SUMMARY OF CHANGES  
Amendment 6, Version Date: May 5, 2006

RTOG 0247, "Randomized Phase II Trial of Neoadjuvant Combined Modality Therapy for Locally Advanced Rectal Cancer"

Study Chair: Neal J. Meropol, MD; ph# 215-728-2450; nj_meropol@fccc.edu

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RTOG 0247 has been amended as follows:

Section 3.1.1: "Adenocarcinoma of the rectum located up to 12 cm from the anal verge…" was revised to "Adenocarcinoma of the rectum originating at or below 12 cm from the anal verge…" to clarify the tumor location requirement for eligibility. Corresponding revisions were made to the Eligibility Checklist (page 1 of 3), Question #1; and to the eligibility synopsis on the schema page.

Section 3.1.5: The creatinine clearance formula for females was corrected; and has been provided in a more user-friendly format. For males, the creatinine clearance was correct; and it has been provided in a more user-friendly format as well. This change was completed in an administrative update on April 21, 2006.
RTOG 0247, "Randomized Phase II Trial of Neoadjuvant Combined Modality Therapy for Locally Advanced Rectal Cancer"

Study Chair: Neal J. Meropol, M.D., phone #: 215-728-2450, email: nj_meropol@fccc.edu

RTOG 0247 has been updated as follows:

Section 3.1.5: The creatinine clearance formula for females was corrected; and has been provided in a more user-friendly format. For males, the creatinine clearance was correct; and it has been provided in a more user-friendly format as well.
SUMMARY OF CHANGES
Amendment 5, Version Date: March 31, 2006

RTOG 0247, "Randomized Phase II Trial of Neoadjuvant Combined Modality Therapy for Locally Advanced Rectal Cancer"

Study Chair: Neal J. Meropol, MD; ph# 215-728-2450; nj_meropol@fccc.edu

RTOG 0247 has been amended as follows:

Index and Appendices: "Appendix IV - Adverse Reporting Guideline" was deleted due to the updated AE reporting guidelines amendment in Section 7.12. As a result all the subsequent appendices were renumbered.

Section 5.1: The first part of this section was rewritten to include the procedure for web registration. This change was completed in an administrative update on April 5, 2005.

Section 6.4: Section was deleted and replaced with the prompt, "For Instructions on Adverse Events Reporting See Section 7.12" as a result of the amendment to the AE reporting guidelines.

Sections 7.3.1 and 7.4.1: Footnote a, "See Appendix IV…" Appendix V was changed to "Appendix IV" as a result of the renumbering of Appendices IV-VII.

Section 7.4.1: In the Dose Modifications During Preoperative Chemotherapy (Arm 2) table, under the Modification column for Diarrhea, Grade 2 or 3, the typo "CPT-11" was deleted and corrected as "oxaliplatin" to correspond with the protocol treatment. This change was completed in an administrative update on September 8, 2005.

Sections 7.12 and 7.13: Adverse Events section has been amended as per the updated AE reporting guidelines.

Section 7.14: This section was renumbered from 7.13 due to the amending of the AE reporting guidelines.

Section 12.0: In the "Summary of Data Submission" table, under the QOL heading, "(12 months)" was added, so the sentence now reads, "Within 1 week of RT end, within 1 week of post-operative chemotherapy end (12 months), and at 24 month follow-up" for consistency.
RTOG 0247, “Randomized Phase II Trial of Neoadjuvant Combined Modality Therapy for Locally Advanced Rectal Cancer”

Study Chair: Neal J. Meropol, M.D., phone #: 215-728-2450, email: nj_meropol@fccc.edu

RTOG 0247 has been updated as follows:

Section 7.4.1: In the Dose Modifications During Preoperative Chemotherapy (Arm 2) table, under the Modification column for Diarrhea, Grade 2 or 3, “CPT-11” was corrected to “oxaliplatin” in accordance with the rest of the protocol.
SUMMARY OF CHANGES
Amendment 4, Version Date: June 29, 2005

RTOG 0247, “Randomized Phase II Trial of Neoadjuvant Combined Modality Therapy for Locally Advanced Rectal Cancer”

**Study Chair:** Neal J. Meropol, MD; 215-728-2450, Fax # 215-728-3639; nj_meropol@fccc.edu

RTOG 0247 has been amended to remove the postoperative chemotherapy (FOLFIRI) in Arm 1 and replaced it with the postoperative chemotherapy (FOLFOX) as in Arm 2 as follows:

**Schema:** Under Arm 1, “Postoperative chemotherapy (FOLFIRI)^4^” has been deleted and replaced by “Postoperative chemotherapy (FOLFOX)^4^”; under Arm 2, the footnote number for “Postoperative Chemotherapy: FOLFOX” has been changed to # 4 from # 6 due to the deletion of the FOLFIRI treatment (original footnote # 4).

**Section 1.5.2:** This section was added to address the reasons for changing the postoperative chemotherapy arm in Arm 1 from FOLFIRI to FOLFOX.

**Section 7.1.2.2:** The section heading, “Treatment will consist of 9 cycles (each cycle = 14 days) of 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX)” and the subsequent table listing the Agents, Doses, Routes and Schedule have replaced, “Treatment will consist of 9 cycles (each cycle = 14 days) of 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI)” and the respective table.

**Section 7.3.2:** The postoperative therapy (FOLFIRI) and the subsequent dose modifications table, which include irinotecan, have been deleted and replaced by the postoperative therapy (FOLFOX).

**Section 13.1.1:** In the second sentence, “(changed from FOLFIRI to FOLFOX on June 29, 2005)” was added to clarify that post-operative FOLFIRI has been removed from treatment. Also, “(FOLFOX)” was added to the same sentence to add further clarification.

**Section 13.2.2:** This section was added to affirm that the sample size will remain at 141 patients following the amendment to change the post-operative systemic therapy from FOLFIRI to FOLFOX.

**Section 13.5:** Two sentences were added at the end of the section to explain the temporary suspension of Arm 1, which was done pending the approval of Amendment 4.

**References:** Five references were added in support of Section 1.5.2. The newly added references are numbered 59 through 63. All references previously numbered 59 through
Informed Consent:

- Under **Why is This Study Being Done?**, in the first sentence, the words “both” and “and after surgery” were deleted from, “…patients both with radiation and after surgery to see which …”

- Under **What is Involved in this Study?** Under Arm 1, “Chemotherapy after surgery” “irinotecan” has been deleted and replaced with “oxaliplatin.”

- Under **Risks Associated with Chemotherapy**, “irinotecan” has been replaced by “oxaliplatin” after surgery in the heading: **Treatment Group A (Capecitabine, irinotecan before surgery, 5-fluorouracil, leucovorin, and oxaliplatin after surgery)** because irinotecan has been removed from postoperative chemotherapy Arm 1.

- Under **Risks Associated with Chemotherapy**: under **Treatment Group A (Capecitabine, irinotecan before surgery, 5-fluorouracil, leucovorin, and oxaliplatin after surgery)**, under “Very Likely,” the following risks have been added: “Numbness and tingling in your hands and/or feet (can feel stronger if exposed to cold)”; “Feeling of tightness or fullness in the throat, making it feel like it is difficult to breathe or swallow”; under, “Less Likely” “Inflammation of the colon” was changed to “Inflammation of the intestines”; “Changes in vision (Blurring); Rash or allergic reaction; Flu-like symptoms such as fever, chills and muscle aches”; “Damage to the kidney” were added to reflect the change from irinotecan to oxaliplatin.

- Under **Risks Associated with Chemotherapy, Treatment Group B (Capecitabine, oxaliplatin before surgery, 5-fluorouracil, leucovorin and oxaliplatin after surgery)** under, “Very Likely” “Inflammation of the bowel” was changed to “Inflammation of the intestines”; under “Less Likely” “(redness and swelling)” was added to “Inflammation (redness and swelling) of fingers and toes”; under “Less Likely, but Serious”, “resulting in shortness of breath (which may be permanent)” was added to “Lung damage”; and the risk of “Blood clots” was added.
RTOG 0247, “Randomized Phase II Trial of Neoadjuvant Combined Modality Therapy for Locally Advanced Rectal Cancer”

Study Chair: Neal J. Meropol, MD; 215-728-2450, Fax # 215-728-3639; nj_meropol@fccc.edu

RTOG 0247 has been updated to include instructions for web registration:

Section 5.1: The first part of this section was rewritten for web registration.
SUMMARY OF CHANGES  
Amendment 3, Version Date: March 22, 2005

RTOG 0247, “Randomized Phase II Trial of Neoadjuvant Combined Modality Therapy for Locally Advanced Rectal Cancer”

Study Chair: Neal J. Meropol, MD; 215-728-2450, Fax # 215-728-3639; nj_meropol@fccc.edu

RTOG 0247 has been amended regarding dose and schedule modifications as follows:

Index: Appendix VII, “Capecitabine/Diarrhea Diary” and Appendix VIII, “Patient Education Sheet” were added here because these appendices were added to the protocol.

Schema:

- Under Arm 1 #2, the text was revised as follows to reflect the change in dosing: “Capecitabine 600 mg/m² q12 hours (1200 mg/ m²/day) orally daily (5 days per week) during radiotherapy starting the evening before day 1 of RT; Irinotecan 50 mg/ m² IV over 1 hour on days 1, 8, 22, 29.” Capecitabine 7 days per week was changed to 5 days per week and day 15 of irinotecan was omitted.
- Under Arm 2 #5, the text was revised as follows to reflect the change in dosing: “Capecitabine 825 mg/ m² q12 hours (1650 mg/ m²/day) orally daily (5 days per week) during radiotherapy starting the evening before day 1 of RT; Oxaliplatin 50 mg/ m² IV over 2 hours days 1, 8, 15, 22, 29.” Capecitabine 7 days per week was changed to 5 days per week and the dose of oxaliplatin was changed from 60 to 50 mg.
- Required Sample Size: Changed to 141.

Section 1.5.1: This new section, “Toxicity update January 2005” was added to explain the rationale for the dose and schedule changes made to the protocol.

Section 7.0: A second sentence was added at the end of the second paragraph: “For the first week of treatment, the capecitabine should be started the evening before the first radiation dose.” A third paragraph “Note” was added concerning the capecitabine/diarrhea diary.

Section 7.1.1.1: The first paragraph was deleted. In the table, the dose schedule for capecitabine was revised; the dose schedule for irinotecan was revised.

Section 7.2.1.1: In the table, the schedule for capecitabine was revised; the dose of oxaliplatin was revised.

Section 7.3.1: The table was revised as follows: “cardiac toxicity, or diarrhea” was added after “hand-foot reaction” in the first box under “Toxicity”; “diarrhea” was added under
“Toxicity” with “Grade “1 with “Modification” of “No change” and “Grade 2 or 3” with “Modification” of “Hold chemotherapy and radiation until symptoms resolve to Grade ≤ 1, then resume at 75% of current capecitabine and CPT-11 doses.” If treatment is held for >14 days, remove patient from protocol therapy.” and “Grade 4” with “Modification” of “Discontinue chemotherapy and radiation.” In footnote a, “Radiation will not be held, where applicable” was deleted and “Radiation doses will not be modified” was added.

Sections 7.3.2 and 7.4.2: The following was added after the second paragraph: “If diarrhea above baseline is present on day 1 of a treatment cycle, OR if the patient has required Imodium within 24 hours, treatment should be delayed until resolution of diarrhea.” In the tables, “the same or a new” was added after “2nd or 3rd occurrence of” and “event” was added after the grade for clarification of hematologic toxicities.

Section 7.4.1: In the table, “cardiac toxicity, diarrhea, veno-occlusive disease” were added to the first box under “Toxicity”; “Diarrhea” was added under “Toxicity” with “Grade “1 with “Modification” of “No change” and “Grade 2 or 3” with “Modification” of “Hold chemotherapy and radiation until symptoms resolve to Grade ≤ 1, then resume at 75% of current capecitabine and CPT-11 doses.” If treatment is held for >14 days, remove patient from protocol therapy”; and “Grade 4” with “Modification” of “Discontinue chemotherapy and radiation.” Under “Cold-induced dysesthesias,” “persist at time of next oxaliplatin dose” the dose modification was changed to 40 mg and “oxaliplatin” was added at end of sentence. Under “2nd occurrence persisting at time of next oxaliplatin dose,” the dose modification was changed to 30 mg and “oxaliplatin was added at the end of the sentence.

Section 7.4.2: Under “Cold-induced dysesthesias,” under “Persists at time of next oxaliplatin dose,” the modification was reworded for clarity, “Hold oxaliplatin until resolved (but continue 5-FU/leucovorin), then resume at oxaliplatin dose level-1. If not resolved to ≤ 1 after 21 day delay (35 days since start of prior cycle) discontinue oxaliplatin”; under “2nd occurrence. Persists at time of next oxaliplatin dose,” the modification was reworded for clarity, “Hold oxaliplatin until resolved (but continue 5-FU/leucovorin), then resume at oxaliplatin dose level-2. If not resolved to ≤ 1 after 21 day delay (35 days since start of prior cycle) discontinue oxaliplatin.

Section 7.5.2: This section “Antibiotics” was added. Subsequent Sections 7.5.2 through 7.5.6 were renumbered as 7.5.3 through 7.5.7.

Section 7.9.6: “See Sections 7.5.1 and 7.5.2.” was added at the end of the section.

Section 7.12: “See Section 7.12.7 for Special Reporting Required for this Study.” was added.

Section 7.12.7: This section, containing Sections 7.12.7.1, 7.12.7.2 and 7.12.7.3, was added to describe special reporting for this study.

Section 11.1: The Pill/Diarrhea Review was added under “Concurrent CT/RT” Weekly
Section 13.2.1: This new section “Sample Size Amendment” was added.

Section 13.3.1: This new section “Toxicity Monitoring Amendment” was added.

Section 13.6.2: b-e were revised.

Section 13.6.2.1: This new section was added stating, “The interim analyses will include information on all patients, including those accrued prior to the amendment changing the treatment regimens.”

Section 13.7: The gender and minority accrual estimates were revised reflecting the increased sample size.

Consent:

- The letter R was deleted from the number on Appendices IA and IB.
- Under How Many People Will Take Part in the Study, 106 was changed to 141 to reflect the change in sample size.
- Under What Is Involved in the Study, the paragraphs under Arm 1 and Arm 2, Chemotherapy were revised in accordance with the revised treatment.
- “Capecitabine/Diarrhea Diary” was added under Standard procedures being done because you are in this study.
SUMMARY OF CHANGES
Amendment 2, Version Date: December 1, 2004

RTOG 0247, “Randomized Phase II Trial of Neoadjuvant Combined Modality Therapy for Locally Advanced Rectal Cancer”

Study Chair: Neal J. Meropol, MD; 215-728-2450, Fax # 215-728-3639; nj_meropol@fccc.edu

RTOG 0247 has been amended as follows in response to the memo from Dr. Percy Ivy regarding the development of VOD associated with oxaliplatin:

Index: Appendix VI has been added to reflect the addition of “Comprehensive Adverse Events and Potential Risks List (CAEPR) For Oxaliplatin” as Appendix VI to the appendices of the protocol. This appendix is cross-referenced in the new Section 7.12.6.

Section 7.2.2.3: This new section was added to address VOD and new references # 94-97 from the NCI Action Letter are cited here. These references were added to the Reference List as 94, 95, 96, and 97.

Section 7.4.1: Veno-occlusive disease and a new footnote “e” was added to the dose modification table.

Section 7.4.2: Veno-occlusive disease and a new footnote “b” was added to the dose modification table.

Section 7.6.7: The following was added to Hepatic Side Effects of 5-Fluorouracil: “Veno-occlusive disease of the liver has been reported with the administration of the combination of 5-FU and oxaliplatin.”

Section 7.8.10: The following was added to Hepatic Adverse Events of Oxaliplatin: “Veno-occlusive disease of the liver has been reported with the administration of the combination of 5-FU and oxaliplatin.”

Consent: Under What Are the Risks of the Study, under Treatment Group B:

- under “Less Likely,” “Changes in liver function tests…” was changed to “Liver damage, which may rarely be severe and life threatening”
- a new category “Rare” was added with the following text: “Liver damage, occurring with the administration of the combination of 5-FU and oxaliplatin that could result in enlarged liver and spleen, liver failure, and bleeding from the esophagus or stomach”

Other Changes to the Protocol:
Section 10.1.5: The email address for LDS Hospital was updated.
Section 12.1: Form FF was deleted as it was included erroneously.

A revised protocol and a protocol with all revisions tracked are attached.
SUMMARY OF CHANGES
Revision 1, Version Date: August 19, 2004

RTOG 0247, “Randomized Phase II Trial of Neoadjuvant Combined Modality Therapy for Locally Advanced Rectal Cancer”

Study Chair: Neal J. Meropol, MD; 215-728-2450, Fax # 215-728-3639; nj_meropol@fccc.edu

RTOG 0247 has been revised as follows:

Eligibility Checklist, p. 2: Deleted # 17 because there is no IMRT in this protocol. Items following were re-numbered.

Section 3.1.5: Typo: changed “AST, alkaline phosphatase” to “AST and alkaline phosphatase”

Section 5.1 and 7.8.8.1: Inserted instructions for Canadian institutions as follows:

“Once all regulatory documents are received at headquarters, the institution’s Research Associate will receive a Study Agent Shipment Form (SASF) for Oxaliplatin. The SASF must be completed and faxed to RTOG headquarters (215-928-0153) prior to registering the first case. Institutions must also notify the RTOG Canadian Regulatory Compliance Associate (215-574-3191) of patient registrations so that Oxaliplatin can be shipped.”

Sections 7.3.1, 7.4.1, 7.6.7, 7.10.7, and new Section 7.13: In these sections the following wording was added concerning cardiac toxicity from capecitabine and 5-FU: “For ≥ Grade 2 cardiac toxicity that is attributable to 5-FU or capecitabine, patients will be permanently discontinued from therapy.” The wording in the Section 7.3.1 and 7.4.1 is slightly abbreviated to fit the table format.

Section 7.4.1: Correction to dose modifications: In the section of the table “for cold-induced dysesthesias that persist at time of next Oxaliplatin dose”: Changed the dose from 65 mg/m² to 45 mg/m².

In the section of the table “for 2nd occurrence persisting at time of next Oxaliplatin dose – second occurrence”: Changed the dose from 45 mg/m² to 35 mg/m².

Section 7.9.6: For clarity, changed the wording of the first sentence to “Irinotecan is administered by IV over 60 to 90 minutes, depending on the dose administered (as per Sections 7.1.1.1 and 7.1.2.2).”

Section 7.1.1.1 Under "ROUTE": For clarity, the wording has changed from "1 hour" to "60 minutes"
Section 7.12: Adverse Drug Reaction Reporting Section (deleted the word “Guidelines”): Replaced all paragraphs except the first paragraph with new wording that is standard RTOG protocol wording.

Sections 7.12.3.7, 7.12.5, and 12.0: Updated RTOG’s mailing address to 1818 Market Street, Suite 1600, Philadelphia, PA 19103.

Section 10.1.2: Typo: Changed (see Section 10.8) to (see Section 10.1.3).
SUMMARY OF CHANGES  
Update Date: May 21, 2004

RTOG 0247, “Randomized Phase II Trial of Neoadjuvant Combined Modality Therapy for Locally Advanced Rectal Cancer”

Study Chair: Neal J. Meropol, M.D., 215-728-2450, nj_meropol@fccc.edu

RTOG 0247 has been updated as follows:

Section 12.1 — Under “QOL Assessments”, added Pretreatment Questionnaire – Female (FS), Pretreatment Questionnaire – Male (FL), and under “Final Dosimetry Information” added Radiotherapy Form (T1).

Appendix I —

- Under “Why Is This Study Being Done?”, deleted typo “and after surgery” in the first sentence.
- Under “How Long Will I Be In The Study?”, in second sentence, changed wording to read “and six to eight weeks after completion of radiation therapy, you will have surgery.”
- Under “Are There Benefits To Taking Part In The Study?”, in second sentence, added the word “cancer” after “rectal” for clarity.

NOTE: These are editorial/administrative changes to the protocol. NCI now requires that these changes be documented on the protocol title page with the date of the update noted as “Update Date”, not as a revision.

An updated protocol is available (no password required) on the RTOG website:  
www.rtog.org
SUMMARY OF CHANGES
Update Date: April 19, 2004

RTOG 0247, “Randomized Phase II Trial of Neoadjuvant Combined Modality Therapy for Locally Advanced Rectal Cancer”

Study Chair: Neal J. Meropol, M.D., 215-728-2450, nj_meropol@fccc.edu

RTOG 0247 has been updated as follows:

Eligibility Checklist, page 1 typos: the measurements in questions 6 and 7 were changed to microliters “per µL”.

Section 1.2.3 — For clarity, the word “slightly” was deleted from the first sentence.

Section 1.6 — Corrected typos in the 4th sentence (deleted “a” after “however”) and 7th sentence (deleted “of” after “degrade”).

NOTE: These are editorial/administrative changes to the protocol. NCI now requires that these changes be documented on the protocol title page with the date of the update noted as “Update Date”, not as a revision.

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