SUMMARY OF CHANGES
Amendment 5, Version Date: November 29, 2011
(Broadcast: December 16, 2011)

RTOG 0921, A Phase II Study of Postoperative Intensity Modulated Radiation Therapy (IMRT) With Concurrent Cisplatin and Bevacizumab Followed by Carboplatin and Paclitaxel for Patients With Endometrial Cancer

Study Chair: Akila Viswanathan, MD, MPH; 617-732-6331; aviswanathan@lroc.harvard.edu

In response to a CTEP Request for Amendment (RA) for protocols using bevacizumab (NSC 704865, IND 7921) RTOG 0921 was amended as follows:

Section 7.2.14: Comprehensive Adverse Events and Potential Risks list (CAEPR) version 2.2 (October 21, 2011) has replaced CAEPR Version 2.1 (May 4, 2010). Specific changes are as follows:

- 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:
  - Likely: Reproductive system and breast disorders - Other (ovarian failure)
  - Less Likely: Febrile neutropenia; Gastrointestinal obstruction
  - Also Reported on Bevacizumab Trials But With the Relationship to Bevacizumab Still Undetermined: Platelet count decreased; Palmar-plantar erythrodysesthesia syndrome

- Increase in Risk Attribution:
  - Changed to Less Likely from Reported But Undetermined: Osteonecrosis of jaw; Peripheral sensory neuropathy

- Decrease in Risk Attribution:
  - Changed to Less Likely from Likely: Diarrhea; Nausea; Vomiting; Fatigue; Headache
  - Changed to Rare But Serious from Less Likely: Acute kidney injury

- Provided Further Clarification:
  - The following footnote was added to Gastrointestinal obstruction: "Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC."
  - The following footnote was added to Osteonecrosis of jaw: "Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates."
  - The following footnote was added to Peripheral sensory neuropathy: "Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone."
  - The following footnote was added to Reproductive system and breast disorders - Other (ovarian failure): "Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL) was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of
menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.”

- Renal and urinary disorders – Other (renal failure) is now reported as part of Acute kidney injury.
- Respiratory, thoracic, and mediastinal disorders – Other (rhinitis) is now reported as Allergic rhinitis.
- Skin and subcutaneous disorders – Other (rash) is now reported as Rash maculo-papular.
- Small intestinal obstruction is now reported as part of Gastrointestinal obstruction.

- **Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:**
  - **Added:** Febrile neutropenia; Colitis; Myalgia
  - **Deleted:** Myocardial infarction; Intracranial hemorrhage; Ischemia cerebrovascular

**Appendix I/Sample Consent, Risks associated with bevacizumab:** The risk profile was updated to reflect the CAEPR as follows:

- **Added New Risk:**
  - **Likely:** Loss of the normal functioning of the ovaries in a woman that can result in temporary or permanent menopause; the impact on fertility (temporary or permanent) is unknown
  - **Less Likely:** Fever associated with dangerously low levels of a type of white blood cell (neutrophils); Blockage in an organ(s)/part(s) of the digestive tract

- **Increase in Risk Attribution:**
  - **Changed to Less Likely from Reported But Undetermined:** Destruction or death of jawbone; Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning

- **Decrease in Risk Attribution:**
  - **Changed to Less Likely from Likely:** Diarrhea; Nausea or the urge to vomit; Vomiting; Fatigue or tiredness; Headache or head pain
  - **Changed to Rare But Serious from Less Likely:** Sudden decrease of kidney function

**Additional editorial/administrative changes:**

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

**Section 5.3.1:** The weblink was updated for the Certification Form, and an option for emailing the form was added.

**Section 10.5, table:** In the DNA line, the redundant “of” was removed and “fand” was corrected to “and.”

**Section 10.6 and Appendix V (Tissue & Blood Collection Kit and Instructions):** The mailing address was updated for the RTOG Biospecimen Resource.

**Section 12.2.1:** The mailing address was updated for the Radiologic Physics Center (RPC).

**Appendix I (Informed Consent):**

- "About Using Tissue for Research": The NCI weblink was updated in the last sentence of the 2nd paragraph.
• “Where can I get more information?”: The NCI TTY number is no longer in service and has been removed.

Appendix V (Tissue & Blood Collection Kit and Instructions), Preparation and Processing of Serum, Plasma and Whole Blood

• (B) Plasma: A space was added between “collected.” and “Label”
• (C) Whole Blood for DNA: A space was added between “as” and “necessary”
SUMMARY OF CHANGES
Amendment 4, Version Date: February 21, 2011
(Broadcast: March 3, 2011)

RTOG 0921, “A Phase II Study of Postoperative Intensity Modulated Radiation Therapy (IMRT) With Concurrent Cisplatin and Bevacizumab Followed by Carboplatin and Paclitaxel for Patients With Endometrial Cancer”

Study Chair: Akila Viswanathan, MD, MPH; 617-732-6331; aviswanathan@lroc.harvard.edu

RTOG 0921 has been amended as follows:

Eligibility Checklist:

- Page 1, Question 5, exclusion of patients with positive washings was removed, as this staging system no longer applies and has since been revised, therefore the phrase “positive peritoneal cytology” was removed. Corresponding changes were also made in Section 1.0, 3rd paragraph, last sentence, Section 3.2.4 and Section 11.2.2
- Page 1, Question 4, the “Note” at the end of the sentence was added for clarity. A corresponding change was made in Section 3.1.2
- Page 2, Question 17, exclusion criteria for patients with grade 1 neuropathy was revised to “> grade 1” from “≥ grade 1” A corresponding change was also made in Section 3.2.8
- Page 3, Question 31, the section of reference was corrected from “3.2.6” to “3.2.7”

Section 3.1.10: Revised to indicate that the CT or PET/CT is now required for all patients. A corresponding change was made to the Eligibility Checklist, Question 16

Section 4.1.1: The appropriate electrolyte references were provided for clarity. Corresponding changes were also made in Section 11.2.3 and Appendix II, 1st column, 9th row

Section 6.5.7: Contours to be submitted for evaluation have been added

Section 7.1: The timing of radiation therapy was revised to indicate that it may now be administered before or after chemotherapy. Corresponding changes were also made to Section 7.2.12 and Section 7.3.8

Section 7.7.1.3: Dose level Modification table for Carboplatin/Paclitaxel. Only 1 dose reduction will now be allowed. Therefore the statement “Patients who require more than 1 dose reduction will be removed from protocol treatment” has been added between the first and second table. As a result, corresponding changes have been made throughout the “Modification” column.

Appendix I/Sample Informed Consent
“What will happen ….” the 4th bullet was revised to indicate that the CT or PET/CT is now required for all patients

Other Changes
Title Page: The email address of the Senior Statistician and the Document History have been revised per current RTOG standard

Section 7.9.3: Text referring to AML/MDS paper report forms has been removed since AdEERS will now be used for reporting AML or MDS and additional notification to CTEP is no longer
required. Instructions for submitting a hard copy of the report, including the RTOG HQ address, have also been deleted per current RTOG standard

**Section 10.2:** 1st paragraph, 1st sentence was revised to clarify the methods being used for translational projects

**Section 10.3:** 2nd paragraph, 2nd bullet. The timepoint for whole blood collection was clarified. A corresponding change was made in the 2nd column, 6th row of the Specimen Collection Summary table

**Section 10.5:** The following changes have been made per current RTOG Biospecimen Resource standard:
- The 2nd column, 1st and 2nd rows of the Specimen Collection Summary table, the collection timepoints were clarified
- The 1st and 2nd columns, 4th row have been revised in the Specimen Collection Summary table. Corresponding changes have been made to Appendix V, 1st bullet, and 3rd note under (A) Serum Processing Instructions
- The 1st and 2nd columns, 5th row have been revised in the Specimen Collection Summary table. Corresponding changes have been made to Appendix V, 1st bullet, and 4th note under (B) Plasma Processing Instructions
- The 1st and 2nd columns, 6th row have been revised in the Specimen Collection Summary table. Corresponding changes have been made to Appendix V, 1st bullet, and 2nd note under (C) Whole Blood Processing Instructions

**Section 11.2:** Numbering sequence was corrected

**Section 12.1:** Follow-up Form (F1), the timing of follow-up has been corrected to indicate it occurs at the end of RT, not the start
In response to CTEP's October 1st Action Letter concerning carboplatin, RTOG 0921 has been amended as follows:

**Section 7.5.6:** Under "Carboplatin Administration"

- The last sentence was added under the first paragraph.
- The last two sentences were added under the second paragraph.
- The last sentence of the third paragraph was revised to clarify the minimum value to be used for the calculation of the GFR.

Under "Note", instructions regarding calculation of the carboplatin dose were added. The Jelliffe formula was replaced with the Cockcroft-Gault formula for measuring Creatinine Clearance and instructions were clarified.

**Section 7.7.1.3:** In the Dose Level Modification Table, the maximum dose level for the AUC 5 and AUC 4 were added to the last row for carboplatin.
In response to a CTEP Request for Amendment (RA) for protocols using bevacizumab (NSC 704865, IND 7921) RTOG 0921 was amended as follows:

Section 7.2.14: Comprehensive Adverse Events and Potential Risks list (CAEPR) version 2.1 (May 4, 2010) has replaced CAEPR Version 1.2 (June 19, 2007). Specific changes are as follows: (NOTE: This CAEPR version includes frequency data. The previous version did not have the categories for Likely, Less Likely or Rare but Serious. The section below utilizes CTCAE version 4.0 language unless otherwise noted.)

Added New Risk:

- **Less Likely:** Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia); Hematuria
- **Rare But Serious:** Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)
- **Reported on Bevacizumab Trials But with the Relationship to Bevacizumab Still Undetermined:** Hepatic failure; Osteonecrosis of jaw

Increase in Risk Attribution:

- Changed to Less Likely from Reported But Undetermined: Infections and infestations - Other (peri-rectal abscess); Syncope

Decrease in Risk Attribution:

- Changed to Reported But Undetermined from Possible: Skin ulceration

Provided Further Clarification:

- Allergic reaction/hypersensitivity (*CTCAE version 3.0 language*) is now reported as Allergic reaction and Anaphylaxis.
- Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip) and Nasal cavity/paranasal sinus reactions (CTCAE version 3.0 language) is now reported as Respiratory, thoracic, and mediastinal disorders - Other (rhinitis).
- Ventricular fibrillation (CTCAE version 3.0 language) is now reported as Ventricular arrhythmia and Ventricular fibrillation.
- Cardiac ischemia/infarction (CTCAE version 3.0 language) is now reported as Acute coronary syndrome and Myocardial infarction.
- Rash/desquamation (CTCAE version 3.0 language) is now reported as Skin and subcutaneous tissue disorders - Other (rash).
- Leak (including anastomotic), GI: large bowel (CTCAE version 3.0 language) is now reported as Gastrointestinal anastomotic leak.
- Mucositis/stomatitis (functional/symptomatic) - Select (CTCAE version 3.0 language) is now only reported as Mucositis oral.
- The following footnotes were added to clarify those adverse events that were previously on the version 1.2 CAEPR under - Select terms (CTCAE version 3.0 language): #2 (Fistula, GI), #3 (Hemorrhage, GI), #4 (Perforation, GI), and #5 (Ulcer, GI).
- Infection with normal ANC or Grade 1 or 2 neutrophils - Select and Infection with normal ANC or Grade 1 or 2 neutrophils - Select (pelvis, peritoneal cavity, rectum, scrotum, skin, wound) (CTCAE version 3.0 language) is now reported as Infection and the following footnote (#6) added: "Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC."
- Rectal abscess/necrosis (verbatim from source documents) is now reported as Infections and infestations - Other (peri-rectal abscess).
- Dizziness (CTCAE version 3.0 language) is now reported as Dizziness and Vertigo.
- Neurology - Other: (Leukoencephalopathy syndrome including reversible posterior leukoencephalopathy syndrome [RPLS]) (CTCAE version 3.0 language) is now only reported as Reversible posterior leukoencephalopathy syndrome.
- Fistula, pulmonary/upper respiratory - Select (CTCAE version 3.0 language) is now reported as Bronchopleural fistula and Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula).
- Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis) (CTCAE version 3.0 language) is now reported as Hoarseness.
- Fistula, GU - Select (CTCAE version 3.0 language) is now reported as Urinary fistula and Vaginal fistula.
- Renal failure (CTCAE version 3.0 language) is now reported as Acute kidney injury, Renal and urinary disorders - Other (Nephrotic Syndrome), and Renal and urinary disorders - Other (renal failure).
- Cytokine release syndrome/acute infusion reaction (CTCAE version 3.0 language) is now reported as Infusion related reaction.
- Visceral arterial ischemia (non-myocardial) (CTCAE version 3.0 language) is now reported as Vascular disorders - Other (arterial thromboembolic event), and the following footnote (#8) added: "Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke".
The following footnote (#7) was added to Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia): "Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates".

Peripheral neuropathy (verbatim from source documents) is now reported as Peripheral motor neuropathy and Peripheral sensory neuropathy.

Modified Agent Specific Adverse Events List (ASAEI) Reporting Requirements:

- **Added**: Pain; Wound dehiscence; Weight loss; Hematuria
- **Deleted (CTCAE version 3.0 language)**: Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10⁹/L); Rigors/chills; Hemorrhage, pulmonary/upper respiratory: lung

**Deleted Risk:**

- **Possible (CTCAE version 3.0 language)**: Hypotension; Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10⁹/L); Rigors/chills; Creatinine; Bronchospasm, wheezing
- **Reported on Bevacizumab Trials But with the Relationship to Bevacizumab Still Undetermined (verbatim from source documents)**: Platelets; Cardiac arrest; Hypopigmentation; Hyperglycemia; Hypoglycemia; Hypomagnesemia; Cataract; Watery eye; Urinary frequency

**Appendix I/Sample Consent, Risks associated with bevacizumab:** The risk profile was updated to reflect the CAEPR.

*Monitoring of proteinuria by urine protein creatinine (UPC) ratio was expanded and clarified throughout the protocol. Changes were made to the following sections:*

- **Sections 3.1.8-3.1.8.1**: The criterion for UPC was moved from Section 3.1.7 and was clarified and expanded. Corresponding changes were made to the Eligibility Checklist. All subsequent sections were appropriately renumbered.
- **Section 7.2.13, Proteinuria**: The bulleted text was added.
- **Section 7.6.1, Table**: The last rows were added
- **Section 11.2.5**: The section was added, and all subsequent sections were appropriately renumbered.
- **Appendix I, During the study**: Urine test was added to be consistent with the protocol.
- **Appendix I, What will happened if I take part in this research study?**: Urine test was removed from the bulleted list of procedures associated with regular cancer care and was added as a separate section to describe procedures associated with care of patients receiving bevacizumab.
- **Appendix II, Study Parameter Table**: The UPC ratio assessment line was clarified.
Other Changes

Cover Page: Contact information for Dr. Miller was updated.

Section 3.1.2, 1st, 2nd, and 3rd bullets: Stages IC or IIA, Stage IB, and Stages III-IVA were deleted for clarity and accuracy. Corresponding changes were made to the Eligibility Checklist.

Section 3.2.2: Carcinosarcoma was added. Corresponding changes were made to the Eligibility Checklist. All subsequent sections were appropriately renumbered.

Sections 5.3.1: The statement, "All pre-registration requirements must be met before registering the first case," was added for clarity.

Section 5.3.3.2: The last paragraph was added for clarity for non-Canadian international sites with approved LOIs.

Section 5.3.4: The entire section was deleted because it was included in error. The study does not incorporate a Study Agent Shipment Form, as all drug is obtained from the NCI Pharmaceutical Management Branch.

Section 6.4.11: The statement, "The vaginal/nodal PTV will exclude the structures listed in section 6.4.9, except for a 2cm region around the nodal GTV, where only small bowel will be excluded," was deleted as the requirement is only for the structures to be deleted from the CTV as already stated.

Section 6.8.5: The middle bullet, "If a cylinder is used, the dose at the apex of the cylinder should be calculated to be as close as possible (within +/-25%) to the lateral vaginal surface dose (Appendix VII)," was deleted since the vaginal apex point is not routinely recorded by most institutions.

Section 7.9: Language concerning the CTCAE Active Version was revised to CTCAE v4.0 per CTEP instructions.

Section 10.2.2

- 1st sentence: per current RTOG Biospecimen Resource standard, "tissue" was clarified as "tumor tissue" and "one skin punch" was revised to "punch tools"; corresponding changes were made to the Table in Section 10.5.
- Last sentence: "core" was corrected to "cores"; corresponding changes were made to the Table in Section 10.5.

Section 10.3: Per current RTOG Biospecimen Resource standard, buffy coat collection was changed to whole blood collection. The timing of serum, plasma and whole blood collection was clarified. Corresponding changes were made to the Table in Section 10.5, Appendix I/Sample Consent/About Using Blood for Research and Appendix.
II/Study Parameter Table.

Section 10.4: Storage conditions were added per current RTOG Biospecimen Resource standard. All subsequent sections were appropriately renumbered.

Section 10.7: Information concerning reimbursement was updated to current RTOG standard.

Section 12.2: Reference to "QA guidelines" was removed, as credentialing and treatment planning guidelines are included in the text of the protocol and/or the ATC/RPC websites.

Appendix I, What will happened if I take part in this research study? The timing of paclitaxel and carboplatin administration was corrected from "3 weeks" to "4 to 6 weeks" post treatment with bevacizumab, cisplatin, and radiation.

Appendix V: The sections for "RTOG FFPE Specimen Plug Kit Instructions" and "RTOG Blood Collection Kit Instructions" were updated to current RTOG Biospecimen Resource standard.
RTOG 0921, A Phase II Study of Postoperative Intensity Modulated Radiation Therapy (IMRT) With Concurrent Cisplatin and Bevacizumab Followed by Carboplatin and Paclitaxel for Patients With Endometrial Cancer

Study Chair: Akila Viswanathan, MD MPH; 617-732-6331; aviswanathan@lroc.harvard.edu

RTOG 0921 was amended as follows:

Appendix I/Sample Consent

- **Risks associated with carboplatin**: The risk profile was added because it was inadvertently omitted.
- **Risks associated with bevacizumab** and **Risks associated with paclitaxel**: The heading verbiage was corrected to RTOG standard and to be consistent with the other risk headings.
SUMMARY OF CHANGES

Update: November 6, 2009

(Broadcast November 6, 2009)

RTOG 0921, A PHASE II STUDY OF POSTOPERATIVE INTENSITY MODULATED RADIATION THERAPY (IMRT) WITH CONCURRENT CISPLATIN AND BEVACIZUMAB FOLLOWED BY CARBOPLATIN AND PACLITAXEL FOR PATIENTS WITH ENDOMETRIAL CANCER

Study Chair: Akila Viswanathan, MD MPH; 617-732-6331; aviswanathan@lroc.harvard.edu

RTOG 0921 has been updated as follows:

Eligibility Checklist - question 4, first bullet, page 1of 4: removed the word "cancer"

Eligibility Checklist - questions 1-24, pages 3 and 4: Revised to be consistent with current RTOG standard language.

Section 1.0: Table 1 - corrected typo in table. Replaced 382% with 22%

Sections 1.2.6, 3.2.7, 3.2.8, 7.5.6, 7.6.1, 7.7.1, 7.7.1.1, 13.1.1.1, 13.1.2.1 and 13.1.2.2, 13.2.1 - Removed all REFERENCES to CTCAE v.4.0 through-out the protocol and referenced section 7.9 which contains the new NCI standard language for CTCAE

Section 6.7.3.4 and 6.9: Revised to be consistent with current RTOG standard language

Section 12.1: The due date for the adjuvant treatment form was clarified within one-week of completion of adjuvant therapy.

Appendix I: 2nd paragraph: Added "and have had a hysterectomy" to the end of the last sentence

Why is this study being done?
1st paragraph: Revised sentence to state "an anti-cancer drug called bevacizumab has when added to standard chemotherapy"

2nd paragraph, 2nd sentence: Deleted "which is the standard therapy"

3rd paragraph, 1st sentence: Corrected typo in Food & Drug Administration

5th paragraph: Moved to section "What will happen in this study? Revised 2nd sentence to state "inside your vagina to treat..." Revised 4th sentence to state treatment will take about "10-30 minutes" and that the procedure will be done on an outpatient basis.

What will happen if I take part in this research study?

5th bullet: Added "test" after "urine"

2nd paragraph, 1st sentence: Added "and you agree" after "eligible to participate"

3rd paragraph, 1st sentence: Revised to "If you are entered onto this study"

5th paragraph/brachytherapy discussion: Revised to combine with text from "Why is this study being done?" (see above)

8th paragraph: Revised heading to read "During the study"

9th paragraph, 1st bullet: Revised" to "yearly thereafter"

Study Plan, 2nd-to-last box: Added "vaginal cuff"

How long will I be in the study?

Added treatment length and revised last sentence to clarify follow-up.

Can I stop being in the study?
Revised this section to be consistent with NCI template text

What side effects or risks can I expect from being in the study?

Risks associated with radiation therapy
- Reviewed and revised risk profile to confirm that risks are in the appropriate categories

Risks associated with cisplatin: changed headers.

Risks associated with bevacizumab
- Less likely/last bullet: Revise "stuff" to "stuffy"
- Rare but serious/4th bullet: Revise "heat failure" to "heart failure"

Risks associated with paclitaxel: Added risk "numbness or tingling in the hands or feet"

Are there benefits to taking part in the study?
Rewrote paragraph to be more specific in terms of the study

What other choices do I have if I do not take part in this study?
1st paragraph, last sentence: Revise" your tumor would continue to grow and your disease would spread" to "there is a high likelihood that your tumor would recur and your disease would spread"

Who can answer my questions about the study?

2nd sentence: Inserted NCI template text

To the tissue/blood consent

About Using Tissue and Blood for Research/1st sentence: Revised to be specific to patients who have had a hysterectomy

About Using Blood for Research/bulleted text: Revised to be consistent with timeframes provided in section 10.4 of the protocol

Risks/1st sentence: Revised to "The greatest risk from the use of your tissue for research is…"

Note: These are editorial/administrative changes to the protocol. NCI requires that these changes be documented on the protocol title page as "Update Date."