" in the 3rd bullet; "Risks and side effects related to paclitaxel", Under "Likely", the risk "Tanning and redness of the skin in the treatment area" was removed, as it is already previously listed as a "Likely" side effect related to radiation.
- "Reproductive Risks", an additional statement stating that the exposure to both trastuzumab and radiation therapy during pregnancy can cause fetal death has been added at the request of the American College of Radiology IRB
- "About Using Tissue, Blood and Urine for Research", the title of and link to access the information sheet has been revised

Appendix II: The "Tissue for banking" assessment has been revised to clarify that the tissue may also be collected from the endoscopic ultrasound and biopsy, if performed.

Other Changes:

Global: All weblinks and related descriptions to sub-pages of the RTOG website were updated.

Title page: Updated to include relative information for both ECOG and NSABP recent protocol endorsements

SUMMARY OF CHANGES
Update: February 3, 2011
(Broadcast: February 3, 2011)

RTOG 1010, "A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2-Overexpressing Esophageal Adenocarcinoma"

Study Chair: Howard Safran, MD; 401-444-6217; hsafran@lifespan.org

---

RTOG 1010 has been updated as follows:

Section 7.2.2: 4th paragraph**,** 1st sentence**,** the timeframe for monitoring blood pressure during infusion of Paclitaxel has been clarified.

Section 7.8.3: The RTOG HQ address has been deleted, as submission of hard copy AML/MDS reports are no longer required per current RTOG standard.

Section 10.3.3: The following changes have been made per current RTOG Biospecimen Resource Standard:

Specimen Collection Summary table, 4th row, 1st and 3rd columns have been revised; Corresponding changes have also made to **Appendix VI RTOG Blood Collection Kit Instructions** in the 1st bullet and 4th note under Plasma processing instructions.

Specimen Collection Summary table, 5th row, 1st and 3rd columns have been revised; Corresponding changes have also been made to **Appendix VI RTOG Blood Collection Kit Instructions** in the 1st bullet and 2nd note under Whole Blood for DNA processing instructions.;

Specimen Collection Summary table, 6th row, 3rd columns have been revised.

Section 12.1: A Post Treatment Response Form (F2) and the time frame for submission were added, as they were inadvertently left out of the protocol at activation.

Appendix II: 1st column, "Tissue banking, if patient consents" has been corrected to indicate that this assessment applies to all patients, per the protocol.

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

RTOG 1010, A Randomized Phase II Study of Adjuvant Concurrent Radiation and Chemotherapy

Versus Radiation Alone in Resected High-Risk Malignant Salivary Gland Tumors

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

RTOG 1010 has been updated as follows:

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

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

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

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