RADIATION THERAPY ONCOLOGY GROUP

RTOG 0247

RANDOMIZED PHASE II TRIAL OF NEOADJUVANT COMBINED MODALITY THERAPY FOR LOCALLY ADVANCED RECTAL CANCER

Study Chairman
Neal J. Meropol, M.D.
Fox Chase Cancer Center
7701 Burholme Avenue
Philadelphia PA 19111
215-728-2450
Fax 215-728-3639
nj_meropol@fccc.edu

Pathology Co-Chair
Asif Rashid, M.B.B.S., Ph.D.
Department of Pathology, Box 85
University of Texas MD Anderson Cancer Center
1515 Holcombe Boulevard
Houston, TX 77030-4095
Phone: (713) 745-1101
Fax: (713) 732-5531
E-mail: arashid@mdacc.tmc.edu

Surgical Oncology Co-Chair
James C. Watson, M.D.
Fox Chase Cancer Center
7701 Burholme Avenue
Philadelphia PA 19111
215-214-1437
jc_watson@fccc.edu

Medical Oncology Co-Chair
Stuart Wong, M.D.
Medical College of Wisconsin
9200 W. Wisconsin Avenue
Milwaukee, WI 53226
414-805-4603
Fax 414-805-4606
swong@mcw.edu

Radiation Oncology Co-Chair
Rani Anne, M.D.
Thomas Jefferson Hospital
111 S. 11th St
Philadelphia, PA 19107
215-955-6045
Fax 215-955-0412
rani.anne@mail.tju.edu

Quality of Life Co-Chair
Lisa Kachnic, M.D.
Boston University Medical Center
88 East Newton Street, EB11
Boston, MA 02118
617-638-7070
Fax: 617-638-7037
lisa.kachnic@bmc.org

Activation Date: March 15, 2004
Closure Date: February 23, 2007
Termination Date: December 15, 2016
Update Date: April 21, 2006
Version Date: May 5, 2006
Includes Amendments 1-6
(Broadcast May 18, 2006)

This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.
INDEX

Schema

Eligibility Check

1.0 Introduction

2.0 Objectives

3.0 Patient Selection

4.0 Pretreatment Evaluations

5.0 Registration Procedures

6.0 Radiation Therapy

7.0 Drug Therapy

8.0 Surgery

9.0 Other Therapy

10.0 Pathology

11.0 Patient Assessments

12.0 Data Collection

13.0 Statistical Considerations

References

Appendix I - Sample Consent Form
Appendix II - Performance Status Scoring
Appendix III - Staging System
Appendix IV - Capecitabine BSA Dose Calculation Tables (3/31/06)
Appendix V - Comprehensive Adverse Events and Potential Risks List For Oxaliplatin (3/31/06)
Appendix VI - Capecitabine/Diarrhea Diary (3/22/05) (3/31/06)
Appendix VII - Patient Education Sheet (3/22/05) (3/31/06)
RADIATION THERAPY ONCOLOGY GROUP

RTOG 0247

Randomized Phase II Trial of Neoadjuvant Combined Modality Therapy for Locally Advanced Rectal Cancer

SCHEMA (3/22/05) (6/29/05) (05/05/06)

Arm 1: Radiation therapy + preoperative chemotherapy
↓
Surgery
↓
Postoperative chemotherapy (FOLFOX)

Arm 2: Radiation therapy + preoperative chemotherapy
↓
Surgery
↓
Postoperative chemotherapy (FOLFOX)

1. Radiation Therapy
Pelvic EBRT 45 Gy in 25 fractions (1.8 Gy/fx), five fractions per week; boost of 5.4 Gy in 3 fractions (1.8 Gy/fx) to conedown volume to a total dose of 50.4 Gy.

Chemotherapy

ARM 1: (3/22/05) (6/29/05)
2. Preoperative Chemotherapy
Capecitabine 600 mg/m\(^2\) q12 hours (1200 mg/ m\(^2\)/day) orally daily (5 days per week) during radiotherapy starting the evening before day 1 of RT; Irinotecan 50 mg/ m\(^2\) IV over 1 hour on days 1, 8, 22, 29.

3. SURGERY
All patients will undergo surgery four to eight weeks following the completion of radiation therapy.

4. Postoperative Chemotherapy: FOLFOX (Administer sequentially as written, except oxaliplatin and leucovorin may be administered concurrently) x 9 cycles (each cycle = 14 days); Oxaliplatin 85 mg/ m\(^2\) IV over 2 hours (day 1, every 14 days); Leucovorin 400 mg/ m\(^2\) IV over 2 hours (day 1, every 14 days); 5-FU bolus 400 mg/ m\(^2\) IV push (day 1, every 14 days); 5-FU infusion 2400 mg/ m\(^2\) IV continuous infusion over 46 hours (beginning day 1, every 14 days).

ARM 2: (3/22/05) (6/29/05)
5. Preoperative Chemotherapy
Capecitabine 825 mg/ m\(^2\) q12 hours (1650 mg/ m\(^2\)/day) orally daily (5 days per week) during radiotherapy starting the evening before day 1 of RT; Oxaliplatin 50 mg/ m\(^2\) IV over 2 hours days 1, 8, 15, 22, 29.

3. SURGERY
All patients will undergo surgery four to eight weeks following the completion of radiation therapy.

4. Postoperative Chemotherapy: FOLFOX (Administer sequentially as written, except oxaliplatin and leucovorin may be administered concurrently) x 9 cycles (each cycle = 14 days); Oxaliplatin 85 mg/ m\(^2\) IV over 2 hours (day 1, every 14 days); Leucovorin 400 mg/ m\(^2\) IV over 2 hours (day 1, every 14 days); 5-FU bolus 400 mg/ m\(^2\) IV push (day 1, every 14 days); 5-FU infusion 2400 mg/ m\(^2\) IV continuous infusion over 46 hours (beginning day 1, every 14 days).
Eligibility: (See Section 3.0 for details)
- Patients with potentially resectable adenocarcinoma of the rectum originating at or below 12 cm from the anal verge without evidence of distant metastases.
- Patients must be 18 years old or greater
- Patients with clinical stage T3, based on endorectal ultrasound; or patients with clinical stage T4 based on endorectal ultrasound or physical exam.
- Patients with lab values within standard protocol parameters
- Zubrod performance status 0-2
- No history of other malignancies within 5 years, except non-melanoma skin cancer, in situ carcinoma of the cervix or ductal carcinoma of the breast. Previous invasive cancer permitted if disease-free at least 5 years
- Patient must sign study-specific consent prior to randomization.

Required Sample Size: 141 (3/22/05)
1. Does the patient have adenocarcinoma of the rectum originating at or below 12 cm from the anal verge? (Y)
2. Is there evidence of distant metastases? (N)
3. How old is the patient? (> 18 yrs.)
4. Does the patient have potentially resectable disease based upon surgical evaluation? (Y)
   What is the T stage? (T3 or T4)
5. If T3, was an endorectal ultrasound done? (Y)
6. What is the absolute neutrophil count? (> 1500 per µL)
7. What is the platelet count? (> 100,000 per µL)
8. Were AST, alkaline phosphatase, LDH, bilirubin, CBC with differential, platelets and CEA obtained prior to registration and within the eligibility parameters? (Y)
9. Was the calculated creatinine clearance > 50 ml/min using Cockcroft-Gault formula? (Y)
10. What is the Zubrod performance status? (0-2)
11. Is there a history of invasive cancer within the past five years? (N)
12. Does the patient have any serious, uncontrolled infection(s). (N)
13. Does the patient have any clinically significant cardiac disease (e.g. congestive heart failure, coronary artery disease and/or arrhythmias not well controlled with medication) or myocardial infarction within the last 12 months? (N)
14. Does the patient have a history of uncontrolled seizure, central nervous system disorders or psychiatric disability judged by the investigator to be clinically significant, precluding informed consent, or interfering with compliance of oral drug intake? (N)
15. Does the patient have any other serious uncontrolled medical conditions that the investigator feels might compromise study participation? (N)
16. Has the patient had major surgery within 4 weeks of the start of study treatment? (N)
17. Does the patient have any known, existing, uncontrolled coagulopathy? (N)
18. Did the patient sign the consent form? (Y)
19. Does the patient have any synchronous primary colon carcinomas other than T1 lesions? (N)
20. Does the disease extend to the anal canal? (N)
21. Does the patient have a lack of physical integrity of the upper gastrointestinal tract or malabsorption syndrome? (N)
22. Is there a history of prior pelvic radiation? (N)
23. Has the patient received prior chemotherapy? (N)
24. Is the patient pregnant or lactating? (N)
25. Is the patient willing to use appropriate contraception? (Y)
26. Has the patient participated in another clinical trial within four weeks prior to study entry? (N)
27. Does the patient demonstrate a willingness to participate and ability to comply with the protocol for the duration of the study? (Y)
The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?
2. Has the Eligibility Checklist (above) been completed? (Y)
3. Is the patient eligible for this study? (Y)
4. Date the study-specific Consent Form was signed? (must be prior to study entry)
5. Patient’s Initials (First Middle Last). (May 2003- if no middle initial, use hyphen)
6. Verifying Physician
7. Patient’s ID Number
8. Date of Birth
9. Race
10. Ethnic Category (Hispanic or Latino, Not Hispanic or Latino, Unknown)
11. Gender
12. Patient’s Country of Residence
13. Zip Code
14. Patient’s Insurance Status
15. Will any component of the patient’s care be given at a military or VA facility?
16. Treatment Start Date
17. What is the T stage? (T3 or T4)
   If T3, was an endorectal ultrasound done? (Y)
18. Tissue used for research in current study? (Y/N)
19. Tissue kept for cancer research? (Y/N)
20. Tissue kept for medical research? (Y/N)
21. Allow contact for future research?
22. Medical Oncologist

23. Treatment Assignment

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by  ___________  Date  ___________
1.0 INTRODUCTION

1.1 Background

In 2000, there are estimated to be 36,400 new cases of cancer of the rectum with an overall 5-year survival of 55%-60%. Surgery has remained the mainstay of treatment of these cancers but because of high local recurrence rates (20-60%), adjunctive chemoradiation has become standard practice for treatment of advanced cancers ($\geq$ T3, N+). Until recently adjunctive therapy consisted primarily of postoperative chemoradiation as established by the GITSG, NCCTG studies and intergroup studies. However, data from the Swedish national trial indicates that preoperative radiation may be a potentially better approach to treatment of this disease than postoperative radiation, both in terms of local control and reduced toxicity. This is especially true for tumors with extension into the perirectal fat and involvement of adjacent structures (stages T3, T4 or N+).

Historically preoperative radiation utilized in low dose regimens of 20-30 Gy in 1.8-2.0 Gy fractions had proven ineffective. More recent data utilizing high dose preoperative radiation (45 Gy $\pm$ boost) appears to be significantly more effective in increasing resectability rates, improving the options for sphincter preservation surgery, reducing local recurrence and improving survival of patients. Preoperative radiation has been combined with cytotoxic agents, especially 5-flourouracil as a radiation sensitizer in an effort to increase the downstaging of tumors and improve the efficacy of treatment. A variety of chemotherapeutic approaches and radiation schedules have been utilized in single institutional studies and have resulted in a range of pathological complete responses of 10%-50%. Patient selection, radiation dose, treatment technique, and mode of drug delivery can significantly affect these rates of complete response. Reporting of treatment related toxicity also is variable and does not lend itself to comparison of the most effective regimen in the preoperative management of these cancers. This study is therefore proposed to examine, in a randomized phase II fashion, two chemoradiation schedules involving CPT-11 and oxaliplatin. The effectiveness of each pre-operative treatment regimen will be measured by pathological complete response rates and the toxicity of these regimens prior to considering a future phase III study for the management of this disease.

1.2 CPT-11 Rationale

The nuclear enzyme topoisomerase I has been recently recognized as the target for the anticancer drug irinotecan (CPT-11). CPT-11 (7-ethyl-10-[4-(l-piperidinol)-l-piperidinol carbonyloxy camptothecin) is a water-soluble analogue of camptothecin synthesized in an attempt to identify camptothecin derivatives with aqueous solubility and antitumor activity. CPT-11 is a prodrug that undergoes deesterification in vivo to yield SN-38, a metabolite that is 1000-fold more potent than the parent compound in vitro.

1.2.1 Background on Camptothecins as Antitumor Agents

Camptothecin is a plant alkaloid obtained from the Camptotheca acuminata tree. The original clinical preparation, camptothecin sodium, was evaluated in clinical trials in the late 1960s and early 1970s but was abandoned due to severe and unpredictable hemorrhagic cystitis. Irinotecan (CPT-11) is a semisynthetic derivative of camptothecin that possesses greater aqueous solubility, greater in vitro and in vivo activity, and is associated with less severe and more predictable toxicity than camptothecin. Both camptothecin and CPT-11 are potent inhibitors of topoisomerase I, a nuclear enzyme that plays a critical role in DNA replication and transcription.

1.2.2 Bioactivation of CPT-11 to SN-38

CPT-11 is converted by carboxylesterases to its more active metabolite, SN-38. In vitro, SN-38 is 250 to 1,000-fold more potent than CPT-11 as an inhibitor of topoisomerase I activity. Similar to camptothecin and its other analogues (e.g., topotecan), both CPT-11 and its more active metabolite, SN-38, are reversibly hydrolyzed from active lactone forms to hydroxy acid (carboxylate) forms. This hydrolysis is pH-dependent, with equilibrium favoring the hydroxy acid form at physiological pH. The closed lactone ring is a structural requirement for activity of the camptothecins, since studies have demonstrated that the open-ring hydroxy acid form is a less potent inhibitor of topoisomerase I and a much less potent antitumor agent.

1.2.3 Clinical Pharmacokinetics of CPT-11 and SN-38 (4/19/04)

The mean terminal half-life of SN-38 in plasma is longer than that for CPT-11: 11.5 $\pm$ 3.8 hours versus 6.3 $\pm$ 2.2 hours (lactone forms). Peak plasma concentrations for CPT-11 occur at the end of the infusion. The time to peak SN-38 concentration is highly interpatient dependent and occurs
30-90 minutes after the end of infusion.\textsuperscript{17} Murine studies suggest that the liver may concentrate CPT-11, convert CPT-11 to SN-38, and eliminate via biliary excretion CPT-11, SN-38 and the glucuronide conjugate of SN-38 (\textit{SN-38G}). In rats, 55\% of radiolabeled CPT-11 was excreted unchanged in the bile within 24 hours while 21.7\% was transferred to SN-38. Overall, 73\% of the radioactivity could be recovered from the feces of rats and 25\% from the urine. It recently was demonstrated that plasma concentrations of SN-38G in patients occur 0.5 to three hours after the SN-38 peak and that plasma levels generally exceeded that of SN-38. In one patient, bile concentrations of CPT-11 were 10 to 560-fold higher than plasma concentrations during the first six hours following administration, whereas bile concentrations of SN-38 were 2 to 9 fold higher. Renal clearance has not been reported to be a major route of elimination for these compounds in humans.\textsuperscript{17}

1.2.4 Trials of CPT-11 and 5-FU in Previously Untreated Patients

Phase II trials of CPT-11 alone in previously untreated patients have shown response rates of 20\%-30\%.\textsuperscript{18,19} The most serious side effects include diarrhea (25\%-30\%) and myelosuppression (25\%-30\%). The incidence of diarrhea is decreased with the early and frequent use of loperamide.\textsuperscript{20} The addition of CPT-11 to 5-FU/leucovorin based therapy has been demonstrated to have an improved response rate and overall survival compared to 5-FU/leucovorin alone in previously untreated patients. Saltz reported the Irinotecan Study Group trial in which patients received CPT-11 (125 mg/m\textsuperscript{2}), (5-FU 500 mg/ m\textsuperscript{2}), Leucovorin (20 mg/ m\textsuperscript{2}), weekly for 4 weeks of a 6 week cycle. This was compared to 5-FU/leucovorin or CPT-11 alone. The combination regimen had a significantly improved response rate (39\% vs. 21\%), progression-free survival (7.0m vs. 4.3m), and median survival (14.8m vs. 12.6m) compared to the 5-FU arm. The single agent CPT-11 arm was similar to the 5-FU arm. Grade 3/4 treatment-related diarrhea was greater in the combination arm compared to 5-FU/leucovorin arm, 22.7\% versus 13.2\%.\textsuperscript{21} A phase III trial reported by Douillard compared 5-FU/leucovorin and CPT-11 to 5-FU/leucovorin. Response rates were improved with combination therapy, from 22\% to 35\%, progression-free survival was improved to 6.7m from 4.4m, and median survival was improved to 17.4m from 14.1m.\textsuperscript{22} Based on these data, the FDA approved the drug combination as first line treatment for metastatic disease, and it became the standard therapy in the US. for metastatic disease.

1.2.5 CPT-11 and Irradiation

Preliminary preclinical and clinical studies demonstrate a synergistic effect of CPT-11 and radiation and suggest radiosensitizing activity of CPT-11. It has been suggested that CPT-11 may potentiate the lethal effects of ionizing radiation by attaching to the DNA-topoisomerase I adducts in sites of DNA single strand breaks (SSBs). Subsequently, the stabilized CPT-11-TOPO1-DNA complexes interact with advancing replication forks during the S-phase of the cell cycle converting SSBs into irreversible DNA double strand breaks resulting in cell death. Fractionated irradiation synchronizes and resorbs the tumor cell population, leaving the majority of cells in the S phase of the cell cycle, and thus more sensitive to CPT-11 treatment.\textsuperscript{23}

Phase I study was done at Memorial Sloan-Kettering Cancer Center to determine the maximal tolerated divided dose (MTD) for bolus administered schedule of CPT-11 (Monday-Friday, weeks 1,2,4, and 5 during a standard 6-week RT cycle (50.4 Gy) for preoperative treatment of locally advanced or unresectable rectal cancer. 2 of 3 patients at 13 mg/m\textsuperscript{2}/day had dose-limiting diarrhea, and thus 10 mg/m\textsuperscript{2}/day was declared MTD. Additional patients were then treated at this dose level. Diarrhea and neutropenia have been dose-limiting toxicities. All patients had a complete resection of their rectal tumor. Following recovery from resection, patients received weekly CPT-11 125 mg/m\textsuperscript{2}, leucovorin 20 mg/m\textsuperscript{2}, and fluorouracil 500 mg/m\textsuperscript{2} for 4 weeks, repeated q 6 weeks x 3 cycles. One patient withdrew from the study and declined to receive post-operative chemotherapy. Two patients developed grade 3 diarrhea and discontinued postoperative treatment. No grade 4 neutropenia or other grade 3-4 non-hematologic toxicities were seen. In summary, this combined modality CPT-11-based schedule is safe and well-tolerated.

A Phase I study was conducted at Thomas Jefferson University Hospital to determine the maximal tolerated dose (MTD) of weekly CPT-11 combined a continuous infusion (CI) of 5-FU and concomitant RT in rectal cancer. The treatment regimen was as follows: Escalating doses of CPT-11 30-60 mg/m\textsuperscript{2} over 90 minutes on days 1, 8, 15, and 22; 5 FU as a protracted CI 300 or 225 mg/m\textsuperscript{2}/day on days 1-5 weekly during the period of RT. The external dose of RT was 45.0 Gy given at 1.8 Gy daily, then increased to 50.4 or 54 Gy for the last dose level. Surgery was performed 8-10 weeks following completion of CMT. Patients received postoperative bolus 5-FU and leucovorin. The Phase I trial was completed with total of 49 patients. Hematological toxicities
were mild with 1 grade-4 neutropenia. The major dose-limiting toxicities were diarrhea and intravenous catheter infections and thrombi. There were no grade 3 or 4 toxicities in the 7 patients who received CPT-11 50 mg/m² and 225 mg/m² 5-FU 5 days/week. The pathologic complete response rate was 24%. It established the MTD for CPT-11 as 50 mg/m² with this combined program. This regimen is currently an arm of RTOG 0012, a randomized phase 2 study of preoperative therapies for rectal cancer.

A phase II protocol performed at Stanford University evaluated preoperative CPT-11 (50 mg/m² days 1, 8, 15, 22), 5-FU (200 mg/m²/day) and 50.4 Gy radiation for patients with T3 rectal cancer. Thirty two patients enrolled. The major toxicity was Grade 3 diarrhea which occurred in 28% of the patients, and grade 3 mucositis which occurred in 21% of the patients. There was a 37.5% pathologic complete response rate. These data suggest that the combination of 5-FU, CPT-11 and radiation has acceptable toxicity and encouraging local response rates in locally advanced rectal cancer.

1.3 Capecitabine Rationale

1.3.1 Capecitabine

Capecitabine was designed as an orally administered, tumor selective fluoropyrimidine, preferentially converted to 5-FU at the tumor site by the higher levels of pyrimidines nucleoside phosphorylase (PyNPase) in tumor tissues compared to normal tissues. Capecitabine is one of a series of 5’-deoxy-5-fluorocytidine (5’-DFCR) derivatives synthesized as orally active prodrugs to 5-FU.  

1.3.2 Pharmacology of Capecitabine

Capecitabine is a prodrug of 5-fluorouracil, activated by a cascade of three enzymes. After oral administration it passes unchanged from the GI tract and is metabolized in the liver by 60 kDa carboxylesterase (previously known as acylamidase isozyme A), to 5’-DFCR. This is then converted to 5’-DFUR by cytidine deaminase located in the liver and also in tumor tissues. Further metabolism of 5’-DFUR then occurs at the site of the tumor under the action of PyNPase, to 5-FU. The exposure of normal body tissues to systemic 5-FU is, therefore, minimized. The peak plasma concentrations for the drug and its two main metabolites occurs shortly (0.5 - 1.5 hours) after administration. The concentrations decline exponentially with a half-life of 0.5 - 1 hour.  

1.3.3 Activity of Capecitabine against Colorectal Cancer

The efficacy and safety of three capecitabine dosing schedules, when administered as first-line treatment, was evaluated in 109 patients with advanced colorectal cancer. The three dosing schedules were as follows: capecitabine 2510 mg/m²/day intermittent (2 weeks with treatment, 1 week without treatment), capecitabine 1657 mg/m²/day intermittent in combination with leucovorin 60 mg/day, capecitabine 1331 mg/m²/day continuous (no rest period). Overall response rates were 22.9%, 20.5% and 23.5% in the three groups, respectively. Thirteen percent of the patients discontinued treatment due to treatment-related adverse events. Two large randomized phase III studies evaluated further the efficacy of capecitabine as first line treatment in metastatic colorectal cancer. Capecitabine was administered at a dose of 2500 mg/m²/day, and was compared with a standard intravenous 5-FU regimen (5-FU at a dose of 425 mg/m² in combination with leucovorin 20 mg/m² days 1-5 every 4 weeks). In a North American trial, 76 of 269 capecitabine patients (28.3%) had an objective response, compared with 34 of 266 patients (12.8%) in the 5-FU/leucovorin group (standard analysis, p=0.0001). Related serious adverse events and the rate of hospitalizations was statistically significantly lower (p<0.05) in the capecitabine group. A similar European study demonstrated responses in 56 of the 265 capecitabine patients (21.2%), and 44 of the 273 5-FU/leucovorin patients (16.1%).  

1.3.4 Capecitabine and CPT-11

Since the addition of CPT-11 to 5-FU significantly increased survival in patients with metastatic disease, CPT-11 has also been evaluated with capecitabine, based on capecitabine’s efficacy and toxicity profiles. Three phase I/II trials in previously untreated patients with metastatic colorectal cancer have been conducted investigating capecitabine/CPT-11. A German study evaluated capecitabine 1000-1250 mg/m² twice daily days 1-14, 22-35, and weekly CPT-11 (70-80 mg/m²) for 6 weeks in a 50 day cycle. Dose limiting toxicities were neutropenia and diarrhea with a response rate of 50%. The recommended doses, using this schedule, for further study are capecitabine 1000 mg/ m² twice daily and CPT-11 70 mg/m². A UK/Dutch study evaluated a three week schedule with capecitabine days 1-14, and CPT-11 day 1. Dose limiting toxicities
were neutropenia and diarrhea with a response rate of 48%. The recommended doses using this schedule are capecitabine 1000 mg/ m² twice daily and CPT-11 250 mg/m² day 1, the cycle repeats every 21 days. In a randomized phase II study from Italy, patients received either capecitabine 1250 mg/m² twice daily days 2-15 and CPT-11 300 mg/m² day 1 (arm 1), or capecitabine at the same dose and CPT-11 on days 1 and 8 at 150 mg/m² (arm 2). Due to excessive toxicity, the trial continued with reduced doses of the drugs, capecitabine 1000 mg/ m² and CPT-11 either 240 mg/ m² or 120 mg/ m². Grade 3 diarrhea was similar in both arms at 12%, grade 3 hematologic toxicity was 3%. The response rate for arm 1 was 51% and for arm 2 it was 45%. A multicenter phase II trial combining capecitabine with CPT-11 as first line therapy required a dose reduction due to unacceptable toxicity with doses of capecitabine 1000 mg/m² and CPT-11 125 mg/m² (cohort 1). Eight of fifteen patients had grade 3 or 4 diarrhea and there were 9 hospitalizations. The trial resumed with doses of capecitabine 900 mg/m² and CPT-11 100 mg/m² (cohort 2). An additional 14 patients were enrolled. The grade 3 or 4 toxicities were diarrhea (5) and there were 5 hospitalizations. The toxicity was acceptable, with an objective response rate of 47% in cohort 1 and 29% in cohort 2. Enrollment continues. These studies indicate that the combination is feasible at doses below those used when the drugs are given as single agents.

1.3.5 Capecitabine and Irradiation

The rationale for the use of capecitabine with radiation is to provide fluorouracil exposure similar to low dose continuous infusion 5-FU without the inconvenience of requiring an infusion pump. Two studies have been performed with rectal cancer and capecitabine. In the first study performed at Halle University, 36 patients were enrolled in a Phase I study of escalating doses of capecitabine with 50.4 Gy radiation. Patients were either treated preoperatively or postoperatively with this regimen. Capecitabine was administered without a break during the radiation, and the MTD was 1,000 mg/m² bid. Dose limiting grade 3 hand-foot syndrome was observed in 2 of the 6 patients at this dose level. Almost all adverse side effects were mild to moderate in intensity in the other cohorts with no grade 3/4 toxicity. The most common side effects were leucopenia and diarrhea; hand-foot syndrome was rare at doses below 1000 mg/m². The recommended dose for further evaluation is 825 mg/ m² bid.

Another study from the Peter McCallum Institute studied capecitabine given 5 days per week with radiation (1.8 Gy/fraction to 45 Gray to the pelvis followed by a 5.4 Gray presacral boost) for patients with extramural or node positive rectal cancer. Dose limiting toxicity was rare with only one case of grade 3 cystitis. The dose escalation continues at 2000 mg/ m²/day.

1.3.6 Capecitabine, CPT-11 and Radiation

There are two phase I studies evaluating CPT-11, capecitabine and radiation for extramural or node positive rectal cancer. In the first study by Kennedy et al, 9 patients have been enrolled in a dose escalating study of capecitabine with CPT-11 50 mg/m² weekly during radiation (54 Gy). The MTD has not been reached with the current capecitabine dose level at 1000 mg bid. The second study at Thomas Jefferson Hospital, is evaluating CPT-11 at 50 mg/m² weekly x 4, with escalating doses of capecitabine, 5 days per week, with 50.4 to 54 Gy radiation. (E. Mitchell, personal communication)

1.4 Oxaliplatin Rationale

Oxaliplatin is a new platinum derivative, which has been shown to have significant activity against fluorouracil-resistant colorectal cancer.

1.4.1 Although not completely understood, studies on the mechanism of action of Oxaliplatin support the concept that biotransformed, aquated products of Oxaliplatin interact with DNA to form mono-adducts and di-adducts, resulting in disruption of DNA synthesis leading to cytotoxicity and anti-tumor effects. The mechanism of action of Oxaliplatin is probably similar to that of cisplatin. In the case of cisplatin, after entry into the cell by simple diffusion, hydrolysis of the chloride ions occurs, resulting in a cis-dichloro structure interacting as a bifunctional alkylating agent with the nucleophilic sites of DNA forming inter- and intrastrand cross-links. The main site of action of cisplatin on DNA is the intrastrand cross-link between two adjacent guanines (dGpG) or two adjacent guanine-adenine (dGpA). These adducts block both replication and transcription. In the case of Oxaliplatin, alkaline elution studies of DNA have shown that the drug produces similar adducts to cisplatin, both quantitatively and qualitatively. The diamino cyclo hexyl (dach) group appears to remain bound to the platinum nucleus, which may alter the ultimate effect on DNA. In contrast, the reaction kinetics with DNA are different. The reaction of cisplatin with the d(GpG) site of DNA occurs in two stages, one rapid (about 15 minutes) and the second slower, lasting four to eight hours. With Oxaliplatin, however, binding is practically complete in 15 minutes. In addition, in vivo studies in mice suggest that Oxaliplatin, in
contrast to cisplatin, is also capable of inhibiting RNA synthesis.\textsuperscript{40}

1.4.2 Preclinical Studies with Oxaliplatin

Preclinical studies with Oxaliplatin have demonstrated \textit{in vitro} activity against a wide range of human tumor cell lines. Oxaliplatin was found to be non-cross resistant to cisplatin against a cisplatin-resistant ovarian carcinoma cell line (A2780), and active against the HT-29 colon carcinoma cell line which shows high intrinsic resistance to cisplatin. Oxaliplatin was not active against the OSCAR-3 ovarian cell line, intrinsically resistant to carboplatin. Studies in HT-29 cell lines show that Oxaliplatin is synergistic with 5-FU, while cisplatin is no better than additive in the same model.\textsuperscript{41,42} Additionally, platinum derivatives similar to Oxaliplatin are known to be \textit{in vitro} as well as clinical radiosensitizers.

1.4.3 Early Clinical Studies with Oxaliplatin

In early Phase II trials, single agent Oxaliplatin showed response rates of 10% with a median survival of 8-9 months in colorectal cancer refractory to multiple previous treatments including 5-FU.\textsuperscript{43,44,45} In patients with previously untreated advanced colorectal cancer, initial studies of Oxaliplatin in combination with 5-FU/folinic acid (Leucovorin) produced response rates of 40-55%, with 8-10% complete responses. Encouraging initial reports of Oxaliplatin plus 5-FU/LV in 5-FU/LV refractory patients also suggested that the response rate may exceed 25% in this setting.\textsuperscript{46,47,48}

A total of 125 patients were treated on 6 phase I trials. Oxaliplatin was given by IV bolus, 30 min-12 hr infusions, constant infusion, or chronomodulation. In all studies the treatments were repeated every 3 weeks. Toxicities are described below. These data suggest that 130 mg/m\textsuperscript{2} every 3 weeks is the recommended dose level. There was no formal phase I study to justify the 85 mg/m\textsuperscript{2} dosing regimen every 2 weeks. That regimen was developed following a pilot study in which 100 mg/m\textsuperscript{2} every 2 weeks was somewhat toxic, and the fact that the dose intensities of 85 mg/m\textsuperscript{2} every 2 weeks is equal to 130 mg/m\textsuperscript{2} every 3 weeks (i.e., 43 mg/m\textsuperscript{2}/wk). Both of these regimens were well tolerated in clinical trial when combined with various schedules of 5-FU/folinic acid. The safety profile established in phase I trials suggests that neurotoxicity (cold-induced dysesthesias and cumulative peripheral neuropathy) and gastrointestinal toxicities were most common. Renal toxicity and ototoxicity characteristic of cisplatin were not commonly observed.

1.4.4 Phase III Trials with Oxaliplatin

The combination of oxaliplatin and 5-FU as therapy for metastatic colorectal cancer has been validated by phase III randomized trials. One of the front-line trials demonstrating a benefit for the combination of oxaliplatin and 5-FU in patients with metastatic disease was the DeGramont study, EFC 4584.\textsuperscript{49} This evaluated oxaliplatin 85 mg/m\textsuperscript{2} on day 1, 5FU 400 mg/m\textsuperscript{2} bolus, leucovorin 200 mg/m\textsuperscript{2} over 2 hours, followed by 5FU 600 mg/m\textsuperscript{2} continuous infusion for 22 hours on days 1 and 2 (FOLFOX4 regimen, repeated every 2 weeks), and compared this to the same 5FU and leucovorin regimen without oxaliplatin. There was a significant improvement in progression free survival (8.1m vs. 5.9m) and response rate (50\% vs. 22\%) for the patients who received oxaliplatin. There was no difference in overall survival, perhaps due to the receipt of subsequent therapy after failure of first-line treatment. Intergroup N9741 compared the FOLFOX4 regimen to a weekly regimen of irinotecan, bolus 5-FU and leucovorin.\textsuperscript{50} There was a significant improvement in response rate, time to progression, and median survival (18 vs. 14 months) for the FOLFOX4 arm. The contribution of crossover receipt of oxaliplatin, and the use of infusional 5-FU in the FOLFOX arm to the observed results is uncertain. Recently, the FDA has approved the FOLFOX4 regimen as second-line therapy following irinotecan, 5-FU and leucovorin, based on the interim results of a phase III trial comparing FOLFOX4, infusional 5-FU/LV, and oxaliplatin alone. When compared with the 5-FU/LV alone arm, the FOLFOX arm was superior in terms of response rate (9.9\% vs. 0\%) and time to progression (4.6 vs. 2.7 months).\textsuperscript{51}

In an effort to avoid the inconvenience of the FOLFOX4 regimen in terms of its requirement for days 1 and day 2 leucovorin and bolus 5-FU administration, schedule modifications have been employed. The so-called FOLFOX6 regimen provides oxaliplatin, leucovorin, and bolus 5-FU on day 1, followed by a 46 hour infusion of 5-FU, repeated every 14 days.\textsuperscript{52}

1.4.5 Oxaliplatin and Capecitabine

Given the activity of capecitabine and the ease of administration compared to intravenous 5-FU, as well as the non-overlapping toxicity profiles, several combination studies have been performed with oxaliplatin. Based on a UK/Spanish trial, the regimen of capecitabine 1000 mg/ m\textsuperscript{2} twice daily, days 1-14 with intravenous oxaliplatin 130 mg/m\textsuperscript{2} day 1, (the cycle repeats every 21 days) was identified for further development.\textsuperscript{53} The principal dose-limiting toxicity was diarrhea.
international phase II study evaluated this dose schedule as first line therapy for metastatic colorectal cancer. Ninety-six patients were assessed, a median of 8 cycles could be given, with an objective response rate of 55%. The most common adverse event was mild to moderate sensory neuropathy. The most common grade 3/4 toxicities were diarrhea (13%), and nausea/vomiting (11%). In a US multicenter study of the same regimen, a dose reduction occurred due to toxicity with capecitabine 1500 mg/m²/day and oxaliplatin 130 mg/m². A response rate of 34% was reported in 35 patients at the lower doses. Toxicity was acceptable with a 17% incidence of grade 3 or 4 diarrhea. Overall, the safety profile is similar to that seen with the combination of oxaliplatin, 5-FU, leucovorin (FOLFOX4).

1.4.6 Oxaliplatin, 5-FU and Radiation

Phase I studies have been reported with the combination of oxaliplatin, 5-FU and preoperative radiation for rectal cancer. In a trial reported by Aschele, 39 patients with clinical T3/4 primary or recurrent rectal cancer were enrolled. Oxaliplatin was given weekly for 6 weeks at escalating doses with 225 mg/m² 5-FU continuous infusion days 1-38. The oxaliplatin dose escalated to 60 mg/m² without reaching the MTD. Five patients experienced grade 3 diarrhea, and 1 grade 3 anemia. 25 patients had grade 1 or 2 neurotoxicity. There was a 29% pathologic complete response rate. A similar trial is being conducted in the United States through the ECOG. Patients receive 200 mg/m² infusional 5-FU throughout the entire radiation course with escalating doses of oxaliplatin. Oxaliplatin is given the first, third and fifth weeks of radiation. There were no dose limiting toxicities and the recommended phase II dose is 85 mg/m². A third trial from France used weekly oxaliplatin (30-80 mg/m²) and continuous infusion of 5-FU days 1 to 35 with 45Gy radiation. The most common toxicities were grade 1-2 asthenia (61%), diarrhea (57%), abdominal pain (46%) and neuropathy (46%). There was an 11% incidence of grade 3 diarrhea and a 1% incidence of anorexia. The MTD was experienced at oxaliplatin 80 mg/m²/day. Five of 16 patients who have completed surgery have had a pathologic complete response. These studies indicate the combination is feasible and well tolerated.

1.5 Selection of Starting Doses for Concurrent Chemoradiotherapy with Chemotherapy Doublets

In the present study concurrent preoperative pelvic radiation and capecitabine is combined with either irinotecan (Arm 1) or oxaliplatin (Arm 2) as described in the schema and section 7.0. Selection of the dose and schedule of irinotecan and oxaliplatin is based upon the reported phase I and II data, as summarized in the above sections. The majority of these trials utilized continuous infusion 5-FU as the backbone drug. The recommended phase II dose of capecitabine in this setting (825 mg/m² BID administered daily throughout the course of preoperative pelvic radiation) has been determined. Therefore, sufficient clinical safety data exists to allow substitution of capecitabine for infusional 5-FU for examination of combination of this drug with either irinotecan or with oxaliplatin. Knowledge of the biochemical and clinical similarities between capecitabine and infusion 5-FU further supports feasibility of this study design.

The selection of starting doses for capecitabine, irinotecan, and oxaliplatin in conjunction with radiation is based upon the following clinical experience as detailed above:

- radiation plus capecitabine
- radiation plus irinotecan
- radiation plus oxaliplatin
- capecitabine plus irinotecan
- capecitabine plus oxaliplatin

Overlapping toxicities of the various modalities and drugs as noted above have been taken into consideration in the design of this study. Furthermore, the phase II schedule of infusional 5-FU when given with concurrent pelvic radiation and irinotecan is based upon a 5 out of 7 day schedule (M-F). Because the present trial utilizes a daily (7 days per week) schedule of capecitabine, the daily capecitabine dose in Arm 1 is reduced accordingly (to 600 mg/m² BID instead of 825 mg/m² BID). This is done to approximate the cumulative 5-FU dose that has been shown to be tolerable in previous phase II studies. Given that formal phase I testing of the specific regimens to be implemented in this study has not been completed, planned interim toxicity analyses will be conducted early in this trial.

1.5.1 Toxicity update January 2005 (3/22/05)

Based upon excessive grade 3-4 non-hematologic toxicity observed in both arms of RTOG 0247 after the first 35 patients were enrolled, the trial was placed on hold, pending further analysis. The toxicity was experienced during neoadjuvant treatment. In the irinotecan arm, 7 of 18 patients experienced grade 3-4 diarrhea. In the oxaliplatin arm, 5 patients had grade 3
diarrhea and 1 patient had grade 5 diarrhea. Another patient was hospitalized with diarrhea and experienced sudden death several days after complete recovery from other toxicities. Based on discussions with NCI, Roche, Pfizer, Sanofi, and representatives from ECOG and NSABP, decisions regarding dose and schedule modifications were made. These modifications include decrease in capecitabine and oxaliplatin dosing, alteration in the irinotecan schedule, and alterations in the dose modification scheme.

1.5.2 When this trial was initially developed, postoperative treatment arms were selected based upon data in patients with metastatic colorectal cancer that demonstrated a survival benefit when either irinotecan or oxaliplatin were added to 5-fluorouracil plus leucovorin. However, recent data in the colon adjuvant setting now inform an amendment of this trial. First of all, two phase III trials have demonstrated an improvement in disease-free survival when oxaliplatin is added to a 5-FU/leucovorin backbone in the adjuvant setting.\(^59,60\) In contrast, three colon adjuvant trials have failed to show a benefit for the addition of irinotecan to 5-FU/leucovorin.\(^61-63\) Based upon these findings, 5-FU, leucovorin, oxaliplatin has become a preferred standard for the adjuvant therapy of colon cancer. Although, these data do not directly address the adjuvant therapy of rectal cancer, the similarity between colon and rectal cancer chemosensitivity renders the inclusion of oxaliplatin in the postoperative treatment of patients on this study reasonable. These recent data do not alter plans for the neoadjuvant treatment approaches being tested in this protocol.

Based on the results of these studies, the randomization to Arm 1 (irinotecan arm) was discontinued on 6/17/05. All patients randomized to Arm 1 prior to 6/17/05, as well as all patients entered after 6/17/05, will receive FOLFOX for their post-op systemic therapy. (6/29/05)

1.6 Correlative Studies (4/19/04)
Pre-operative radiation combined with new drugs, such as those examined in the present study, may improve the outcome of selected subgroups of patients with rectal cancer. Future advances in the management of rectal cancer may be achieved by validating predictive molecular tumor markers. Predictive tumor assays for rectal cancer may be used to identify prognostic patient subsets and may be pertinent to the design of future clinical trials that examine predictive treatment strategies. As yet, however, no predictive markers for rectal cancer have been rigorously studied in this fashion. Standard assays used to measure mRNA expression require fresh frozen tissue because of susceptibility of RNA to degradation. However the logistics of obtaining fresh tissue from pre-operative biopsy specimens in the setting of a multicenter trial significantly limits the likelihood of compliance to tissue sample submission. Whereas fixation of paraffin-embedded tissue can degrade mRNA and prevent its usefulness for quantitative assays, specific technical applications can overcome this obstacle. In the present study we propose a quantitative real-time RT-PCR method that permits use of paraffin-embedded tissue as the target tissue. Demonstration of the feasibility and validity of this assay that examines the proposed molecular markers is a crucial preliminary step before the predictive value of these markers can be tested.

1.6.1 Biologic Rationale for TS, TP, DPD and p53R2
In retrospective studies of patients with colorectal cancer, investigators have correlated enzyme expression of thymidylate synthase (TS), dihydrofolate reductase (DPD), and thymidine phosphorylase (TP) with clinical outcome. While in rectal cancer high TS has correlated with worse survival, in metastatic colon cancer low TS, DPD, and TP has correlated with favorable response to chemotherapy.\(^64,65\) Because the final step in conversion of capecitabine to its active form (5-FU) is catalyzed by TP (an enzyme that is concentrated in higher levels in tumors cells than in normal cells), levels of tumor TP expression may have predictive value in patients treated with capecitabine.\(^66\) For these reasons, TS, TP, and DPD are likely candidates as predictive molecular markers. In the present study we will examine an assay for mRNA expression of these potential predictive tumor markers.

Increased understanding of molecular pathways that influence cell cycle control, apoptosis, or repair of radiation induced DNA damage has led to the discovery of candidate genes that may be clinically useful clinically as predictive tumor markers. A recently identified gene, called p53R2, belongs to a family of ribonucleotide reductases-enzymes that catalyze the rate limiting step of DNA synthesis (conversion of ribonucleotide diphosphates into deoxyribonucleotide diphosphate.)\(^67\) p53R2 is thought to play an important role in repair of radiation-induced DNA
damage. The 5′-untranslated region of p53R2 mRNA contains a p53 binding domain that influences its expression. In vitro studies, suggest that, in addition to mediating repair of radiation-induced DNA damage, p53R2 plays a role in the molecular pathogenesis of cancer.

In the present trial we will also explore the potential role of p53R2 as a predictive marker for rectal cancer treatment.

### 1.6.2 Biologic Rationale for TS Gene Promoter and ABCB1 Genotyping

Thymidylate synthase (TS) gene promoter is a polymorphic sequence composed of either double or triple repeats of a 28-bp sequence. In a retrospective pilot study of colorectal cancer patients treated with capecitabine, patients homozygous for triple tandem repeats (S/L) of a 28bp sequence expressed significantly higher TS mRNA levels than did patients who were homozygous for double tandem repeats (S/S) of the 28bp sequence. The investigators furthermore demonstrated that response to capecitabine was higher in patients with the S/S genotype, compared to S/L or L/L genotypes. Prospective confirmation of these observations would provide meaningful data regarding the predictive value of TS gene promoter polymorphisms in rectal cancer patients treated with fluorouracil-based therapy.

Elimination of irinotecan is mediated in part by proteins that belong to the superfamily of adenosine triphosphate binding cassette (ABC) transporters that serve to facilitate efflux of drugs via membrane-localized energy-dependent pumps. The ABCB1 (MDR1 P-glycoprotein) gene is a member of this family. Mathijsen et al showed that specific polymorphisms of this gene (ABCB1 1236 C>T) has been associated with significant increase AUC measurements of irinotecan and its active metabolite SN-38. The effect of ABCB1 polymorphisms on irinotecan pharmacokinetics may therefore predict toxic effects or clinical efficacy of irinotecan.

### 1.6.3 Quality of Life Associated with Pelvic Chemoradiation Therapy

Combined modality cancer therapy may have pronounced effects on general health related quality of life (QOL) as well as selected areas of function. In view of the potential toxicities associated with pre-operative pelvic radiation and concurrent combination chemotherapy, consideration of how this therapy affects QOL is warranted. QOL measurements have been shown to augment morbidity evaluations and contribute to the “cost benefit” ratio involved in assessments of these treatments. Interestingly, the evaluation of QOL was instrumental in the choice of rectal cancer therapy in one recent study. In this series, loco-regional therapy demonstrated superiority in terms of QOL as compared to systemic therapy in patients with colorectal liver metastases.

There have been few prospective investigations of the QOL of patients with rectal cancer receiving curative therapy. Studies identified have focused primarily upon post-surgical measurements of anorectal function alone. Only three prospective series to date have incorporated validated QOL instruments incorporating the minimally recommended domains as well as tools specific for patients with rectal cancer. Two of these studies measured QOL following surgical resection alone. One phase II trial assessed QOL for patients with resectable rectal cancer receiving preoperative chemoradiation therapy.

Using the European Organization for Research and Treatment of Cancer 30-item questionnaire (QLQ-C30) and its colorectal cancer-specific module (QLQ-CR38), a deterioration in QOL on all subscales following chemoradiation and surgical resection was demonstrated, as compared to baseline assessment. The symptoms most adversely affected were micturition, defecation, bowel patterns, body image and sexual function. It is unclear as to whether QOL was restored over time, as QOL was not assessed in continued follow-up.

Additionally, the importance of sexual functioning as a QOL issue should not be underestimated. In a study of 413 impotent men and 109 controls, satisfaction with sexual life was found to be a powerful predictor of satisfaction with life as a whole. Likewise, the importance of sexual functioning as a major issue in patient decision making regarding prostate cancer treatment has been demonstrated. The assessment of sexual function and satisfaction following curative therapy for rectal cancer is considerably less defined. The few studies identified are either retrospective in nature or do not use validated questionnaires.

Two prospective studies utilizing the International Prostatic Symptom Score reported preserved sexual and voiding function in greater than 80% of the patients following total mesorectal excision; however, sexual satisfaction was impaired. The secondary QOL objective of this trial is to assess whether combined modality therapy for patients with rectal cancer may be associated with significant changes in general as well as
specific QOL patient concerns. Although disturbance in the pattern of elimination is often the most commonly reported complaint following combined modality therapy, others may include fatigue, or changes in body image and sexuality. Such disease or treatment-related concerns may impact QOL in various ways. The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 instrument will be used to determine the patient's self-assessment of the impact of pelvic chemoradiation on overall QOL, health and daily activity. The EORTC QLQ-CR 38 tool will address the treatment-specific patient concerns. The Sexual Adjustment Questionnaire (SAQ) will measure patient sexual function and satisfaction. These instruments are found on the RTOG web site.

The EORTC QLQ-C30 is a 30-item QOL self-reporting questionnaire grouped into five functional subscales (role, physical, cognitive, emotional and social functioning). In addition, there are three multi-item symptom scales (fatigue, pain, and nausea and vomiting), individual questions concerning common symptoms in cancer patients, and two questions assessing overall QOL. The EORTC QLQ-CR 38 instrument is a 38-item colorectal cancer-specific module which includes items concerning symptoms and side effects related to different treatment modalities (such as micturition, ano-rectal and bowel function), and four functional scales on body image, sexual functioning, sexual enjoyment and future prospective. These EORTC instruments are well-established tools for the assessment of QOL with proven reliability and validity.

The Sexual Adjustment Questionnaire (SAQ) is a 20-item patient self-assessment questionnaire modified from the 30-item version developed by Metcalfe and Waterhouse. SAQ rates most responses on a 5-point Likert-type scale, with a higher score indicating a higher level of sexual adjustment. Combined data from two RTOG prostate cancer studies was used to assess the psychometric properties of the RTOG modified SAQ. The RTOG modified SAQ retained 5 of the original 8 subscales, including: desire, activity, arousal, orgasm, and satisfaction, and dropped relationship, technique, and miscellaneous, due to concern for patient burden in large clinical trials. Construct validity for this RTOG modified SAQ has been demonstrated, and this questionnaire appears to provide more accurate assessment of patient sexual function compared to physician assessment, reinforcing the value of quality of life patient self-assessments in clinical trials.

2.0 OBJECTIVES

2.1 To estimate the pathologic complete response rate following neoadjuvant combined-modality in rectal cancer. Two regimens will be investigated: 1) neoadjuvant radiation with concurrent capecitabine plus irinotecan, followed postoperatively by systemic therapy for 4 months, and 2) neoadjuvant radiation with concurrent capecitabine plus oxaliplatin, followed postoperatively by systemic therapy for 4 months.

2.2 To estimate time to treatment failure, and patterns of failure.

2.3 To estimate the incidence of hematologic and non-hematologic grade 3-4 toxicity with each of two treatment regimens. The following distinct treatment periods will be considered: preoperatively, postoperatively, and overall for entire program.

2.4 To evaluate the potential use of TS, TP, DPD, and p53R2 as prognostic or predictive markers by examining the variability and reproducibility of marker expression in tumor and normal tissue from preoperative biopsy and surgically resected tissue specimens. To evaluate the predictive value of TS gene promoter polymorphisms with TS expression and fluorouracil response and of ABCB1 polymorphisms with clinical effects of irinotecan.

2.5 To assess whether the combined modality therapy produces changes in general, as well as specific QOL concerns from baseline to three time points (completion of chemoradiation, completion of post-operative chemotherapy [approximately one year] and two years).

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (8/19/04)

3.1.1 Adenocarcinoma of the rectum originating at or below 12 cm from the anal verge without evidence of distant metastases (05/05/06)

3.1.2 Patient must be 18 years of age or greater.

3.1.3 Potentially resectable en bloc based upon surgeon evaluation

3.1.4 Clinical stages T3 or T4, based upon endorectal ultrasound, or physical examination (only acceptable for T4 lesions).

3.1.5 Absolute neutrophil count of > 1500 per microliter and platelet count > 100,000 per microliter; AST
and alkaline phosphatase < 2.5 X ULN, bilirubin < = 1.5 ULN, calculated creatinine clearance > 50 ml/min using Cockcroft-Gault formula: \( \frac{140 \text{ – age}}{\text{wt. in kg}} \times \frac{\text{Serum Cr}}{72} \)

\[
\text{CrCl male} = \frac{(140 - \text{age}) \times (\text{wt. in kg})}{(\text{Serum Cr}) \times 72}
\]

\[
\text{CrCl female} = 0.85 \times (\text{CrCl male})
\]

3.1.6 Zubrod performance status 0-2
3.1.7 No history of other malignancies within 5 years, except non-melanoma skin cancer, in situ carcinoma of the cervix, or ductal carcinoma in situ of the breast. Previous invasive cancer permitted if disease free at least 5 years.
3.1.8 Signed study-specific informed consent prior to randomization

### 3.2 Conditions for Patient Ineligibility

3.2.1 Any evidence of distant metastasis
3.2.2 Synchronous primary colon carcinomas, except T1 lesions (full colonoscopy not required for enrollment)
3.2.3 Extension of malignant disease to the anal canal
3.2.4 Prior radiation therapy to the pelvis
3.2.5 Prior chemotherapy for malignancies
3.2.6 Pregnancy or lactation, (exclusion due to potential adverse effects of therapy). Women of childbearing potential with either a positive or no pregnancy test (serum or urine) at baseline. Women/men of childbearing potential not using a reliable and appropriate contraceptive method. (Postmenopausal women must have been amenorrheic for at least 12 months to be considered to be of non-childbearing potential.) Patients will agree to continue contraception for 30 days from the date of the last study drug administration.
3.2.7 Serious, uncontrolled, concurrent infection(s).
3.2.8 Participation in any investigational drug study within 4 weeks preceding the start of study treatment.
3.2.9 Clinically significant cardiac disease (e.g. congestive heart failure, symptomatic coronary artery disease and cardiac arrhythmias not well controlled with medication) or myocardial infarction within the last 12 months.
3.2.10 Evidence of uncontrolled seizures, central nervous system disorders or psychiatric disability judged by the investigator to be clinically significant, precluding informed consent, or interfering with compliance of oral drug intake.
3.2.11 Other serious uncontrolled medical conditions that the investigator feels might compromise study participation.
3.2.12 Major surgery within 4 weeks of the study treatment.
3.2.13 Lack of physical integrity of the upper gastrointestinal tract or malabsorption syndrome.
3.2.14 Known, existing uncontrolled coagulopathy.
3.2.15 No concurrent cimetidine allowed.

### 4.0 Pretreatment Evaluations

(in addition to required evaluations in section 3.0)

4.1 Complete physical examination (within two weeks prior to enrollment)
4.2 Laboratory evaluations (within two weeks prior to enrollment):
4.2.1 CBC, platelets and differential, CEA, serum or urine pregnancy test within 7 days prior to starting therapy (female patients of childbearing potential).
4.2.2 Liver and renal functions (alkaline phosphatase, AST, LDH, bilirubin, and creatinine)
4.2.3 Tissue biopsy

4.3 Imaging (within eight weeks prior to enrollment):
4.3.1 Lower endoscopy or endorectal ultrasound to determine the location and extent of the tumor from the anorectal junction
4.3.2 Chest x-ray (PA and lateral)
4.3.3 CT scan of abdomen and pelvis to determine the location, extent, size pretreatment and extent of involvement of adjacent tissues as well as possible metastasis to the liver
4.3.4 Endorectal ultrasound (TRUS) for TNM staging, unless tumor is fixed (T4) by physical examination
4.3.5 MRI scan of pelvis for corroboration of TNM staging (optional)
4.4 Quality of Life
4.4.1 EORTC Instruments: QLQ-C30 (QF) and QLQ-CR38 (PF)
4.4.2 SAQ (SA)

5.0 REGISTRATION PROCEDURES (8/19/04)(4/5/05)
5.1 Online Registration

Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met.

Institutions must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The Investigator must have completed Human Subjects Training and been issued a certificate (Training is available via http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp).
- The institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (www.rtog.org), going to "Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET.

Canadian Institutions: 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.

5.2 Radiation and chemotherapy should be initiated on a Monday or Tuesday within 2 weeks of study enrollment, with 5 days of consecutive treatment strongly preferred.

6.0 RADIATION THERAPY (3/22/05)
Radiation and chemotherapy should be initiated on a Monday or Tuesday within 2 weeks of study enrollment, with 5 days of consecutive treatment strongly preferred.

Note: Intensity Modulation Radiation Therapy (IMRT) is not allowed.

6.1 Fractionation and Total Dose
Conventional doses of 1.8 Gy per fraction, five fractions per week will be delivered with...
all fields treated every day. The dose to the pelvis will be 45 Gy/25 fractions/five weeks with a boost dose of 5.4 Gy/3 fractions to a cone down volume. The total dose to the tumor bed will be 50.4 Gy. IMRT is not allowed on this study.

6.1.1 Modality: External beam photon radiation shall be used.
6.1.2 Energy: Megavoltage radiation shall be used, i.e., accelerator beams of energy no less than 6 MV. Equipment of 10 MV or higher energy is strongly recommended.
6.1.3 Simulation: All fields must be simulated. Either a simulator or CT simulator may be used. Bowel exclusion techniques should be used if possible. This includes the use of the prone position, a belly board and/or treatment with a full bladder. The buttocks should be taped apart to decrease self-bolus effect. For conventional simulation: oral contrast will be administered 1 hour prior to simulation to allow visualization of small bowel on simulation films. An anal marker and rectal barium contrast will be used to allow visualization of the primary tumor and rectum. Patients who undergo CT simulation do not require the catheter, but should have the primary tumor region and rectum drawn on the simulation films. The anal verge should be marked with a radio-opaque marker. Patients will be treated with 4-field box pelvis technique or 3-field technique with PA, right and left laterals for the initial pelvic field. Two-three field techniques are recommended for the final boost. Field borders are listed below.

6.1.4 Field Definition
The fields are designed to cover the primary disease, pelvic soft tissue, principal nodal drainage areas and perineum. Shaped fields or blocks will be used to shield non-essential tissue.

6.1.5 Minimum boundaries of whole pelvic fields for conventional simulation:
6.1.5.1 Standard opposed anterior-posterior portals:
  - Inferior: The minimum would be at least a 4 cm margin from the inferior extent of the cancer or the anal verge for tumors within 2-3 cm of the anal verge, as identified by a marker on simulation.
  - Lateral: 2 cm lateral to the bony pelvis or on nodes > 1.5 cm taken at its widest point.
  - Superior: L5-S1 junction.

6.1.5.2 Standard opposed lateral portals:
  - Superior: To correspond to A/P fields.
  - Inferior: To correspond to A/P fields.
  - Anterior: This will cover the internal iliac, presacral lymph nodes and at least 3 cm margin on the anterior rectal wall/tumor for T3 lesions. For T4 lesions the external iliac nodes should be included with a field border 1 cm anterior to the symphysis pubis.
  - Posterior: This must include the entire sacrum with a 2 cm margin for T4 lesions or 1 cm posterior to the presacrum for T3 lesions.

6.1.6 Minimum boundaries for the conventional simulated boost field: a 2-3 cm margin around the rectal tumor and any lymph nodes > 1.5 cm as identified on pre-treatment evaluation, but must include the whole of the sacral hollow. Exclusion with custom blocking of as much of small bowel as possible is recommended.

6.1.7 CT simulation guidelines:
ICRU-50 prescription methods and nomenclature shall be used. Gross tumor volume (GTV) is defined as the full extent of the pre-surgical rectal tumor volume and lymph nodes > 1.5 cm identified on pre-treatment examination including CT/MRI. Clinical target volume (CTV) includes the GTV, the internal iliac lymph node drainage, the peri-rectal soft tissue space, and the presacral space with a 2 cm margin. External iliac nodes should be included for T4 lesions. The initial planning target volume for the pelvic field (PTV1) includes the CTV plus a 1 cm margin for set-up error and/or patient motion. Exact margins will be left to the discretion of the treating radiation oncologist and the field arrangement and borders should be similar to the conventional simulation recommendations. The boost planning target volume (PTV2) includes the GTV plus a 3 cm margin in all directions. The whole of the sacral hollow must also be included.

6.2 Treatment Planning
6.2.1 Treatment Dose Prescription Point
For the following portal arrangements, the target dose shall be specified as follows:
6.2.1.1 For two opposed co-axial equally-weighted beams: on the central ray at mid-separation of beams, this is acceptable for the boost portion of the treatment only.
6.2.1.2 For an arrangement of two or more intersecting beams: at the intersection of the central ray of the beams
6.2.1.3 For complete rotation or arc therapy: in the plane of rotation at the center of rotation
6.2.1.4 For CT-based or complex treatment arrangements: at the center of the clinical target volume
6.2.1.5 The technique of using two opposing co-axial unequally-weighted fields is not acceptable for
the initial dose fields due to unacceptable hot spots and unacceptable dose inhomogeneity.

6.2.2 Total Treatment Dose

6.2.2.1 Original Pelvic Treatment Volume: The total dose to the prescription point shall be 45 Gy in 25 (1.8 Gy/fx) fractions. For CT planning, the PTV1 will receive 45 Gy in 25 fractions.

6.2.2.2 Boost Volume: The dose for the boost volume or PTV2 is 5.4 Gy in 3 (1.8 Gy/fx) fractions for a cumulative dose within the tumor volume to the prescription point (or GTV) of 50.4 Gy.

6.2.3 Time-Dose Considerations

6.2.3.1 Daily Dose: The daily dose to the prescription point of original and boost volumes shall be 1.8 Gy daily.

Fractionation: Treatment shall be given five days per week. All radiation fields shall be treated once each day.

6.2.3.2 Dose Homogeneity: The dose throughout the treatment volume will be within 10% of the prescribed dose. Wedges, compensation, and other methods of generating a uniform dose distribution are encouraged.

6.2.3.3 Isodose Plans

The isodose distribution for the composite plan shall be calculated. The prescription point and the outline or the tumor volume shall be shown.

6.2.3.4 Portal Verification: Portal verification of all fields should be performed prior to the delivery of the initial fractions and then at least weekly thereafter to assure accuracy and consistency of field placement.

6.2.3.5 Treatment Modification: Uninterrupted treatment is planned. Treatment may be interrupted for acute toxicity. Chemotherapy will be held if RT is held. The specific reason(s) for treatment interruption will be recorded in the treatment summary. Treatment may be interrupted for grade ≥ 3 diarrhea or other grade ≥ 3 regional symptoms (skin desquamation, cystitis, tenesmus). No modifications in dose will be made for interruptions in therapy.

6.2.3.6 The patient will be examined at least once a week during the course of radiation with a CBC and platelets. RT interruption is to be minimized and is allowed only for regional symptoms. (See 6.2.3.5 for description.)

6.2.3.7 Protocol Compliance Criteria

| TOTAL DOSE + or – IN EITHER DIRECTION | FIELD BORDERS | OVERALL SCORE |
|--------------------------------------|---------------|---------------|
| ≤ 5 %                                | 2 cm to ≤ 2.5 cm | Per Protocol |
| > 5% to ≤ 10%                        | MIN 1.5 to < 2 cm OR MAX > 2.5 to ≤ 3.5 cm | Minor Variation, Acceptable |
| > 10%                                | < 1.5 cm OR > 3.5 cm | Major Deviation, Unacceptable |

6.3 R.T. Quality Assurance Reviews

The Radiation Oncology Co-Chair, Rani Anne, MD will perform an RT Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Dr. Anne will perform the next review after complete data for the next 20 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 30 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever comes first. These reviews will be ongoing and performed at the RTOG semi-annual meetings as well as at RTOG Headquarters.

6.4 Radiation Adverse Events Reporting (3/31/06)

For Instructions on Adverse Events Reporting See Section 7.12.

7.0 DRUG THERAPY (3/22/05)

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedure Manual.
Radiation and chemotherapy should be initiated on a Monday or Tuesday within 2 weeks of study enrollment, with 5 days of consecutive treatment strongly preferred. For the first week of treatment, the capecitabine should be started the evening before the first radiation dose.

Note: The Capecitabine/Diarrhea diary will be checked for compliance/completeness by the investigator. A copy of the diary will be retained in the patient’s record for submission to RTOG only upon request; i.e., diaries are not to be submitted but will be retained at the site as source documents.

7.1 Arm 1
Dose calculation should be based upon actual body weight and not modified for obesity. Dose calculations that deviate from the use of actual body weight will be considered a major protocol violation.

7.1.1 Preoperative Therapy (8/19/04)(3/22/05)

| Agent    | Dose        | Route                  | Schedule                                                                 |
|----------|-------------|------------------------|--------------------------------------------------------------------------|
| Capecitabine | 600 mg/m² q12 hours (1200 mg/m²/day) | oral                   | 5 days per week during radiotherapy. The 1st dose will begin the evening prior to day 1 of RT. Begin all subsequent weekly courses on Sunday night, and end with Friday morning dose. Final dose of capecitabine is administered on the morning of the final radiation dose. |
| Irinotecan | 50 mg/m²    | IV over 60 minutes     | Weekly x 4; days 1, 8, 22, and 29. Omit day 15.                          |

7.1.2 Postoperative Therapy
7.1.2.1 Postoperative therapy will be administered to all patients who have a complete resection of rectal cancer with negative surgical margins. Patients with unresectable disease or involved margins will discontinue protocol therapy. Postoperative therapy will begin 4-6 weeks after surgery.

7.1.2.2 Treatment will consist of 9 cycles (each cycle = 14 days) of 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX). (6/29/05)

| Agent                  | Dose       | Route                | Schedule                          |
|------------------------|------------|----------------------|-----------------------------------|
| Oxaliplatin+           | 85 mg/m²   | IV over 2 hours      | Day 1, every 14 days             |
| Leucovorin+            | 400 mg/m²  | IV over 2 hours      | Day 1, every 14 days             |
| 5-fluorouracil bolus+  | 400 mg/m²  | IV push              | Day 1, every 14 days             |
| 5-fluorouracil infusion+ | 2400 mg/m² | IV continuous infusion over 46 hours | Beginning day 1, every 14 days |
| +Administer sequentially as written, except oxaliplatin and leucovorin may be administered concurrently |

7.2 Arm 2
Dose calculation should be based upon actual body weight and not modified for obesity. Dose calculations that deviate from the use of actual body weight will be considered a major protocol violation.

7.2.1 Preoperative Therapy (3/22/05)
7.2.1.1 Chemotherapy will begin on the first day of radiotherapy and continue until the completion of
radiotherapy. Capecitabine will be administered orally twice daily, and oxaliplatin will be administered intravenously weekly × 5 weeks.

| Agent       | Dose                  | Route       | Schedule                                                                 |
|-------------|-----------------------|-------------|--------------------------------------------------------------------------|
| Capecitabine| 825 mg/m² g12 hours  | oral        | 5 days per week during radiotherapy. The 1st dose will begin the evening prior to day 1 of RT. Begin all subsequent weekly courses on Sunday night, and end with Friday morning dose. Final dose of capecitabine is administered on the morning of the final radiation dose. |
| Oxaliplatin | 50 mg/ m²             | IV over 2 hours | Weekly x 5; days 1, 8, 15, 22, 29                                         |

7.2.2 Postoperative Therapy

7.2.2.1 Postoperative therapy will be administered to all patients who have a complete resection of rectal cancer with negative surgical margins. Patients with unresectable disease or involved margins will discontinue protocol therapy. Postoperative therapy will begin 4-6 weeks after surgery.

7.2.2.2 Treatment will consist of 9 cycles (each cycle = 14 days) of 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX).

| Agent          | Dose                  | Route                   | Schedule                      |
|----------------|-----------------------|-------------------------|-------------------------------|
| Oxaliplatin+   | 85 mg/m²              | IV over 2 hours         | Day 1, every 14 days          |
| Leucovorin+    | 400 mg/m²             | IV over 2 hours         | Day 1, every 14 days          |
| 5-fluorouracil bolus+ | 400 mg/m² | IV push                  | Day 1, every 14 days          |
| 5-fluorouracil infusion+ | 2400 mg/m² | IV continuous infusion over 46 hours | Beginning day 1, every 14 days |

+Administer sequentially as written, except oxaliplatin and leucovorin may be administered concurrently

7.2.3 Veno-occlusive disease (VOD)99-102 (12/1/04)

Veno-occlusive disease is a very rare AE associated with the administration of the combination of 5-FU and oxaliplatin. VOD disease is characterized by hepatomegaly, ascites, and jaundice. Especially in patients without liver metastases, these signs and symptoms should prompt consideration of VOD. A Doppler ultrasound showing reversal of portal blood flow or other evidence of portal hypertension is suggestive of this diagnosis. In addition, standard clinical practice for evaluation of VOD should include observation of liver and spleen size, history of or gastrointestinal bleeding, development of esophageal varices, ascites, bleeding, or jaundice. All patients on and off therapy who develop signs and symptoms suggestive of VOD should be thoroughly evaluated and closely monitored and supported as clinically dictated.

7.3 Dose modifications – Arm 1

**NOTE:** All adverse events should be graded according to the Common Terminology Criteria for Adverse Events (Version 3.0). The final dose modification according to the following tables should be based upon the worst grade of the adverse event experienced. If preoperative treatment is discontinued because of toxicity, further therapy will be at the discretion of the treating physicians.

7.3.1 Dose modifications during preoperative therapy (Arm 1) (8/19/04)(3/22/05)(3/31/06)

Dose calculation should be based upon actual body weight and not modified for obesity. Dose calculations that deviate from the use of actual body weight will be considered a major protocol violation.
### Capecitabine, CPT-11, Concurrent Pelvic Radiation Dose Modification

| Toxicity                                      | Grade    | Modification                                                                 |
|-----------------------------------------------|----------|------------------------------------------------------------------------------|
| Any toxicity/adverse event except Rash: hand-foot reaction, cardiac toxicity, or diarrhea | Grade 1 or 2 | No change                                                                    |
|                                               | Grade 3  | 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. |
|                                               | Grade 4  | Discontinue chemotherapy and radiation                                        |
| Diarrhea                                      | Grade 1  | No change                                                                    |
|                                               | Grade 2 or 3 | 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. |
|                                               | Grade 4  | Discontinue chemotherapy and radiation                                        |
| RASH: hand-foot skin reaction                  | Grade 1  | No change                                                                    |
|                                               | Grade 2  | Hold capecitabine until Grade ≤ 1, resume at previous capecitabine dose. If treatment is held for >14 days, remove patient from protocol therapy. |
| 2\textsuperscript{nd} occurrence of Grade 2   |          | Hold capecitabine until Grade ≤ 1 resume at 75% of initial capecitabine dose. If treatment is held for >14 days, remove patient from protocol therapy. |
| 3\textsuperscript{rd} occurrence of Grade 2   |          | Hold capecitabine until Grade ≤ 1 resume at 50% of initial capecitabine dose. If treatment is held for >14 days, remove patient from protocol therapy. |
|                                               | Grade 3  | Hold capecitabine until Grade ≤ 1 resume at 75% of initial capecitabine dose. If treatment is held for >14 days, remove patient from protocol therapy. |
| 2\textsuperscript{nd} occurrence of Grade 3   |          | Hold capecitabine until Grade ≤ 1 resume at 50% of initial capecitabine dose. If treatment is held for >14 days, remove patient from protocol therapy. |
| 3\textsuperscript{rd} occurrence of Grade 3   |          | Discontinue capecitabine                                                     |
| Cardiac toxicity\textsuperscript{c}           | ≥ Grade 2 | Patients to be permanently discontinued from therapy                        |

a. See Appendix IV for tables of capecitabine dose modification. Radiation doses will not be modified.
b. If therapy is held, radiation will be made up to achieve planned total dose. Chemotherapy will continue throughout course of pelvic radiation.
c. Attributable to 5-FU or capecitabine.

#### 7.3.2. Postoperative Therapy: Dose modifications for 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) (Arm 1). (6/29/05)

All adverse events should be graded according to the Common Terminology Criteria for Adverse Events (Version 3.0). The final dose modification according to the following tables should be based upon the worst grade of adverse event experienced. If patients require dose reductions lower than level-2, protocol therapy should be discontinued.

Dose calculation should be based upon actual body weight and not modified for obesity. Dose calculations that deviate from the use of actual body weight will be considered a major protocol violation.

| Toxicity  | Grade | Modification |
|-----------|-------|--------------|
| Hematologic | Grade 1-2 | No change    |
| Grade 3-4 | Hold until grade $\leq 1$, then decrease to dose level $-1$ what if no resolution |
|----------|----------------------------------------------------------------------------------|
| 2$^{nd}$ occurrence of Grade 3-4 | Hold until grade $\leq 1$, then decrease dose level $-2$. If not resolved to $\leq 1$ after 21 day delay (35 days since start of prior cycle) discontinue chemotherapy. |
| 3$^{rd}$ occurrence of Grade 3-4 | Discontinue chemotherapy |

Non-hematologic toxicity, except pulmonary fibrosis, and cold-induced dysesthesias

| Grade 1-2 | No change |
| Grade 3 | Hold until grade $\leq 1$, then decrease to dose level $-1$. If not resolved to $\leq 1$ after 21 day delay (35 days since start of prior cycle) discontinue chemotherapy. |
| 2$^{nd}$ occurrence of Grade 3 | Hold until grade $\leq 1$, then decrease to dose level $-2$. If not resolved to $\leq 1$ after 21 day delay (35 days since start of prior cycle) discontinue chemotherapy. |
| Grade 4 | Hold until grade $\leq 1$, then decrease to dose level $-2$. If not resolved to $\leq 1$ after 21 day delay (35 days since start of prior cycle) discontinue chemotherapy. |
| 3$^{rd}$ occurrence of Grade 3 or 2$^{nd}$ occurrence of Grade 4, or Grade 3 followed by Grade 4 | Discontinue chemotherapy |

Pulmonary fibrosis

| See comment$^a$ | Suspected diagnosis |
| Hold oxaliplatin until pulmonary fibrosis is ruled out or an alternate diagnosis is confirmed; oxaliplatin may then be resumed at previous doses. |

Cold-induced dysesthesias

| Resolve between doses of oxaliplatin | No dose modification |
| Persists at time of next oxaliplatin dose | Hold oxaliplatin until resolved, then resume at oxaliplatin dose level-1. If not resolved to $< 1$ after 21 day delay (35 days since start of prior cycle) discontinue chemotherapy. |
| 2$^{nd}$ occurrence. Persists at time of next oxaliplatin dose | Hold oxaliplatin until resolved, then resume at oxaliplatin dose level-2. If not resolved to $< 1$ after 21 day delay (35 days since start of prior cycle) discontinue chemotherapy. |
| 3$^{rd}$ occurrence. Persists at time of next oxaliplatin dose | Discontinue oxaliplatin |

---

a. Signs and symptoms associated with pulmonary fibrosis (cough, dyspnea, rales, hypoxia, tachypnea) should be investigated to rule out pulmonary fibrosis as their cause. Evaluation for pulmonary fibrosis should include (chest x-ray, pulse oximetry or arterial blood gas, and PFTs with DLCO).

| Oxaliplatin | Leucovorin | Bolus 5-FU | Infusion 5-FU |
|------------|------------|-----------|--------------|
| Start Level | 85 mg/m$^2$ | 400 mg/m$^2$ | 400 mg/m$^2$ | 2400 mg/m$^2$ |
| Level $-1$ | 65 mg/m$^2$ | 400 mg/m$^2$ | 300 mg/m$^2$ | 1800 mg/m$^2$ |
| Level $-2$ | 45 mg/m$^2$ | 400 mg/m$^2$ | 200 mg/m$^2$ | 1200 mg/m$^2$ |

### 7.4 Dose Modifications – Arm 2

**NOTE:** All adverse events should be graded according to the Common Terminology Criteria for Adverse Events (Version 3.0). The final dose modification according to the following tables should be based upon the worst grade of the adverse event experienced. If preoperative treatment is discontinued because of toxicity, further
therapy will be at the discretion of the treating physicians.

### 7.4.1 Dose Modifications During Preoperative Chemotherapy (Arm 2) (8/19/04)(12/1/04)(3/22/05) (9/8/05)(3/31/06)

*Dose calculation should be based upon actual body weight and not modified for obesity. Dose calculations that deviate from the use of actual body weight will be considered a major protocol violation.*

| Capecitabine, Oxaliplatin, Concurrent Pelvic Radiation Dose Modification |
|-----------------------------|------------------|------------------|
| **Toxicity**                | **Grade**        | **Modification** |
| Any toxicity except rash: hand foot reaction; pulmonary fibrosis; cardiac toxicity, diarrhea, veno-occlusive disease, or cold-induced dysesthesias | Grade 1 or 2     | No change        |
| Grade 3                     | Hold chemotherapy and radiation until symptoms resolve to Grade ≤ 1, then resume at 75% of current capecitabine and oxaliplatin doses\(^a\)\(^b\). If not resolved to ≤ 1 after 21 day delay (35 days since start of prior cycle) discontinue chemotherapy. |
| Grade 4                     | Discontinue chemotherapy and radiation. |
| Diarrhea                    | Grade 1          | No change        |
| Grade 2 or 3                | Hold chemotherapy and radiation until symptoms resolve to Grade ≤ 1, then resume at 75% of current capecitabine and oxaliplatin doses\(^a\)\(^b\). If treatment is held for >14 days, remove patient from protocol therapy. |
| Grade 4                     | Discontinue chemotherapy and radiation. |
| Rash: hand-foot skin reaction | Grade 1         | No change        |
| Grade 2                     | Hold capecitabine until Grade ≤ 1, resume at previous capecitabine dose. If not resolved to ≤ 1 after 21 day delay (35 days since start of prior cycle) discontinue chemotherapy. |
| 2\(^{nd}\) occurrence of Grade 2 | Hold capecitabine until Grade ≤ 1, resume at 75% of initial capecitabine dose\(^a\). If not resolved to ≤ 1 after 21 day delay (35 days since start of prior cycle) discontinue chemotherapy. |
| 3\(^{rd}\) occurrence of Grade 2 | Hold capecitabine until Grade ≤ 1 resume at 50% of initial capecitabine dose\(^a\). If not resolved to ≤ 1 after 21 day delay (35 days since start of prior cycle) discontinue chemotherapy. |
| Grade 3                     | Hold capecitabine until Grade ≤ 1 resume at 75% of initial capecitabine dose\(^a\). If not resolved to ≤ 1 after 21 day delay (35 days since start of prior cycle) discontinue chemotherapy. |
| 2\(^{nd}\) occurrence of Grade 3 | Hold capecitabine until Grade ≤ 1 resume at 50% of initial capecitabine dose\(^a\). If not resolved to ≤ 1 after 21 day delay (35 days since start of prior cycle) discontinue chemotherapy. |
| 3\(^{rd}\) occurrence of Grade 3 | Discontinue capecitabine |
Pulmonary fibrosis

Suspected diagnosis

Hold oxaliplatin until pulmonary fibrosis is ruled out or an alternate diagnosis is confirmed; oxaliplatin may then be resumed at previous doses.

Confirmed diagnosis

Discontinue oxaliplatin

Veno-occlusive disease (VOD)

Suspected diagnosis

Hold oxaliplatin until VOD is ruled out or an alternate diagnosis is confirmed; oxaliplatin may then be resumed at previous doses.

Confirmed diagnosis

Discontinue oxaliplatin

Cold-induced dysesthesias

Resolve between doses of oxaliplatin

No dose modification.

Persist at time of next oxaliplatin dose

Hold oxaliplatin until resolved, then resume at 40 mg/m². If not resolved to < 3 after 21 day delay (35 days since start of prior cycle) discontinue oxaliplatin.

2nd occurrence Persisting at time of next oxaliplatin dose-second occurrence

Hold oxaliplatin until resolved, then resume at 30 mg/m². If not resolved to < 1 after 21 day delay (35 days since start of prior cycle) discontinue oxaliplatin.

3rd occurrence Persisting at time of next oxaliplatin dose

Discontinue oxaliplatin

Cardiac toxicity

≥ Grade 2

Patients to be permanently discontinued from therapy

a. See Appendix IV for table of Capecitabine dose modification.
b. If therapy is held radiation will be made up to achieve planned total dose. Chemotherapy will continue throughout course of pelvic radiation.
c. Signs and symptoms associated with pulmonary fibrosis (cough, dyspnea, rales, hypoxia, tachypnea) should be investigated to rule out pulmonary fibrosis as their cause. Evaluation for pulmonary fibrosis should include (chest x-ray, pulse oximetry or arterial blood gas, and PFTs with DLCO).
d. Attributable to 5-FU or capecitabine.
e. See Section 7.2.2.3.

7.4.2 Postoperative Therapy: Dose modifications for 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) (Arm 2) (12/1/04) (3/22/05)

All adverse events should be graded according to the Common Terminology Criteria for Adverse Events (Version 3.0). The final dose modification according to the following tables should be based upon the worst grade of adverse event experienced. If patients require dose reductions lower than level-2, protocol therapy should be discontinued.

Dose calculation should be based upon actual body weight and not modified for obesity. Dose calculations that deviate from the use of actual body weight will be considered a major protocol violation.

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.

| Toxicity | Grade | Modification |
|----------|-------|--------------|
| Hematologic | Grade 1-2 | No change |
| Grade 3-4 | Hold until grade < 1, then decrease to dose level −1 |
| 2nd occurrence of the same or a new Grade 3-4 event | Hold until grade < 1, then decrease dose level −2. If not resolved to < 1 after 21 day delay (35 days since start of prior cycle) discontinue chemotherapy. |
| 3rd occurrence of the same or a new Grade 3-4 | Discontinue chemotherapy |
### Non-hematologic toxicity, except pulmonary fibrosis, and cold-induced dysesthesias

| Grade 1-2 | No change |
|-----------|-----------|
| Grade 3  | Hold until grade ≤ 1, then decrease to dose level –1. If not resolved to ≤ 1 after 21 day delay (35 days since start of prior cycle) discontinue chemotherapy. |
| 2\textsuperscript{nd} occurrence of the same or a new Grade 3 event | Hold until grade ≤ 1, then decrease to dose level –2. If not resolved to ≤ 1 after 21 day delay (35 days since start of prior cycle) discontinue chemotherapy. |
| Grade 4  | Hold until grade ≤ 1, then decrease to dose level –2. If not resolved to ≤ 1 after 21 day delay (35 days since start of prior cycle) discontinue chemotherapy. |
| 3\textsuperscript{rd} occurrence of the same or a new Grade 3 event or 2\textsuperscript{nd} occurrence of the same or a new Grade 4 event, or Grade 3 followed by Grade 4 | Discontinue chemotherapy |

#### Pulmonary fibrosis

- **Suspected diagnosis**
  - Hold oxaliplatin until pulmonary fibrosis is ruled out or an alternate diagnosis is confirmed; oxaliplatin may then be resumed at previous doses.
- **Confirmed diagnosis**
  - Discontinue oxaliplatin

#### Veno-occlusive disease (VOD)

- **Suspected diagnosis**
  - Hold oxaliplatin until VOD is ruled out or an alternate diagnosis is confirmed; oxaliplatin may then be resumed at previous doses.
- **Confirmed diagnosis**
  - Discontinue oxaliplatin

#### Cold-induced dysesthesias

- **Resolve between doses of oxaliplatin**
  - No dose modification
  - **Persist at time of next oxaliplatin dose**
    - 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.
  - **2\textsuperscript{nd} occurrence. Persist at time of next oxaliplatin dose**
    - 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.
  - **3\textsuperscript{rd} occurrence. Persist at time of next oxaliplatin dose**
    - Discontinue oxaliplatin

---

a. Signs and symptoms associated with pulmonary fibrosis (cough, dyspnea, rales, hypoxia, tachypnea) should be investigated to rule out pulmonary fibrosis as their cause. Evaluation for pulmonary fibrosis should include (chest x-ray, pulse oximetry or arterial blood gas, and PFTs with DLCO).

b. See Section 7.2.2.3.

| Oxaliplatin | Leucovorin | Bolus 5-FU | Infusion 5-FU |
|-------------|------------|------------|---------------|
| Start Level | 85 mg/m²   | 400 mg/m²  | 400 mg/m²     | 2400 mg/m²    |
| Level –1    | 65 mg/m²   | 400 mg/m²  | 300 mg/m²     | 1800 mg/m²    |
| Level –2    | 45 mg/m²   | 400 mg/m²  | 200 mg/m²     | 1200 mg/m²    |

### Supportive Therapy (3/22/05)

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) and documented on each institution’s case report forms as source documentation.
7.5.1 **Loperamide (Imodium®)**
All patients should be instructed to begin taking loperamide at the earliest signs of diarrhea and/or abdominal cramping that occur more than eight hours after receiving CPT-11. Patients will be instructed to begin taking loperamide at the earliest signs of (1) a poorly formed or loose stool, (2) the occurrence of 1 to 2 more bowel movements than usual in one day, or (3) unusually high volume of stool. Loperamide should be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every two hours around the clock until diarrhea-free for at least 12 hours. Patients may take 4 mg of loperamide every four hours during the night. Additional antidiarrheal measures may be used at the discretion of the treating physician.

7.5.2 **Antibiotics**
In patients with diarrhea and neutropenia, even in the absence of fever, empiric use of antibiotics as prophylaxis against bowel sepsis should be strongly considered. Use of a quinolone is suggested in this setting (Rothenberg ML, Meropol NJ, Poplin EA, Van Cutsem E, Wadler S. Mortality associated with irinotecan plus bolus 5-fluorouracil/leucovorin: summary findings of an independent panel. *J Clin Oncol* 19: 3801-3807, 2001).

7.5.3 **Atropine**
Lacrimation, diaphoresis, abdominal cramping, diarrhea, or other symptoms of early cholinergic syndrome that occur during or within one hour after receiving CPT-11 can be treated with i.v. atropine (0.25 to 1 mg i.v. or as indicated). Patients experiencing cholinergic symptoms following irinotecan may be given prophylactic atropine with subsequent dosing. Atropine should be used with caution in patients with potential contraindications (e.g., obstructive uropathy, glaucoma, tachycardia, etc.).

7.5.4 **Antiemetics**
Antiemetics should be prescribed by the treating physician as clinically indicated if a patient develops nausea and/or vomiting. Patients should receive dexamethasone (Decadron®) 10 mg i.v. and either ondansetron (Zofran®) at 32 mg i.v., or granisetron (Kytril®) at 10 μg/kg i.v. as pretreatment antiemetics before irinotecan and oxaliplatin unless there is a relative or absolute contraindication to use of these medications. The use of lorazepam (Ativan®) or prochlorperazine (Compazine®) may also be considered as clinically indicated.

7.5.5 **Anticoagulants**
Patients who are taking Coumadin® may participate in this study; however, it is recommended that prothrombin time (or INR) be monitored carefully (at least weekly), particularly during treatment with capecitabine given a known interaction between these medications. Subcutaneous heparin or fractionated heparin products are also permitted.

7.5.6 **Growth Factors**
Routine prophylactic use of G-CSF is not permitted; however, administration of G-CSF in patients with neutropenic complications is permitted at the discretion of the treating physician. Growth factors may not be used in lieu of dose modifications as specified in the protocol. Use of erythropoietin is permitted at the discretion of the treating physician.

7.5.7 **Other Concomitant Medications**
Other concomitant medications should be avoided except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems. If possible, the use of drugs with laxative properties should generally be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact the study physician to discuss any laxative use.

7.6 **5-Fluorouracil**

7.6.1 **Other Names**
5-Fluorouracil, 5-FU, Adrucil, Efudex.

7.6.2 **Classification**
Antimetabolite.

7.6.3 **Mode of Action**
Fluorouracil is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthetase, thus inhibiting the formation of thymidylic acid from deoxyuridylic acid, thus interfering in the synthesis of DNA. It also interferes with RNA synthesis.

7.6.4 **Storage and Stability**
Stable for prolonged periods of time at room temperature, if protected from light. Inspect for precipitate; if apparent, agitate vial vigorously or gently heat to not greater than 140°F in a water bath. Do not allow to freeze.

7.6.5 **Administration**
5-FU will be administered as an IV bolus, and as a 46 hour infusion as described in sections 7.1.2.2, 7.2.2.2, 7.3.2, and 7.4.2.

### 7.6.6 Availability
Commercially available in 500 mg/10 ml ampules and vials, and 1 gm/20 ml, 2.5 gm/50 ml, and 5 gm/100 ml vials.

### 7.6.7 Side Effects (8/19/04)(12/1/04)
Please refer to the approved package insert for complete prescribing and toxicity information.
- **Hematologic**: Leukopenia, thrombocytopenia, anemia, can be dose limiting; less common with continuous infusion.
- **Dermatologic**: Dermatitis, nail changes, hyperpigmentation, Hand-Foot Syndrome with protracted infusions, alopecia.
- **Gastrointestinal**: Nausea, vomiting, anorexia, diarrhea, can be dose limiting; mucositis, more common with 5-day infusion, occasionally dose limiting; severe, cholera-like diarrhea which can be fatal when given with leucovorin.
- **Neurologic**: Cerebellar Syndrome (headache and cerebellar ataxia).
- **Cardiac**: Angina, noted with continuous infusion. For ≥ Grade 2 cardiac toxicity that is attributable to 5-FU or capecitabine, patients will be permanently discontinued from therapy.
- **Ophthalmic**: Eye irritation, nasal discharge, watering of eyes, blurred vision.
- **Hepatic**: Hepatitis with hepatic infusion.

### 7.7 Leucovorin Calcium

#### 7.7.1 Other Names
Leucovorin, Wellcovorin, citrovorum factor, folic acid, 5-formyl tetrahydrofolate, LV, LCV.

#### 7.7.2 Classification
Tetrahydrofolic acid derivative.

#### 7.7.3 Mode of Action
Leucovorin acts as a biochemical cofactor for 1-carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolate reductase (DHFR) for conversion to tetrahydrofolic acid. The effects of methotrexate and other DHFR-antagonists are inhibited by leucovorin. Leucovorin can potentiate the cytotoxic effects of fluorinated pyrimidines (i.e., fluorouracil and floxuridine). After 5-FU is activated within the cell, it is accompanied by a folate cofactor, and inhibits the enzyme thymidylate synthetase, thus inhibiting pyrimidine synthesis. Leucovorin increases the folate pool, thereby increasing the binding of folate cofactor and active 5-FU with thymidylate synthetase.

#### 7.7.4 Storage and Stability
All dosage forms are stored at room temperature. The reconstituted parenteral solution, 10 mg/ml, is stable for at least 7 days at room temperature. At concentrations of 0.5-0.9 mg/ml the drug is chemically stable for at least 24 hours at room temperature under normal laboratory light.

#### 7.7.5 Preparation
The 50 and 100 mg vials for injection are reconstituted with 5 and 10 ml of sterile water or bacteriostatic water, respectively, resulting in a 10 mg/ml solution. The 350 mg vial is reconstituted with 17 ml of sterile water resulting in a 20 mg/ml solution.

#### 7.7.6 Compatibilities
Leucovorin (0.5-0.9 mg/ml) is chemically stable for at least 24 hours in normal saline, 5% dextrose, 10% dextrose, Ringer's injection or lactated Ringer's injection. Leucovorin is also compatible with fluorouracil and oxaliplatin.
7.7.7 **Availability**
Commercially available in parenteral formulations (3 and 5 mg ampule; 50 mg, 100 mg and 350 mg vial).

7.7.8 **Side Effects**
Please refer to the approved package insert for complete prescribing and toxicity information.

7.7.9 Other: Leucovorin may potentiate the toxic effects of fluoropyrimidine therapy, for example resulting in increased hematologic and gastrointestinal (diarrhea, stomatitis) adverse effects.

7.8 **Oxaliplatin**

7.8.1 **Other Names**
NSC 266046, Eloxatin, trans-1-diamino cyclohexane oxaliplatin, cis-[oxalato(trans-1,2-diamino cyclohexane)platinum(II)]/-OHP, Eloxatine®, Dacplat™, SR96669.

7.8.2 **Classification**
Alkylating agent. Cytotoxic.

7.8.3 **Mode of Action**
The mechanism of action of oxaliplatin is similar to cisplatin. The main site of action is intrastrand cross-linking, therefore inhibiting DNA replication and transcription.

7.8.4 **Storage and Stability**
Oxaliplatin vials are stored at room temperature between 20° and 25°C. Reconstituted solution in sterile water or 5% dextrose may be stored and will remain stable for 24 hours at 2°-8°C (36°-46°F).

7.8.5 **Preparation**
Reconstitute with 10 mL for 50 mg and 20 mL for 100 mg product sterile water or 5% dextrose to provide an initial concentration of 5 mg/mL. Subsequent dilution with 250-500 mL 5% Dextrose.

7.8.6 **Route of Administration**
The diluted solution of oxaliplatin in 250 ml 5% dextrose is administered IV by an infusion pump over 2 hours.

7.8.7 **Incompatibilities**
Do not mix or administer with saline or other chloride containing solutions. Oxaliplatin is unstable in the presence of chloride. Oxaliplatin may be administered simultaneously with leucovorin by the same infusion line, provided that they are reconstituted in D5W. Do not mix with alkaline solutions. Oxaliplatin is unstable under alkaline conditions. Do not use components containing aluminum for the preparation of oxaliplatin administration. There is a risk of drug degradation when in contact with aluminum.

7.8.8 **Availability (8/19/04)**
Oxaliplatin is commercially available in the US.

7.8.8.1 **Oxaliplatin** is not commercially available in Canada. 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.

7.8.9 **How Supplied**
Freeze-dried powder for IV infusion in vials containing 50 mg or 100 mg of oxaliplatin. The powder is a white to off-white cake or powder contained in clear glass vials, sealed with an elastomeric stopper and aluminum seal with a flip-off cover. The excipient is lactose monohydrate, 450 mg and 900 mg respectively.

7.8.10 **Adverse Events (12/1/04)**
Please refer to the approved package insert for complete prescribing and toxicity information.
- **Allergy/Immunology:** Allergic/Hypersensitivity reactions (including drug fever)
- **Auditory:** Middle ear/hearing (otoxicity, mild), inner ear/hearing (mild hearing loss)
- **Blood/Bone Marrow:** decreased hemoglobin, hemolysis (e.g. immune hemolytic anemia, drug-related hemolysis), decreased leukocytes, decreased platelets, neutropenia
- **Cardiovascular (Arrhythmia):** Sinus tachycardia, supraventricular arrhythmias (SVT/atrial fibrillation/flutter), ventricular arrhythmias (PVCs/ bigeminy/trigeminy/ventricular tachycardia)
- **Cardiovascular (General):** Edema, hypertension, phlebitis (superficial), thrombosis/embolism (including pulmonary embolism)
- **Coagulation:** DIC (Disseminated intravascular coagulation)
- **Constitutional Symptoms:** Fever (in the absence of neutropenia), weight loss, fatigue
lethargy, malaise, asthenia)

- Dermatology/Skin: Erythema or skin eruptions, alopecia, hand-foot skin reaction, injection site reaction, rash/desquamation
- Endocrine: Hot flashes/flushes
- Gastrointestinal: Anorexia, constipation, dehydration, dysphagia, diarrhea, esophagitis, odynophagia (painful swallowing), gastrointestinal reflux, enteritis, ascites (NOS), intestinal obstruction, stomatitis/pharyngitis (oral/pharyngeal mucositis), taste disturbance (dysgeusia), nausea, vomiting, colitis, ileus (or neuroconstipation), typhilitis
- Hemorrhage: CNS hemorrhage/bleeding, hemoptysis, hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, melena/GI bleeding, rectal bleeding/hematochezia, other (hemorrhage NOS)
- Hepatic: increased alkaline phosphatase, increased bilirubin, increased GGT (gamma-glutamyl-transpeptidase), hepatic enlargement, increased AST (AST) (serum glutamic oxaloacetic transaminase), increased SGPT (ALT) (serum glutamic pyruvic transaminase). Veno-occlusive disease of the liver has been reported with the administration of the combination of 5-FU and oxaliplatin.
- Infection/Febrile Neutropenia: Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented fever (ANC < 1.0 x 10^9/L, fever > 38.5°C) infection (documented clinically or micro-biologically with grade 3 or 4 neutropenia (ANC < 1.0 x 10^9/L), infection without neutropenia
- Metabolic/Laboratory: Acidosis (metabolic or respiratory) hyperuricemia, hypokalemia, hypophosphatemia, hyponatremia, hypocalcemia, hypomagnesemia, hyponatremia
- Musculoskeletal: Involuntary muscle contractions
- Neurology: Ataxia (incoordination, including abnormal gait) insomnia, mood alteration (depression, anxiety) neuropathy cranial (ptosis), vertigo, neuropathy sensory (including acute laryngeo-pharyngeal dysesthesias, L’Hermitte’s sign, paresthesia)
- Ocular/Visual: Conjunctivitis, vision abnormalities (including blindness, optic neuritis, papilledema, hemianopsia, visual field defect, transient blindness
- Pain: abdominal pain or cramping, arthralgia (joint pain), bone pain, chest pain (non-cardiac and non-pleuritic), headache (including migraine), myalgia (muscle pain including cramps and leg cramps)
- Pulmonary: Pulmonary fibrosis, cough, dyspnea (shortness of breath), hiccoughs (hiccups, singultus), pneumonitis/pulmonary infiltrates (including eosinophilic pneumonia, interstitial pneumonitis, and interstitial lung disease), laryngospasm
- Renal/Genitourinary: Increased creatinine, renal failure, urinary retention
- Also reported on oxaliplatin trials but with the relationship to oxaliplatin still undetermined: Anemia, tongue paralysis, abnormal hepatic function, dysarthria, hyporeflexia, anxiety.

**NOTE:** Oxaliplatin in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

### 7.9 Irinotecan

#### 7.9.1 Other Names
Camptothecin-11, CPT-11, Camptosar®

#### 7.9.2 Classification
Topoisomerase I inhibitor.

#### 7.9.3 Mode of Action
Topoisomerase I is intimately involved in DNA replication and RNA transcription as it relieves the torsional strain introduced ahead of the moving replication fork. The cytotoxicity of irinotecan results from single and double strand DNA breaks that are produced by inhibiting topoisomerase I during the course of NDA and RNA synthesis. Irinotecan is an inactive prodrug and must be metabolized *in vivo* by carboxyesterases to the active compound SN-38.

#### 7.9.4 Storage and Stability
Undiluted vials are stored at room temperature (15-30°C), and protected from light.

#### 7.9.5 Preparation
Irinotecan must be diluted before infusion. The recommended diluent for short intravenous administration of irinotecan is 500 ml of dextrose 5%. Stability is less in normal saline. The
diluted solution should be inspected visually for particulate matter.

7.9.6 Route of Administration (8/19/04) (3/22/05)
Irinotecan is administered IV over 60 to 90 minutes, depending on the dose administered (as per Sections 7.1.1.1 and 7.1.2.2. For diarrhea occurring during or immediately after the infusion of irinotecan, atropine 1 mg can be administered by IV. (Anticipate mydriasis and tachycardia). For more delayed diarrhea, usually beginning 5-7 days after starting treatment, the patient should take 4 mg loperamide orally at the first loose stool. (Note: The loperamide regimen is in excess of the labeled “maximum” dose of 16 mg/day. Refer questions regarding the dose to the article by Conti, et al). See Sections 7.5.1 and 7.5.2.

7.9.7 Incompatibilities
Solutions other than dextrose 5% should not be used for dilution. Other compatibility information is not available.

7.9.8 Availability
Commercially available in 100 mg single dose 5 ml vials containing 20 mg/ml. A 40 mg vial is also available.

7.9.9 Reported Adverse Events and Potential Risks
Please refer to the approved package insert for complete prescribing and toxicity information.

Hematologic: Leukopenia and neutropenia
Gastrointestinal: Diarrhea, requiring immediate treatment with loperamide; nausea and vomiting, anorexia, abdominal pain
Hepatic: Elevated transaminases
Dermatologic: Alopecia
Other: Asthenia

7.10 Capecitabine

7.10.1 Other names
Xeloda®

7.10.2 Classification
Antimetabolite, cytotoxic.

7.10.3 Mode of action
Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil.

7.10.4 Storage and stability
Capecitabine should be stored at room temperature, excursions permitted to 15° to 30°C (59° to 86°F), with container tightly closed.

7.10.5 Route of administration
Tablets should be swallowed with water 30 minutes after the end of a meal (breakfast and dinner). If necessary, tablets can be crushed.

7.10.6 Availability
Capecitabine is supplied as a biconvex, oblong film-coat tablets for oral administration. Each light-peach colored tablet contains 150 mg capecitabine, and each peach colored tablet contains 500 mg capecitabine. Capecitabine is commercially available.

7.10.7 Adverse Events (8/19/04)
Please refer to the approved package insert for complete prescribing and toxicity information.
- **Blood**: neutropenia, coagulation disorder, idiopathic thrombocytopenic purpura, pancytopenia.
- **Cardiac**: angina pectoris, cardiomyopathy. For ≥ Grade 2 cardiac toxicity that is attributable to 5-FU or capecitabine, patients will be permanently discontinued from therapy.
- **Gastrointestinal**: Diarrhea, nausea, vomiting, stomatitis, intestinal obstruction, rectal bleeding, GI hemorrhage, esophagitis, gastritis, colitis, duodenitis, hematemesis, necrotizing enterocolitis.
- **Dermatologic**: Hand-and-Foot Syndrome (painful erythema and swelling of the hands and/or feet), increased sweating, photosensitivity, radiation recall syndrome.
- **Infections**: fever, oral candidiasis, upper respiratory tract infection, urinary tract infection, bronchitis, pneumonia, sepsis, bronchopneumonia, gastroenteritis, gastrointestinal candidiasis, laryngitis, esophageal candidiasis.
- **Immune System**: drug hypersensitivity
- **Hepatobiliary**: hepatic fibrosis, cholestatic hepatitis, hepatitis.
• Metabolism: cachexia, hypertriglyceridemia.
• Drug interactions
  Sorivudine and Brivudine. A metabolite of these investigational antiviral agents, 5-
  bromovinyluracil, is a potent inhibitor of dihydropyrimidine dehydrogenase, the enzyme that
catabolizes 5-FU. Patients should not receive concurrent therapy with either of these
antiviral agents while receiving capecitabine.
• Musculoskeletal: bone pain, joint stiffness.
• Neurological: ataxia, encephalopathy, depressed level of consciousness, loss of
  consciousness.
Phenytoin: Increased phenytoin plasma concentrations have been reported during
concomitant use of capecitabine with phenytoin, suggesting a potential interaction. Patients
taking phenytoin concomitantly with capecitabine should be regularly monitored for
increased phenytoin plasma concentrations and associated clinical symptoms
• Psychiatric: confusion.
• Respiratory: dyspnea, epistaxis, bronchospasm, respiratory distress.
• Renal and Urinary: nocturia
• Vascular: hypotension, hypertension, venous phlebitis and thrombophlebitis, deep venous
  thrombosis, lymphoedema, pulmonary embolism, cerebrovascular accident.

7.11 Chemotherapy Quality Assurance Review
The Study Chair, Neal Meropol, M.D. or the Medical Oncology Co-Chair, Dr. Stuart Wong, M.D.
will perform a Chemotherapy Assurance Review of all patients who receive or are to receive
chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review
process is contingent on timely submission of chemotherapy treatment data as specified in
Section 12.1. The scoring mechanism is: variation acceptable; deviation unacceptable; not
evaluable for chemotherapy review, or incomplete chemotherapy.

7.12 Adverse Events (8/19/04)(12/1/04)(3/22/05)(3/31/06)
See Section 7.13.1.1 for Special Reporting Required for this Study.
This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0
for grading of all adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP
home page (http://ctep.cancer.gov). The CTEP home page also can be accessed from the
RTOG web page at http://www.rtog.org/regulatory/regs.html. All appropriate treatment areas
should have access to a copy of the CTCAE v3.0.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse
Event Expedited Reporting System) application accessed via the CTEP web site
(https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup).

Serious adverse events (SAEs) as defined in the table below will be reported via AdEERS. Sites
also can access the RTOG web site (http://www.rtog.org/members/toxicity/main.html) for this
information.

7.12.1 Adverse Events (AEs) — RTOG AE PHONE: 215-717-2762; 800-227-5463 ext. 4189
(available 24 hours/day)
Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory
finding), symptom, or disease temporally associated with the use of a medical treatment or
procedure regardless of whether it is considered related to the medical treatment or procedure
( attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited
Adverse Event Reporting Requirements. December 2004.]

The following guidelines for reporting adverse events (AEs) apply to all NCI/RTOG research
protocols. AEs, as defined above, experienced by patients accrued to this protocol should be
reported via AdEERS. Use the patient's case number as the patient ID when reporting via
AdEERS. AEs reported using AdEERS also must be reported on the AE case report form
(see Section 12.1). NOTE: If the event is a Serious Adverse Event (SAE) [see next
section], further reporting may be required. Reporting AEs only fulfills Data Management
reporting requirements.

7.12.2 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE
definition below must be reported to RTOG (SAE PHONE: 215-717-2762, 800-227-5463
ext. 4189; available 24 hours/day) within 24 hours of discovery of the event.

Definition of an SAE: Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

Outside of regular business hours (8:30-5:00 EST), leave a message that includes the study/case numbers and the caller’s contact information. A Data Manager will return the call the next business day requesting details of the event and also will inform the caller which type of report is required for that study (5 or 10 day AdEERS). The required report must be completed in AdEERS within 5 or 10 calendar days of the initial phone report, as directed by the Data Manager taking the call. SAEs reported using AdEERS also must be reported on the AE case report form (see Section 12.1).

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported to RTOG via the AE/SAE telephone line within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

All supporting source documentation, if applicable or if being faxed to NCI, must be properly labeled with the study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. All forms (and supporting source documentation) submitted to RTOG Headquarters must include the RTOG study/case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient’s case number as the patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note: Sites must print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.12.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at http://ctep.cancer.gov/forms/index.html. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.

RTOG Headquarters
AML/MDS Report
1818 Market Street, Suite 1600
Philadelphia, PA 19103
7.12.3 See Appendix V Comprehensive Adverse Events and Potential Risks List (CAEPR) for oxaliplatin.

7.13 Phase 2 Trials Utilizing an Agent under a Non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days of the Last Dose of the Commercially Available Agents in this Study (3/31/06)

|                     | Grade 1 | Grade 2 | Grade 2 | Grade 2 | Grade 3 | Grade 3 | Grades 4 & 5 | Grades 4 & 5 |
|---------------------|---------|---------|---------|---------|---------|---------|-------------|-------------|
|                     | Unexpected and Expected | Unexpected | Expected | Unexpected with Hospitalization | without Hospitalization | Expected with Hospitalization | without Hospitalization | Unexpected | Expected |
| Unrelated           | Not Required | Not Required | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | 10 Calendar Days |
| Unlikely            | Not Required | Not Required | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | 10 Calendar Days |
| Possible            | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | 10 Calendar Days | 10 Calendar Days | Not Required | 24-Hour; 5 Calendar Days | 10 Calendar Days |
| Probable            |          |         |         |         |         |         |             |             |
| Definite            |          |         |         |         |         |         |             |             |

1. Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a Non-CTEP IND require reporting as follows:
   - AdEERS 24-hour notification followed by complete report within 5 calendar days for:
     - Grade 4 and Grade 5 unexpected events
   - AdEERS 10 calendar day report:
     - Grade 3 unexpected events with hospitalization or prolongation of hospitalization
     - Grade 5 expected events

2. Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under section entitled “Additional Instructions.”

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

- ** Expedited AE reporting timelines defined:**
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

7.13.1 Additional Instructions for Phase 2 Trials Utilizing an Agent under a Non-CTEP IND:

7.13.1.1 Special Reporting for this Study (telephone 215-574-3150)(3/22/05)

7.13.1.1.1 All ≥ grade 3 non-hematologic adverse events (excluding nausea/vomiting controllable with antiemetics, alopecia) must be reported to RTOG Headquarters within 24 hours.

7.13.1.1.2 Data submission must adhere to the timetable specified by the patient calendar and Section 12.0.

7.13.1.1.3 The Capecitabine/Diarrhea diary will be checked for compliance/completeness by the investigator. A copy of the diary will be retained in the patient’s record for submission to
RTOG only upon request; i.e., diaries are not to be submitted but will be retained at the site as source documents.

7.14 **Criteria for Removal From Protocol Treatment** (8/19/04)(3/31/06)

**Cardiac Toxicity from capecitabine or 5-FU:**
For ≥ Grade 2 cardiac toxicity that is attributable to 5-FU or capecitabine, patients will be permanently discontinued from therapy.

8.0 **SURGERY**

8.1 All patients will undergo surgery four to eight weeks following the completion of radiation therapy. The use and method of bowel preparation is at the discretion of the surgeon.

8.1.1 **General operative evaluation**

8.1.1.1 Perform thorough examination of the abdomen to detect for metastatic disease. Negative as well as positive findings should be recorded in the operative report.

8.1.1.2 The finding at surgery of unresectable hepatic metastases or peritoneal seeding will preclude radical resection of the primary unless at the discretion of the surgeon it is indicated for local control and palliation.

8.1.2 **Operative procedure**

8.1.2.1 The choice of procedure abdominoperineal resection (APR), low anterior resection (LAR), or LAR/coloanal anastomosis) is at the discretion of the surgeon. *En bloc* hysterectomy, vaginectomy, and/or multivisceral resection should be performed if felt to be indicated without violation of primary tumor mass. The ureters will be identified bilaterally and preserved.

8.1.2.2 Techniques for anastamosis are at the discretion of the surgeon, as are use, placement, and removal of pelvic drains. Total mesorectal excision (TME) is recommended for all procedures.

8.1.2.3 APR will involve resection of the rectum and mesorectum from the perineum to the sacral promontory. The distal left colon is divided with a linear stapler to prevent spillage of intraluminal contents at a minimum of 5 cm proximal to the tumor mass *in vivo* (not required to be documented *ex vivo* due to potential retraction). Closure of the perineum and use of pelvic drain(s) is recommended.

8.1.2.4 For an LAR, the entire left colon is mobilized, with ligation of the inferior mesenteric artery and vein. The distal left colon is divided with a linear stapler to prevent spillage of intraluminal contents at a minimum of 5 cm proximal to the tumor mass *in vivo* (not required to be documented *ex vivo* due to potential retraction). The rectum and mesorectum will be removed with a distal rectal margin of at least 2 cm in vivo for sphincter preservation. Unirradiated colon from outside the pelvis should be used for the anastomosis. If necessary takedown of the splenocolic ligament should be performed to ensure adequate length to reach the planned anastomosis without tension.

8.1.2.5 If a LAR/coloanal anastomosis is performed, the entire left colon is mobilized, with ligation of the inferior mesenteric artery and vein. The distal left colon is divided with a linear stapler to prevent spillage of intraluminal contents at a minimum of 5 cm proximal to the tumor mass *in vivo* (not required to be documented *ex vivo* due to potential retraction). A radical resection of the rectum and mesorectum to the levators (distal rectal margin of at least 2 cm *in vivo*) is performed from the abdominal incision. The rectosacral fascia is incised posteriorly to mobilize the entire rectum to the level of the anorectal ring. Using technique of Parks, the mucosa is stripped from the dentate line to just above the levators. The level of the anorectal ring, the muscular rectal wall is divided by cautery and the specimen removed. The colon is brought into the anal canal and an anastomosis performed to the dentate line with interrupted full-thickness sutures. Unirradiated colon from outside the pelvis should be used for the anastomosis. If necessary, takedown of the splenocolic ligament should be performed to avoid undue tension on the anastomosis. Use of pelvic drain(s) is recommended. Temporary diversion of the fecal stream (through the formation of either an ileostomy or transverse colostomy) should be performed. A petrolatum-impregnated gauze role or a Penrose drain is placed in the anal canal to prevent "side-to-side" healing, and removed 4-5 days later. The temporary ostomy should not be closed until at least 6-8 weeks after the completion of all cycles of post-operative chemotherapy. Following closure, patients should be kept on a regular diet with Metamucil twice daily and constipating agents as needed.

8.1.2.6 Adequacy of bowel prep, estimated proximal and distal *in vivo* surgical margins, use of TME,
anastomotic method, location of drains, need to takedown splenocolic ligament, and concomitant procedures should be clearly documented in the operative report.

8.1.3 Surgical Pathology

8.1.3.1 The resected specimen is oriented for pathologic examination by placing a suture on the distal anterior rectal wall. The pathologist should ink the specimen, prior to fixation, for radial margin determination.

8.1.3.2 Separate biopsies of unresected tissue at the closest tumor margins may be taken to rule out histologically residual tumor and submit in a separate bottle.

8.1.3.3 Biopsy of suspicious areas on the peritoneum, liver or any other sites is recommended.

8.2 Surgical Quality Assurance Reviews

The Surgical Oncology Co-chair, James C. Watson, M.D., will perform a Quality Assurance Review after complete data for the first 20 cases enrolled have been received at RTOG Headquarters. Dr. Watson will perform the next review after complete data for the next 20 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been performed at the RTOG Headquarters, whichever occurs first. These reviews will be ongoing and performed at the RTOG semi-annual meetings as well as at RTOG Headquarters.

9.0 OTHER THERAPY

Patients will receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. Treatment with chemotherapeutic agents or radiation can be administered, as necessary for recurrent or metastatic disease.

See Section 7.5- Supportive Therapy.

10.0 PATHOLOGY

10.1 RTOG Tissue Bank (for patients who have consented to participate in the tissue component of the study)

10.1.1 Rationale: The purposes of the RTOG Tissue Bank are to acquire and maintain high quality specimens from RTOG trials, to provide uniform access to investigators for correlative studies, and to preserve tissue from each block through careful block storage and processing for future studies. Correlative studies using these specimens are meant to integrate new research findings into future protocol development and to provide tissue for future correlative grant applications, testing important biologic questions.

10.1.2 Specimen Collection (8/19/04): Tissue specimens for banking should be taken from pre-treatment diagnostic biopsy AND from surgical resection tissue. Specimens for tissue banking will be stored for an indefinite period of time. (See Section 10.1.3)

The following must be provided:

- One H&E stained slide.
- A paraffin-embedded tissue block of the tumor or a 2 mm diameter core of tissue, punched from the tissue block containing the tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. NOTE: A kit with the punch, tube, and instructions can be obtained from the Tissue Bank. If both of these tissue types are unavailable, 15 unstained slides may be submitted. Block, core, or slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.
- Pathology report documenting that submitted block or slides contain tumor.
- A Pathology Submission Form must be included and must clearly state that it is being submitted for the RTOG Tissue Bank.
- Pathology report documenting histopathological assessment of the resected specimen after chemoradiation therapy.

RTOG will reimburse pathologists from submitting institutions $300 per case for fresh or flash frozen tissue or for serum, $200 per case for a block or core of material, or $100 per case for unstained slides. RTOG Administration will prepare the proper paperwork and send a check to your institution after confirmation from LDS that they have received the appropriate number of slides/blocks. Pathology payment cycles are run with institution’s regular case reimbursement.
10.1.3 Confidentiality/Storage

(See Appendix IB and the RTOG Patient Tissue Consent Frequently Asked Questions, http://rtog.org/tissuebank/tissuefaq.html for further details.)

Patient consent form should give the Pathology Department authority and responsibility to comply with this request (pathology blocks belong to the patient from whom tissue has been removed).

Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The Tissue Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

Specimens for central review will be retained until the study is terminated; specimens for translational research will be retained until the study is terminated, unless the patients consents to storage for future studies; specimens for tissue banking will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

10.1.4 Blood Samples

10.1.4.1 Blood samples will be collected prior to protocol treatment for translational research tyo genotyping studies

10.1.4.2 Peripheral blood will be collected by venipuncture into two 12 ml Vacutainer® tubes containing EDTA (purple top tubes). A single tube will suffice if two cannot be collected. The blood should be stored at refrigerator temperature and shipped on wet ice the same day. Alternatively, the blood can be shipped and stored frozen at –20°C and shipped on dry ice. This second method allows for the collection of several samples over time; they can be shipped together thus lowering shipping costs. Specimens should be labeled with study number, case number, and institution name only. Questions regarding blood collection or shipment should be directed to LDS Hospital, Department of Pathology. Ship by express overnight service and avoid a weekend or holiday arrival date.

10.1.5 Materials will be sent to (12/1/04):

LDS Hospital
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
(801) 408-5626; FAX (801) 408-5020
holly.goold@ihc.com

10.2 Histopathological Assessment of the Resected Specimen

10.2.1 The histopathological assessment after chemoradiation therapy of the cancer will be made to assess depth of invasion, grade, mucin production, and blood vessel, lymphatic or perineural invasion. The proximal colonic, distal colonic for low anterior resection or anal for abdominoperineal resection, and circumferential radial (deep) margins will be assessed in millimeters. Intra-operative frozen section will be used to assess the adequacy of the margins of resection at the discretion of the surgeon.

10.2.2 The circumferential radial margin will be inked prior to fixation. The size of the specimen will be measured in length, width and thickness following fixation. After chemoradiation no grossly appreciable residual tumor may be present, and the tumor site may have a scar or ulcer. The size of the tumor, scar or ulcer will be measured in length, width and thickness in fixed condition. The pathology report will indicate the status of macroscopic or microscopic tumor at the proximal, distal or anal, and radial margins of resection. The central portion of the tumor, scar or ulcer will be serially sectioned to determine the maximum depth of cancer penetration.

10.2.3 The pathology report will specify the presence or absence of mucin production. In a subset of treated cancers mucin production may be secondary to treatment. A cancer will be scored as mucin positive if 30% or more of the cells are producing mucin. The pathology will specify the presence or absence of signet ring cell morphology and a cancer will be considered a signet ring cell cancer if 90% or more of cells exhibit this morphology. The pathology report will report the presence or absence of colloid cancer morphology. The pathology report will specify depth of invasion of tumor in a fashion such that it is clear whether the tumor is:

- Confined to the mucosa
- Confined to submucosa
- Confined to muscularis propria
- Transmural into perirectal fat grossly or microscopically

### 10.2.4 The pathology report will specify histological grade as follows:
- Well differentiated, 76-100% of tumor forming glands
- Moderately differentiated, 25-75% of tumor forming glands
- Poorly differentiated or undifferentiated, less than 25% of tumor forming glands or tumors which contain foci which are undifferentiated or anaplastic, even if the majority of tumor forms recognizable glands.

The pathology report will comment on the presence or absence of endothelial lined space invasion with cancer and the presence or absence of perineural and/or lymphatic invasion. An endothelial lined space containing both cancer and mature blood cells will be reported as blood vessel invasion.

The number of lymph nodes involved by metastatic cancer and total number of lymph nodes will be recorded. Cytokeratin immunohistochemistry and/or step sections will be used to demonstrate viable tumor cells if lymph node(s) contain acellular mucin in the initial H&E section.

### 10.2.5 Documentation of Tumor Response

Tumor response to high-dose preoperative radiation will be evaluated following surgical resection and pathological assessment of the specimen. The report will evaluate the percent of tumor that is viable (0-100%) and categorized according to the following criteria:
- **Pathologic complete response**: No evidence of residual cancer.

### 10.3 Correlative Studies

Evaluation of correlative marker studies are summarized in the following table:

| Marker          | Method          | Results Format                                      | Laboratory                                      |
|-----------------|-----------------|-----------------------------------------------------|------------------------------------------------|
| TS, TP, DPD     | Quantitative RT-PCR | Crossing point value with algorithm for RT-PCR   | University of Alabama Dr. Martin Johnson       |
| p53R2           | Quantitative RT-PCR | Gene copy number expression normalized by reference 18s rRNA expression | Laboratory of Dr. Stuart Wong, Medical College of Wisconsin |
| Polymorphisms   | PCR, Direct sequencing |                                                      | Human and Molecular Genetics Center, Medical College of Wisconsin, Dr. Stuart Wong |
| TS Gene Promoter ABCB1 |               |                                                      |                                                 |

### 10.4 Gene Expression Methods/Experimental Procedures

Paraffin blocks stored in the RTOG Tissue Repository will be cut into 10 μM sections onto plain glass slides. Tumor and normal cells will be isolated by microdissection and total RNA was extracted from the purified tumor samples using a slight modification of methods previously described. Separate aliquots of isolated total RNA samples from normal and tumor tissue will be shared between Dr. Wong, and Dr. Johnson for QRT-PCR. An ABI 7700 Sequence Detection System will be used to amplify and detect fluorescent emission using TP, DPD, TS and S9 using primers, probes with modification as previously described by Dr. Johnson. All PCR reactions will be run in triplicates and standard curves with correlation coefficients falling below 0.98 will be repeated. Detailed information on the development, precision and validation of this Q-RT-PCR method has previously been published.

The primary objective of the correlative studies is to examine the potential clinical usefulness of this quantitative biomarker assay. To do so we will examine the reproducibility of the expression
assay; the prevalence and range of expression of these markers in rectal cancer specimens; and the ability of the assay to discriminate marker expression between normal vs. tumor tissue, and between unirradiated vs. radiated tissue.

10.4.1 **Gene Polymorphism Methods/Experimental Procedures**
Genonomic DNA will be extracted from whole blood using the Gentra PureGene Blood Kit (Gentra, Minneapolis, MN) following the manufacturers instructions. SNPs and other genetic variations will be identified from the literature and SNP databases. Genotyping of TS gene promoter tandem repeats and ABCB1 polymorphisms will be performed by PCR and direct automated sequencing using an ABI 3700 with BigDye™ Terminator Cycle Sequencing Ready Reaction Kit v2.0, in 0.2-ml MicroAmp® 96-well plates (Applied Biosystems, Foster City, CA).

10.5 **Documentation of Tumor Response**
Tumor response to high-dose preoperative radiation will be evaluated following surgical resection and pathological assessment of the specimen and categorized according to the following criteria:

10.5.1 Pathologic complete response: No evidence of tumor.

10.6 **Documentation and Diagnosis of Tumor Relapse**
The following terminology will be used to document evidence of locally recurrent or metastatic disease:

10.6.1 Local Failure: recurrence or persistence of disease within radiation portals.
10.6.2 Regional Failure: failure outside of treatment field on basis of direct and/or lymphatic spread to include aortic nodes.
10.6.3 Distant Failure: includes both peritoneal seeding (PS) and distant metastasis (DM) on hematologic basis.
10.6.4 Disease Relapse: will be documented by biopsy whenever possible, together with clinical or radiographic evidence.
10.6.5 Progression: defined as one of the following:

- Evidence of new areas of malignant disease (*palpable or measurable*).
- Liver metastasis diagnosed by clinically significant hepatomegaly and/or positive liver scan.
- Other evidence of progression, e.g., jaundice, ascites, pleural effusion - Class V, persistent sacral pain with or without x-ray verification of bone destruction, neurologic changes consistent with metastatic disease with positive brain or CT scan, includes both peritoneal seeding (PS) and distant metastasis (DM) on hematologic basis.
### 11.0 PATIENT ASSESSMENTS

#### 11.1 Study Parameters: Entry and During Treatment (3/22/05)

| Assessment                                      | Study Entry<sup>a</sup> | Concurrent CT/RT Weekly | Pre-Surgery<sup>c</sup> | Post Op Prior to each Chemo Cycle |
|------------------------------------------------|-------------------------|-------------------------|-------------------------|----------------------------------|
| Physical Exam                                   | X                       | X                       | X                       | X                                |
| CBC diff, Platelets                             | X                       | X                       | X                       | X                                |
| CEA                                             | X                       |                         |                         |                                  |
| Alk Phos, AST, total bilirubin, creatinine, LDH | X                       | X                       | X                       | X                                |
| Serum or urine pregnancy test<sup>e</sup>       | X                       |                         |                         |                                  |
| CT Scan (abd/pelvis) to include liver           | X                       | X                       |                         | As indicated                    |
| MRI pelvis                                      | X<sup>a</sup>           |                         |                         |                                  |
| Transrectal ultrasound (Optional for T4)        | X                       |                         |                         |                                  |
| Chest x-ray                                     | X                       |                         |                         |                                  |
| Lower endoscopy                                 | X                       |                         |                         |                                  |
| QOL assessments<sup>d</sup>                     | X<sup>d</sup>           |                         | X<sup>d</sup>           |                                  |
| Zubrod performance                              | X                       |                         |                         |                                  |
| Toxicity Assessments                            | X                       | X                       | X                       | X                                |
| Pill/Diarrhea Review                            | X<sup>f</sup>           |                         |                         |                                  |

a. For corroboration of TNM staging (optional)
b. Labs and physical exam within two weeks prior to study entry; scans within eight weeks prior to study entry.
c. Within 2 weeks of surgery
d. QOL assessments are performed at baseline and completion of chemoradiation. Study Parameters: Follow-up Post Treatment
e. Within 7 days prior to starting protocol therapy (Females of childbearing potential)
f. Refer to Section 7.12.7.3.

#### Months Post Adjuvant

| Assessment           | 3  | 6  | 9  | 12 | 15 | 18 | 24 then every 6 mo. To 60 mo. |
|----------------------|----|----|----|----|----|----|-------------------------------|
| Physical Exam        | X  | X  | X  | X  | X  | X  | X                             |
| CEA                  | X  | X  | X  | X  | X  | X  | X                             |
| Lower endoscopy      | X  |    |    |    |    |    | As indicated                  |
| QOL Assessments      | X  |    |    |    |    |    | X at 24 mo. only              |
| Zubrod Performance   | X  | X  | X  | X  | X  | X  | X                             |
| Toxicity Assessment  | X  | X  | X  | X  | X  | X  | X                             |
| CT Scan              |    |    |    | X  | X  | X  | As Indicated                  |
| MRI pelvis           |    |    |    | X  | X  | X  | As Indicated                  |
| TRUS                 |    |    |    | X  | X  | X  | As Indicated                  |
QOL Assessments are performed after completion of post-operative chemotherapy (approximately one year) and at 2 years.

11.2 **Documentation of Tumor Response**

Tumor response to high-dose preoperative radiation will be evaluated following surgical resection and pathological assessment of the specimen and categorized according to the following criteria:

11.2.1 **Pathologic complete response:** No evidence of residual cancer histologically.

11.3 **Documentation and Diagnosis of Tumor Relapse**

11.3.1 The following terminology will be used to document evidence of locally recurrent or metastatic disease:

11.3.1.1 **Local Failure:** recurrence or persistence of disease within radiation portals.

11.3.1.2 **Regional Failure:** failure outside of treatment field on basis of direct and/or lymphatic spread to include aortic nodes.

11.3.1.3 **Distant Failure:** includes both peritoneal seeding (PS) and distant metastasis (DM) on hematologic basis.

11.3.1.4 **Disease Relapse:** will be documented by biopsy whenever possible, together with clinical or radiographic evidence.

11.3.1.5 **Progression:** defined as one of the following:

- Evidence of new areas of malignant disease (*palpable or measurable*).
- Liver metastasis diagnosed by clinically significant hepatomegaly and/or positive liver scan.
- Other evidence of progression, e.g., jaundice, ascites, pleural effusion- Class V, persistent
- Sacral pain with or without x-ray verification of bone destruction, neurologic changes consistent with metastatic disease with positive brain or CT scan.

11.4 **Assessments**

11.4.1 Complications of treatment will be recorded as to site and severity.

11.4.2 The major complaint is most likely to be GI related, and documentation of this will be extremely important to help evaluate treatment complications. Treatment will be conservative whenever possible, with surgical intervention called upon only when conservative methods fail.

11.4.3 Patients who have evidence of locoregional failure either by scans or clinical examination will undergo exploratory laparotomy and radical resection if possible. The radical resection will be appropriate for the site of recurrence.

11.4.4 Associated medical disease will be evaluated and treated as per accepted practice. Radiation can be administered as necessary for recurrent or metastatic disease.

12.0 **DATA COLLECTION (8/19/04)(12/1/04)(3/31/06)**

*(RTOG, 1818 MARKET STREET, SUITE 1600, PHILADELPHIA, PA 19103)*

12.1 **Summary of Data Submission**

The patient will be identified by first, middle and last initials (F M L). If there is no middle initial, a hyphen will be used. Last names with apostrophes will be identified by the first initial.

| Item (5/21/04) | Due |
|---------------|-----|
| Demographic Form (A5) | Within 2 weeks of study entry |
| Initial Evaluation Form (I1) | |
| Pathology Report (P1) | |
| Slides/Blocks (P2) | |
| QOL Assessments | |
| QOL Cover Sheet (CS) | |
| EORTC QLQ-C30 (QF) | |
| EORTC QLQ-CR-38 (PF) | |
| Sexual Adjustment Questionnaire (SAQ) | |
| Pretreatment Male (SA) | |
| Sexual Adjustment Questionnaire (SAQ) | |
| Pretreatment Female (FA) | |
| Pretreatment Questionnaire – Female (FS) | |
| Pretreatment Questionnaire – Male (FL) | |
Preliminary Dosimetry Information:
- RT Prescription *(Protocol Treatment Form)* (T2)
- Films *(simulation and portal)* (T3)
- Calculations (T4)

Final Dosimetry Information:
- Daily Treatment Record (T5)
- Isodose Distribution (T6)
- Boost Films *(simulation and portal)* (T8)
- Radiotherapy Form (T1)

QOL Assessments
- QOL Cover Sheet (CS)
- EORTC QLQ-C30 *(QF)*
- EORTC QLQ-CR38 *(PF)*
- Sexual Adjustment Questionnaire (SAQ) Follow-up male (SC)
- Sexual Adjustment Questionnaire (SAQ) Follow-up female (FC)

Preoperative Chemoradiotherapy Treatment Form (TF)
- Adverse Event Evaluation Form (AE)

Postoperative Chemotherapy Treatment Form (SF)
- Adverse Event Evaluation Form (AE)

Follow-up Form (F1)
- Adverse Event Evaluation Form (AE)

Surgical Pathology Materials (P7)
- Surgical Form (S1)
- Operative Report (S2)
- Surgical Pathology Report (S5)

Autopsy Report (D3)

Within 1 week of start of RT

Within 1 week of RT end

Within 1 week of RT end, within 1 week of post-operative chemotherapy end (12 months), and at 24 month follow-up.

At the end of concurrent pre-operative therapy

At the end of concurrent pre-operative therapy

Three times during postoperative chemotherapy *(once every three cycles)*

Monthly during postoperative chemotherapy

Every 3 months from start of treatment for 2 years; q 6 months x 3 years, then annually. Also at progression/relapse and at death.

Every 3 months from start of treatment for 2 years; q 6 months x 3 years, then annually. Also at progression/relapse and at death.

Within two weeks of surgery

As applicable

12.1.1 Quality of Life Documentation Submission

All quality of life forms for this study are available for download from the RTOG web site. Consistent with the belief that the most meaningful information is elicited from the patient, the QOL instruments are designed for self-administration and self-report of the patients' perceived QOL and function. The patient will complete the QOL tools while alone in an undisturbed setting. The same clinical individual should administer the tool to the patient each time if possible. The quality of life questionnaires are to be mailed one week ahead or given to the patients at their scheduled visits and should be filled out before leaving the clinic. Patients who fail to return for a scheduled visit will receive follow-up phone calls and an appointment should be rescheduled as close to the original date as possible. Patients who cannot or refuse to come in for an appointment must be asked if they will accept a telephone interview; if a telephone interview is acceptable to the patient, an appointment for the telephone interview should be set in advance. The patient may receive assistance filling out the questionnaire if necessary (i.e., cannot read, forgot their glasses, etc.). It is, however,
important to avoid influencing their response. Any assistance along with the reason for assistance must be noted on the cover form. Family members are not permitted to assist the patient filling out the questionnaire. The questionnaire must be reviewed after the patient completes the form to be sure all items are answered and that each item has only one response circled. It is permissible to send the questionnaire home with the patient in a sealed envelope with a return addressed, stamped envelope if he/she refuses to fill them out at the time of their appointment.

Every effort possible should be made to collect the data on time and to follow up by telephone with the patient on any missing quality of life questionnaires

13.0 STATISTICAL CONSIDERATIONS

13.1 Endpoints
13.1.1 To estimate the pathologic complete response rate following neoadjuvant combined-modality in rectal cancer. Two regimens will be investigated: 1) neoadjuvant radiation with concurrent capecitabine plus irinotecan, followed postoperatively by systemic therapy (changed from FOLFIRI to FOLFOX on June 29, 2005) for 4 months, and 2) neoadjuvant radiation with concurrent capecitabine plus oxaliplatin, followed postoperatively by systemic therapy (FOLFOX) for 4 months. (6/29/05)
13.1.2 To estimate time to treatment failure, and patterns of failure.
13.1.3 To estimate the incidence of hematologic and non-hematologic grade 3-4 toxicity with each of two treatment regimens. The following distinct treatment periods will be considered: preoperatively, postoperatively, and overall for entire program.
13.1.4 To evaluate the potential use of TS, TP, DPD, and p53r2 as tumor markers by examining the variability and reproducibility of marker expression in tumor and normal tissue from preoperative biopsy and surgically resected tissue specimens.
13.1.5 To assess whether combined modality therapy produces changes in general, as well as specific QOL concerns from baseline to three time points (completion of chemoradiation, completion of post-operative chemotherapy (approximately one year), and two years

13.2 Sample Size
The sample size consideration is based on the pathological complete response (pCR). A disease progression or death before surgery will be considered as a less than pCR (even without surgical specimen), and will be included in the denominator where the path CR rate is calculated. An experimental arm that results in a pCR rate of at least 25% would merit further study. With 48 analyzable patients per arm, we will have 90% power to reject that null hypothesis that the true pCR rate of a regimen is ≤ 10% with a type I error level of 5%. Adjusting the sample size by 10% to guard against ineligibility, we will target 53 patients per arm, for a total of 106 patients. The Fleming design will be used to identify early if either or both arms have unacceptably lower response rate. If both arms yield an estimated pCR > 25%, we will use statistical selection theory to choose the arm for further testing in the follow-up phase III trial. Briefly, its criterion is to select the treatment arm with highest response regardless how small or “nonsignificant” its advantage over the other treatment is. With 48 patients in each arm, we have greater than a 90% probability of correctly selecting the better treatment when there is an absolute difference of 15% in response rates between the two experimental arms. Note that toxicity will also play a role in determination of best regimen

13.2.1 Sample Size Amendment (3/22/05)
Based upon excessive grade 3-4 non-hematologic toxicity observed in both arms of RTOG 0247 after the first 35 patients were enrolled, the trial was placed on hold, pending further analysis. The toxicity was experienced during neoadjuvant treatment. In the irinotecan arm, 7 of 18 patients experienced grade 3-4 diarrhea. In the oxaliplatin arm, 5 patients had grade 3 diarrhea and 1 patient had grade 5 diarrhea. Another patient was hospitalized with diarrhea, and experienced sudden death several days after complete recovery from other toxicities. Based on discussions with NCI, Roche, Pfizer, Sanofi, and representatives from ECOG and NSABP, decisions regarding dose and schedule modifications were made. These modifications include decrease in capecitabine and oxaliplatin dosing, alteration in the irinotecan schedule, and alterations in the dose modification scheme.

The same study design described in 13.2 will hold for the primary endpoint of pCR. Given the changes that are being made to the treatment regimens, the patients already accrued will not be
used to answer the primary endpoint question. A total of 106 patients will be accrued to the new treatment regimens (53 for each arm). Including the 35 patients already accrued, 141 patients will be entered onto this study.

13.2.2 The sample size will remain at 141 patients. The amendment to change the post-op systemic therapy from FOLFIRI to FOLFOX for the arm 1 patients as of June 29, 2005 does not affect the sample size, which is based on the primary endpoint of pCR following the pre-op chemotherapy and RT regimen. (6/29/05)

13.3 Drug Modifications for Unacceptable Toxicity
Because of limited phase I testing with both treatment sequences, they will separately be monitored for excessive toxicity using the method of Fleming. The toxicities, that will be monitored, are grade 3 and 4 non-hematologic and are anticipated to occur during treatment.
For the purpose of defining acceptability of the treatment program, the preoperative and postoperative treatment portions will be considered independently. The frequency of grade 3 or 4 non-hematologic toxicities (excluding nausea/vomiting controllable with antiemetics, alopecia) would be acceptable if it is no more than 10%. Modifications to either treatment plan will be considered if its frequency is more than 30%. If there are five or more patients with grade 3 or 4 toxicities among the first 15 patients in a treatment arm, or if there are seven or more such cases among the first 30 patients entered, the treatment plan may be modified for the remaining patients to be entered. The modification will be only made after a conference call or meeting of the GI Steering Committee and the study chairs. If there is any fatal treatment related toxicity on a treatment arm, it will be immediately reviewed by the study chairs and followed by a conference call with the GI Steering Committee to determine if a dose modification is warranted. If there are two such fatal treatment toxicities on a treatment arm, accrual will be immediately suspended pending such review.

13.3.1 Toxicity Monitoring Amendment (3/22/05)
For the purpose of defining acceptability of the treatment program, the preoperative and postoperative treatment portions will be considered independently. As before, excessive toxicity will be monitored using the method of Fleming and modifications to either treatment plan will be considered if the frequency of grade 3 or 4 non-hematologic toxicities (excluding nausea/vomiting controllable with antiemetics, alopecia) is more than 30%. To allow for an ineligible patient, after 15 patients are accrued to each arm, accrual to the study will be suspended pending the toxicity analyses in the preoperative phase. If there are five or more patients with grade 3 or 4 toxicities, as defined above, among the first 15 eligible patients in a treatment arm, there will be a conference call or a meeting of the GI Steering Committee and the study chairs to determine the next course of action. If this excessive toxicity rule is not met, accrual will resume and toxicity will be evaluated after 30 patients have been accrued on each arm. At this point, if there are seven or more such cases among the first 30 eligible patients entered, there will be a conference call or a meeting of the GI Steering Committee and the study chairs to determine the next course of action. If there is any fatal treatment related toxicity on a treatment arm, it will be immediately reviewed by the study chairs and followed by a conference call with the GI Steering Committee to determine if a dose modification is warranted. If there are two such fatal treatment toxicities on a treatment arm, accrual will be immediately suspended pending such review.

13.4 Accrual for the Study
Based upon wider use of pre-operative radiation therapy for rectal cancer and the accrual of the RTOG phase II rectal study R-0012, we estimate a monthly accrual for this study of five patients and anticipate that the accrual can be achieved in 24 months allowing two months for institutional IRB approvals. If the monthly accrual rate is less than 2.5 cases a month after the first year, the study will be re-evaluated.

13.5 Randomization Plan (6/29/05)
Patients will be stratified before randomization with respect to tumor clinical stage (T3 vs. T4). The treatment allocation scheme described by Zelen will be used because it balances patient factors other than institution. The randomization to Arm 1 (irinotecan arm) was discontinued on 6/17/05. All patients randomized to Arm 1 prior to 6/17/05, as well as all patients entered after 6/17/05, will receive FOLFOX for their post-op systemic therapy.

13.6 Analyses Plan
13.6.1 Early Termination of Treatment Arms
There will be one interim look at the data. It will come after the first 24 patients have been entered onto an arm. If at that time only 1 patient has experienced a pathologic CR, we conclude that the null hypothesis would not be rejected and the arm will be dropped from further randomization. Alternately, the boundary for stopping an arm and rejecting the null hypothesis will be reached if there are 7 pCRs among the first 24 patients. If this boundary is crossed, the results will be forwarded to the GI Committee, which will determine whether the arm should be closed and considered in a future phase III study.

13.6.2 Interim Analysis (3/22/05)
Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. In general, the interim reports will contain information about:

a. The patient accrual rate with a projected completion date for the accrual phase;
b. Institutional accrual;
c. Pretreatment characteristics;
d. The compliance rate of treatment delivery with respect to protocol prescription;
e. The frequency and severity of adverse events.

Through examining the above items, the study chairs and the statistician can identify problems with the execution of the study. These problems will be reported to the RTOG GI committee responsible for the study and, if necessary, to the RTOG Research Strategy Committee, so that corrective action can be taken.

13.6.2.1 The interim analyses will include information on all patients, including those accrued prior to the amendment changing the treatment regimens.

13.6.3 Analysis for Reporting the Initial Treatment Results To preserve the overall 0.05 type I error, we will reject the null hypothesis of 10% path CR rate for any given treatment arm if there are at least 9 pCRs achieved. The initial analysis of treatment results will be performed after all patients have been followed at least 3 months post surgery. The usual components of this analysis are:

Tabulation of all cases entered, and any excluded from the analysis along with the reasons form the exclusion:

a. Institutional accrual
b. Distribution of important prognostic baseline variables
c. Distribution of treatment-related toxicities
d. Observed results with respect to the endpoints described above. The 95% confidence interval for the treatment’s pCR rate will be estimated.

Selection of the treatment arm with higher pCR rate if both are greater than 25%. If the difference between the two arms is less than 10, toxicity differences will be considered in finalizing the treatment selection.

13.6.4 Analysis for Reporting the Long Term Treatment Results The second analysis of treatment results will be performed after all patients have been followed at least 1 year. The focus of this analysis will be on disease recurrence patterns. It will include items a-d from Section 13.6.2.

13.6.5 TRP Analysis
Pre-treatment tissue is being collected on the study with two primary purposes. The first is to estimate its frequency being submitted. The second is to estimate the frequency that QRT-PCR assay for TS, TD DPD and p53R2 can be successfully performed with a small tissue sample. It is desirable that tumor tissue is received from at least 90% of patients on the study. With 96 analyzable patients, we would have 85% power to reject a null hypothesis that the true submission rate is no better than 80% (with a one-sided test and alpha of 0.05).

As with submission of tissue, it would be desirable that assay be successfully performed on 90% of the samples for each tumor marker. With 90%, 85% and 80% submission compliance (Corresponding to 87, 82, and 77 patients respectively) we would have corresponding power to reject a null hypothesis of 80% an assay success rate for a given tumor marker. (one-sided test with alpha of 0.05) of 82%, 79% and 76%.

The second aim with the pretreatment tissue is to correlate the four tumor markers with achieving pCR. Cutpoints for the markers will be used from literature wherever possible.

With resected tumor the primary aim is to estimate the amount of change in expression of TP and p53R2 in patients with less pCR from the baseline. The change will be expressed both as a relative percent and absolute difference. The changes will be reported as mean with its associated standard deviation and quartiles.
13.6.6 QOL Analysis

The EORTC QLQ-C30 and QLQ-CR38 are validated instruments. All the scores obtained are linearly transformed such that all scales range from 0 to 100. SAQ rates most responses on a 5-point Likert-type scale, with a higher score indicating a higher level of sexual adjustment. Construct validity for this RTOG modified SAQ has been demonstrated and this questionnaire appears to provide more accurate assessment of patient sexual function compared to physician assessment, reinforcing the value of value quality of life patient self-assessments in clinical trials. Missing values will be calculated such that if at least half the items from the scale are completed, it will be assumed that the missing items would have been equal to the average of the completed items. According to Cella et al., patients with missing values within a questionnaire have the values imputed using the average of the other questions within a subscale. However, no imputation will be used for a missing form. The responses to all instruments will be scored using standard, previously described scoring methods. Only patients with pretreatment and the follow-up time point of interest will be used in these analyses. For the total QOL and other QOL domains of each patient, the difference between the pretreatment score and a follow-up score at one of three time points (after completion of chemoradiation, after the completion of post-operative chemotherapy, and at 24 months) will be derived and then the patient will be categorized into clinically significant improvement, clinically significant deterioration, or no change. If the positive difference is greater than the SEM, then the patient is classified as having clinically significant QOL improvement. If the negative difference is less than the SEM, then the patient is classified as having clinically significant QOL deterioration. If the difference fails to meet either criteria, then the patient is classified as no change.

13.7 Inclusion of Women and Minorities (3/22/05)

We would anticipate a similar distribution of race and gender in this study as was seen in the previous RTOG study of rectal cancer. The projected distributions of race and gender for this study are shown below.

| Ethnic Category      | Females | Males | Total |
|----------------------|---------|-------|-------|
| Hispanic or Latino   | 4       | 8     | 12    |
| Not Hispanic or Latino| 48      | 81    | 129   |
| Ethnic Category: Total of all subjects | 52 | 89 | 141 |

| Racial Category            | Females | Males | Total |
|----------------------------|---------|-------|-------|
| American Indian or Alaskan Native | 0       | 0     | 0     |
| Asian                      | 1       | 3     | 4     |
| Black or African American  | 4       | 6     | 10    |
| Native Hawaiian or other Pacific Islander | 0 | 2 | 2 |
| White                      | 47      | 78    | 125   |
| Racial Category: Total of all subjects | 52 | 89 | 141 |
REFERENCES (12/1/04) (6/29/05)

1. NIH Consensus Conference. Adjuvant therapy with colon and rectal cancer. JAMA 264(11): 1444-1450, 1990.
2. Gastrointestinal Tumor Study Group. Survival after postoperative combination treatment of rectal cancer. N Engl J Med 315:1294-1295, 1986.
3. Krook JE, Moertel CG, Gunderson L, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N Engl J Med 324:710-715, 1991.
4. O'Connell MJ, Martenson JA, Weiand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med 331:502-507, 1994.
5. Stockholm Colorectal Cancer Study Group. Randomized study on preoperative radiotherapy in rectal carcinoma. Ann Surg Oncol 3:423-430, 1996.
6. Dosoretz DE, Gunderson LL, Hedberg S, Hoskins B, Blitzer PH, Shipley W, Cohen A. Preoperative irradiation for unresectable rectal rectosigmoid carcinomas. Cancer 52:814.
7. Valentini V, Coco C, Cellini N, Picciocchi A, Genovesi D, Mantint G, Barbaro B, Cogliandolo S, Mattana C, Ambesi-Impiombato F, Tedesco M, Cosimelli M. Preoperative chemoradiation for extraperitoneal T3 rectal cancer: acute toxicity, tumor response, and sphincter preservation. Int J Radiation Oncology Biol Phys 40:1067-1075, 1998.
8. Mohiuddin M, Marks G. Adjuvant radiation therapy for colon and rectal cancer: Sem. Oncol. 18(5):411-420; 1991.
9. Marks G, Mohiuddin M, Kakinic J. New Hope and promise for sphincter preservation in the management of cancer of the rectum. Semin Oncol 18:388-398, 1991.
10. Mendenhall WM, Bland KL, Copeland EM, Summers GE, Pfaff WW, Souba WW, Million RR. Does preoperative radiation therapy enhance the probability of local control and survival in high-risk distal rectal cancer? Ann. Surg. 215:696-706; 1992.
11. Chen ET, Mohiuddin M, Brodovsky H, Fishbein G, Marks G. Downstaging of advanced rectal cancer following combined preoperative chemotherapy and high dose radiation, Int J Radiat Oncol Biol Phys 30:169-175, 1994.
12. Landry JC, Kroetz MJ, Wood WC, Bhan S, Smith RG, Costa M, Daneker GW, York MR, Sarma PR, Lynn M, Ward AA, McGinley PH, Davis LW. Preoperative irradiation and fluorouracil chemotherapy for locally advanced rectosigmoid carcinoma: Phase I-II Study. Radiology 188:423-426, 1993.
13. Minsky BD, Cohen AM, Kemeny N, Enker WE, Kelson DP, Reichman B, Saltz L, Sigurdson ER, Frankel J. Enhancement of radiation-induced downstaging of rectal cancer by fluorouracil and high-dose leucovorin chemotherapy. J Clin Oncol 10:79-84, 1992.
14. Chan A, Wong A, Langevin J, Khoo R. Preoperative concurrent 5-fluorouracil infusion, mitomycin-c and pelvic radiation therapy in tethered and fixed rectal carcinoma. Int J Radiat Oncol Biol Phys 25:791-799, 1993.
15. Rich TA, Skibber JM, Ajani JA, et al: Preoperative infusional chemoradiation therapy for stage T3 rectal cancer. Int J Radiat Oncol Biol Phys 32:1025-1029, 1995.
16. Mohiuddin M, Regine WF, John WJ, Hagihara PF, McGrath PC, Kenady DE, Marks G. Preoperative chemoradiation in fixed distal rectal cancer: dose time factors for pathological complete response. Int J Radiat Oncol Biol Phys 46(4):883-8; 2000 Mar 1.
17. Investigator's brochure, Pharmacia and Upjohn, 1996
18. Conti JA, Kemeny NE, Saltz CB, et al. Irinotecan is an active agent in untreated patients with metastatic colorectal cancer. J. Clin Oncol 14:709-715; 1996
19. Dietz AJ, von Hoff DD, Ragual RJ, Miller LL. Upjohn Technical Report, Dec. 1995

20. Saltz L, Kanowitz J, Kemeny N, Schafl, Spriggs D, Staton BA, et al. A phase I clinical and pharmacokinetic study of irinotecan hydrochloride (CPT-11), 5-FU and leucovorin in patients with advanced solid tumors. Journal of Clinical Oncology; 14: 2959-67, 1996

21. Saltz LB, Cox JV, Blanke C, et al: Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med 343:905-914, 2000

22. Douillard JY, Cunningham D, Roth AD, et al: Irinotecan combined with fluorouracil alone as first-line treatment for metastatic colorectal cancer: A multicentre randomized trial. Lancet 355:1041-1047 2000

23. Szumiel I, Buracewska I, Gradzka I, Gasinska A. Effects of topoisomerase I-targeted drugs on radiation response of L5178Y sublines differentially radiation and drug sensitive. Int J Radiation Biology. 67 (4): 441-8, 1995.

24. Minsky BD, O'Reilly E, Wong D, Sharma S, et al: Daily Low-Dose Irinotecan (CPT-11) Plus Pelvic Irradiation as Preoperative Treatment of Locally Advanced Rectal Cancer. J Clin Oncol [18], pg. 266a, Abs. #1023, 1999.

25. Mitchell EP, Anne’PR, Fry R, Palazzo J, et al: Chemoradiation with CPT-11, 5FU in neoadjuvant treatment of locally advanced or recurrent adenocarcinoma of the rectum: A phase I/II study update. (Abstr 1052) Proc Am Soc Clin Oncol 22: 262 2003

26. Mehta VK, Cho C, Ford JM, Jambalos C, Poen J, Koong A, Lin A, Bastidas JA, Young H, Dunphy EP, Fisher G. Phase II trial of preoperative 3D conformal radiotherapy, protracted venous infusion 5-fluorouracil, and weekly CPT-11, followed by surgery for ultrasound-staged T3 rectal cancer. International Journal of Radiation Oncology, Biology, Physics. 55(1):132-7, 2003 Jan 1.

27. Xeloda Investigator Drug Brochure (Ro 09-1978) December 1997.

28. Findlay M, Van Cutsem E, Kocha W et al. A randomized phase II study of Xeloda™ (capecitabine) in patients with advanced colorectal cancer. Proc Am Soc Clin Oncol 1997;16(A798).

29. A Phase III Trial (SO14695) of Xeloda® (Capecitabine) in Previously Untreated Advanced/Metastatic Colorectal Cancer. Proc Am Soc Clin Oncol 1999.

30. Twelves C, Van Cutsem E, Thibault A et al. A Phase III Trial (SO14796) of Xeloda® (Capecitabine) in Previously Untreated Advanced/Metastatic Colorectal Cancer. Proc Am Soc Clin Oncol 1999.

31. Schleucher N, Tewes M, Achterrath T, et al: Extended phase I study of capecitabine in combination with a weekly schedule of irinotecan as first-line chemotherapy in metastatic colorectal cancer. Proc Am Soc Clin Oncol 20:141a 2001 (Abst 561)

32. Kerr DJ, Ten Bokkel Huinink WW, Ferry DR, et al: A phase I/II study of CPT-11 in combination with capecitabine as first-line chemotherapy for metastatic colorectal cancer. Proc Am Soc Clin Oncol 21:161a, 2002. (abstract 643).

33. Cassata A, Stani SC, Alu M, et al: Ongoing phase II trial with two schedules of irinotecan (CPT-11) in combination with capecitabine as first-line chemotherapy in patients with advanced colorectal cancer. Proc Am Soc Clin Oncol 20:144a 2001 (abstract 573)

34. Gold P, Godfrey T, Dhami M, et al: Capecitabine and irinotecan as 1st line therapy for patients with metastatic colorectal cancer: Phase II preliminary results. Proc Am Soc Clin Oncol 22: 288 2003 (abstract 1158)

35. Dunst J, Reese T, Sutter T, Zühlke H, et al: Phase I Trial Evaluating the Concurrent Combination of Radiotherapy and Capecitabine in Rectal Cancer. J Clin Oncol 20:19: 3983-3991. 2002

36. Ngan S, Zalcberg J, Kell A, et al: A phase I study of capecitabine combined with radio-therapy for locally advanced potentially operable rectal cancer. Proc Am Soc Clin Oncol 20:149a, 2001.

37. Kennedy A, Van Echo D, Volpe C, et al: Phase I studies using capecitabine combined with conformal
radiation therapy (RT), paclitaxel, CPT-11 and celecoxib in gastrointestinal malignancies. Proc Am Soc Clin Oncol 21: 2002, abstract 3021

38. Boudny V, Vrana O, Gaucheron F, Kleinwachter V, Leng M, Brabec V. Biophysical analysis of DNA modified by 1.2-diaminocyclohexane platinum(II) complexes. Nucleic Acid Res 1992; 20:267-272.

39. Jennerwein MM, Eastman A, Kokhar AR. The role of DNA repair in resistance of L1210 cells to isomeric 1.2 diaminocyclohexane platinum(II) complexes. Chem-Biol Interactions 1989; 70:39-49.

40. Tashiro T, Kawada Y, Sakuri Y, Kidani Y. Antitumor activity of a new platinum complex, oxalato (trans-l-1-diaminocyclohexane platinum(II): new experimental data. Biomed Pharmacother 1989; 43:251-260.

41. Sanofi-Winthrop. Oxaliplatin: Clinical Investigator's Brochure.

42. Raymond E, Gespach C. In vitro and in vivo antitumor activity of Oxaliplatin in combination with 5FU and other cytotoxic agents in human colorectal, ovarian and breast cancer cell lines. Debiopharm Internal Report. September 15, 1995.

43. Machover D, Diaz-Rubio E, et al. Two consecutive phase II studies of Oxaliplatin for treatment of patients with advanced colorectal carcinoma who were resistant to previous treatment with fluoropyrimidines. Annals of Oncology 1996; 7:95-98.

44. Diaz-Rubio E, Abad A, Cervantes A, Conroy T, Gameline e, Malet M, Marty M, Mrsic Z, Oliveira J, Seitz JF, Ychou M, Francois D. Phase II open study evaluating the antitumor efficacy of Oxaliplatin as monotherapy in patients suffering from advanced colorectal adenocarcinoma resistant to fluoropyrimidines. Debiopharm Internal Report. October 1994.

45. Levi F, Perpoint B, Misset JL, Chollet P, Garufi C, Focan C. Phase II study of Oxaliplatin in circadian-rhythm modulated administration in advanced colorectal cancer. Debiopharm Internal Report. May 1993.

46. DeGramont A. Feasibility study of the combination of Oxaliplatin with high-dose 5-fluorouracil by continuous infusion and folinic acid (high dose) in the treatment of colorectal cancer previously treated with chemotherapy. Debiopharm Internal Report, June 1994.

47. Levi F, Misset JL, Brienza S, Mathe G. Phase II study of Oxaliplatin combined with 5-FU and folinic acid in the treatment of advanced colorectal cancer. Debiopharm Internal Report, January 1994.

48. Garufi C, Levi F, Misset JL. Activity of Oxaliplatin in colonic cancer: a report of 25 demonstrative cases. Debiopharm Internal Report, October 1994.

49. de Gramont A, Figer A, Seymour M, et al: Leucovorin and flourouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18: 2938-2947, 2000

50. Goldberg RM, Morton RF, Sargent DJ, et al: N9741: Oxaliplatin or CPT 11 + 5-fluorouracil/leuorovorin or oxaliplatin + CPT-11 in advanced colorectal cancer: Initial toxicity and response data from a GI Intergroup study (abstract 511). Proc Am Soc Clin Oncol 21:128a, 2002.

51. Rothenberg, ML, Oza AM, Burger B, et al: Phase III trial of bolus – infusional 5-FU/leucovorin vs oxaliplatin vs the combination in patients with recurrent metastatic colorectal cancer following irinotecan, bolus 5-FU, and leucovorin: interim results abstract 20). Ann Oncol 13 (suppl 5):2, 2002.

52. Tournigand C, Louvet C, Quinaux E, Andre T, Lledo G, Flesch M, Ganem G, Landi B, Colin P, Denet C, Mery-Mignard D, Risse M, Buyse M, de Gramont A. FOLFIRI followed by FOLFOX vs. FOLFOX followed by FOLFIRI in metastatic colorectal cancer (MCRC): final results of a phase III study. Proceeds Am. Soc. Clin. Oncol. Abstract #494, 2001.

53. Diaz-Rubio E, Evans TRJ, Tabernero J, et al: Capecitabine in combination with oxaliplatin: A phase I, dose-escalation study in patients with advanced or metastatic solid tumors, Ann Oncol 13:558-565, 2002.

54. Twelves C, Butts C, Cassidy J et al: Capecitabine in combination with oxaliplatin as first line therapy for patients (pts) with advanced or metastatic colorectal cancer (ACRC): preliminary results of an international
multicenter phase II study. Eur J Cancer 2001:37 (suppl. 6): 272 (abstract 1005)

55. Shields A, Zalupski M, Marshall J, et al: A phase II trial of oxaliplatin and capecitabine in patients with advanced colorectal cancer. Proc Am Soc Clin Oncol 21: 2002, (abstract 568)

56. Aschele C, Friso M, Pucciarelli S, et al: A phase I-II study of weekly oxaliplatin (OXA), 5-fluorouracil (FU) continuous infusion (CI) and preoperative radiotherapy (RT) in locally advanced rectal cancer (LARC). Proc Am Soc Clin Oncol 21: 2002 (abstract No: 527)

57. Rosenthal D, Catalano P, Haller D, et al: ECOG 1297: A phase I study of preoperative radiation therapy (RT) with concurrent protracted continuous infusion 5-FU and dose escalating oxaliplatin followed by surgery, adjuvant 5-FU, and leucovorin for locally advanced (T3/4) rectal adenocarcinoma. Proc Am Soc Clin Oncol 22:273 2003 abstract 1094

58. Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernerio J, Hickish T, Topham C, Zarinelli M, Clingan P, Bridgewater I, Tabah-Fisch I, de Gramont, A for the Multicenter International Study of Oxaliplatin/5Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer. N Engl J Med 350(23):2343-51, 2004.

59. Saltz LB, Niedzwiecki D, Hollis D, Goldberg RM, Hantel A, Thomas JP, Fields ALA, Carver G, Mayer, RJ. The role of thymidylate synthase expression in prognosis and outcome of adjuvant chemotherapy in patients with rectal cancer. J Clin Oncol 1994; 12:2640-2647
pathway for DNA synthesis in a p53-regulated cell cycle checkpoint. Cancer Res 61: 8256-8262, 2001.

69. Park DJ, Stoehlmacher JU, Zhang W et al, Int J Colorectal Dis. 202 Jan; 17(1):46-49

70. Mathijssen RHJ, Marsh S, Karlsson MO, Xie R et al, Clin Canc Res, 9; 3246-3253, 2003

71. Moinpour CM, Feigl P, Metch B, et al: Quality of Life endpoints in cancer clinical trials: Review and recommendations. Journal of the National Cancer Institute 81: 485-495, 1989.

72. Aaronson NK, Meyerowitz BE, Bard M, et al: Quality of life research in oncology: Past achievements and future priorities. Cancer 67: 839-843, 1991.

73. Earlam S, Glover, Davies M, et al: Effect of regional and systemic fluorinated pyrimidine chemotherapy on quality of life in colorectal liver metastases patients. J Clin Oncol 15: 2022-2029, 1997.

74. Fuhrman GM, Talamonti MS, Curley SA. Sphincter-preserving extended resection for locally advanced rectosigmoid carcinoma involving the urinary bladder. Journal of Surgical Oncology 50: 77-80, 1992.

75. Arnaud A, Sarles JC, Sielezneff I, et al: Sphincter repair without overlapping for fecal incontinence. Dis Colon Rectum 34: 744-747, 1991.

76. Camilleri-Brennan J and Steele R. Prospective analysis of quality of life and survival following mesorectal excision for rectal cancer. Br J Surg 88(12): 1617-1622, 2001.

77. Grumann M, Noack E, Hoffman I, et al. Comparison of quality of life in patients undergoing abdominanoperineal extirpation or anterior resection for rectal cancer. Annals of Surgery 233 (2): 149-156, 2001.

78. Tjandra J, Reading D, McLachlan S, et al. Phase II clinical trial of preoperative combined chemoradiation for T3 and T4 resectable rectal cancer. Dis Colon Rectum 44: 1113-1122, 2001.

79. Fugl-Meyer AR, et al: On life satisfaction in male erectile dysfunction. Int J Impotence Research 9(3): 141-148, 1997.

80. Singer PA, et al: Sex or survival: Trade-offs between quality and quantity of life. J Clin Onc 9(2): 328-334, 1991.

81. Olweny CLM, et al: Long-term effects of cancer treatment and consequences of cure: Cancer survivors enjoy quality of life similar to their neighbors. European J Cancer 29A(6): 826-830, 1993.

82. Havenga K, Enker W, McDermott K, et al. Male and female sexual and urinary function after total mesorectal excision with autonomic nerve preservation for carcinoma of the rectum. J Am Coll Surg 182(6): 495-502, 1996.

83. Bonnel C, Parc Y, Pocard M, et al. Effects of preoperative radiotherapy for primary respectable rectal adenocarcinoma on male sexual and urinary function. Dis Colon Rectum 45(7): 934-939, 2002.

84. Mannaerts G, Schijven M, Hendrikx, et al. Urologic and sexual morbidity following multimodality treatment for locally advanced primary and locally recurrent rectal cancer. Eur J Surg Oncol 27(3): 265-272, 2001.

85. Kim N, Aahn T, Pasr J, et al. Assessment of sexual and voiding function after total mesorectal excision with pelvic autonomic nerve preservation in males with rectal cancer. Dis Colon Rectum 45(9): 1178-1185, 2002.

86. Pocard M, Zinzindohoue, HF, et al. A prospective study of sexual and urinary function before and after total mesorectal excision with autonomic nerve preservation for rectal cancer. Surgery 131(4): 368-372, 2002.

87. Aaronson NK, Cull A, Kaasa S, et al. The European Organization for Research and Treatment of Cancer (EORTC) modular approach to quality of life assessment in oncology. Int J Ment Health 23(2): 75-96, 1994.

88. Sprangers MAG, te Velde A and Aaronson NK. The construction and testing of the EORTC colorectal cancer-specific quality of life questionnaire module (QLQ-CR 38). Eur J Cancer 35: 238-247, 1999.
89. Bruner DW, et al: The RTOG modified sexual adjustment questionnaire: Psychometric testing in the prostate cancer population. Int J Rad Onc Biol Phys 42(1) 202, 1998.

90. Lewis F, Maughan NJ, Smith V, Hillan K, and Quirke P. Unlocking the archive gene expression in paraffin embedded tissue. J Pathology, 195:66-71, 2001

91. Johnson, M. R., Wang, K., Smith, J. B., Heslin, M. J., and Diasio, R. B. Quantitation of dihydropyrimidine dehydrogenase expression by real-time reverse transcription polymerase chain reaction. Anal. Biochem., 278: 175-184, 2000.

92. Miller, C. R., Gustin, A. N., Buchsbaum, D. J., Vickers, S. M., Manne, U., Grizzle, W. E., Cloud, G. A., Diasio, R. B., and Johnson, M. R. Quantitation of cytosine deaminase mRNA by real-time reverse transcription polymerase chain reaction: a sensitive method for assessing 5-fluorocytosine toxicity in vitro. Anal. Biochem., 301: 189-199, 2002.

93. Blanquicett, C., Johnson, M., Heslin, M., and Diasio, R. B. Housekeeping gene (HKG) variability in normal and carcinomatous colorectal and liver tissues; applications in pharmacogenomic gene expression studies. Anal. Biochem., 303: 210-215, 2002.

94. Fleming, T.R. (1982). One-sample multiple testing procedure for Phase II clinical trials. Biometrics. 38: 143-151.

95. Gibbons JD, Olkin I, and Sobel M. Selecting and ordering Populations: A New Statistical Methodology. New York, Wiley, 1977.

96. Simon R, Wittes RE, Ellenberg SS. Randomized Phase II Clinical Trials. Cancer Treat Rep 69: 1375-1381, 1985.

97. Zelen, M. (1994). The randomization and stratification of patients to clinical trials. J. Chron. Dis. 27: 365-375.

98. Cella DF: Manual for the Functional Assessment of Cancer Therapy (FACT) Scales version 2, April 1993.

99. Bearman, SI (1995). The syndrome of hepatic veno-occlusive disease after marrow transplantation. Blood. 85:3005-3020.

100. DeLeve, LD, Shulman, HM, and McDonald, GB. (2002). Toxic injury to hepatic sinusoids: Sinusoidal obstruction syndrome (veno-occlusive disease). Sem Liver Dis. 22:27-41.

101. Rubbia-Brandt, L, Audard, V, Sartoretti, P et al. (2004). Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol. 15:460-466.

102. Tisman, G, MacDonald, D, Shindell, N, et al, (2004). Oxaliplatin toxicity masquerading as recurrent colon cancer. J Clin Oncol. 22:3202-3204.
APPENDIX IA
RTOG 0247(3/22/05)

SAMPLE CONSENT FOR RESEARCH STUDY

RANDOMIZED PHASE II TRIAL OF NEOADJUVANT COMBINED MODALITY THERAPY FOR LOCALLY ADVANCED RECTAL CANCER

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, “Taking Part in Clinical Trials: What Cancer Patients Need To Know,” is available from your doctor.

You are being asked to take part in this study because you have cancer of the rectum.

WHY IS THIS STUDY BEING DONE? (5/21/04) (6/29/05)

The purpose of this study is to compare two different chemotherapy medication combinations that will be given to patients with radiation to see which combination is better. We want to find out what effects (good and bad) each of these treatments have on rectal cancer. This research is being done because although surgery is the standard treatment for advanced rectal cancer, there is a high rate of the cancer coming back. We want to find out if radiation and chemotherapy given before surgery and chemotherapy after surgery will help control this disease. Having chemotherapy and radiation therapy before surgery may also reduce the tumor size so that less surgery may be necessary.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY (3/22/05)

About 141 people will take part in this study nationally.
WHAT IS INVOLVED IN THE STUDY?

If you agree to participate you will have a physical exam and your medical history taken. You will be asked to fill out some forms, which describe your impression of your quality of life. These forms will be given to you before you start treatment, during treatment, at one year and two years after treatment is completed. They will take five to fifteen minutes to fill out.

You will be “randomized” into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. Which group you are put in is done by a computer. Neither you nor the researcher will choose what group you will be in. You will have an equal chance of being placed in one of the following two groups.

Arm 1: (3/22/05) (6/29/05)

Radiation Therapy: Once a day, five days per week (Monday through Friday) for six weeks.

Chemotherapy: Capecitabine pills will be given to you by mouth twice a day throughout the course of radiation (5 days per week.) starting the evening before the first day of radiation therapy. Irinotecan will be given to you by an infusion in your vein (IV) once a week during radiation every week except the third week (only 4 doses).

Surgery: Removal of tumor four to eight weeks after radiation treatment ends.

Chemotherapy after surgery: Four to six weeks after completion of surgery you will receive additional chemotherapy consisting of 9 courses of treatment with 5-fluorouracil, leucovorin and oxaliplatin by infusions into your vein. These three medicines will be given in the study doctor’s office over approximately four hours. Following this, 5-flourouracil will also be given for 46 hours through a catheter in a vein using a portable pump (a small machine which controls the flow of drug) at home. This course is repeated every two weeks for a total of nine times or 18 weeks.

Arm 2: (3/22/05)

Radiation Therapy: Once a day, five days per week (Monday through Friday) for six weeks.

Chemotherapy: Capecitabine pills will be given to you by mouth twice a day throughout the course of radiation (5 days per week) starting the evening before the first day of radiation therapy. Oxaliplatin will be given...
to you by an infusion in your vein (IV) once a week during radiation (only 5
doses).

**Surgery:** Removal of tumor four to eight weeks after radiation treatment
ends.

**Chemotherapy after surgery:** Four to six weeks after completion of
surgery you will receive additional chemotherapy consisting of 9 courses of
treatment with 5-fluorouracil, leucovorin and oxaliplatin by infusions into
your vein. These three medicines will be given in the study doctor’s office
over approximately four hours. Following this 5-fluorouracil will also be
given for 46 hours through a catheter in a vein using a portable pump (a
small machine which controls the flow of drug) at home. This course is
repeated every two weeks for a total of nine times or 18 weeks.

If you take part in this study you will have the following tests and
procedures:

• **Procedures that may are part of regular cancer care and be done even if
you do not join the study.**
  - Physical exam
  - Blood counts and chemistries
  - Chest x-ray
  - MRI of pelvis
  - Examination of the bowel with a fiberoptic flexible tube
  - Examination of the bowel with a small flexible tube with an
    ultrasound device
  - CT of abdomen and pelvis, including the liver

• **Standard procedures being done because you are in this study.**
  - Tumor specimens will be sent to a central storage laboratory for
    future testing if you agree to participate in the tissue part of the
    study.
  - Quality of Life questionnaires
  - Capecitabine/Diarrhea Diary

**HOW LONG WILL I BE IN THE STUDY? (5/21/04)**

Treatment will last eight to nine months. You will receive radiation therapy
and chemotherapy for five to six weeks, and six to eight weeks after
completion of radiation therapy, you will have surgery. Four to six weeks
after your surgery you will receive additional chemotherapy for about four
and a half months. After treatment is completed, you will be seen by your
doctor once every three months for two years, then every six months for
three years, and after that once a year for the rest of your life. You can
stop participating at any time. However, if you decide to stop participating
in the study, we encourage you to talk to the researcher and your regular
doctor first. If you do not

49
you will still have regular checkups with your doctor for the rest of your life. You will have these checkups once every three months for two years, then once every six months for three years, and then once a year after that.

If your disease gets worse in spite of the treatment, the researcher may decide to take you off this study treatment regimen. If the side effects of the treatment are too dangerous for you, or new information about the treatment becomes available and this information suggests the treatment will be ineffective or unsafe for you, the researcher may decide to take you off the study treatment regimen. Even if you are not getting the study treatment regimen, you will still be in the follow-up part of the study. It is unlikely, but the study may be stopped early due to lack of funding or participation.

**WHAT ARE THE RISKS OF THE STUDY? (12/1/04) (6/29/05)**

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the radiation therapy and chemotherapy are stopped, but in some cases side effects can be serious or long-lasting or permanent.

**Risks and side effects related to radiation therapy we are studying include:**

**Very likely:**

Skin irritation  
Diarrhea  
Tiredness  
Nausea  
Temporary loss of pubic hair  
For women: Sterility in pre-menopausal women. Hormones may be given orally to replace hormones normally produced by the ovaries.

**Less Likely, but Serious:**

Intestinal blockage and/or intestinal bleeding which may require surgery  
For men: Permanent sterility.

**Risks Associated with Chemotherapy:**

**Treatment Group A (Capecitabine, irinotecan before surgery, 5 fluorouracil, leucovorin, and oxaliplatin after surgery.)**
Very Likely:
Lower blood counts, which can lead to risk of infection and bleeding.
Painful redness and swelling of the hands and/or feet.
Loss of appetite
Mouth sores
Sore throat
Nausea and/or vomiting
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
Diarrhea with cramping or bleeding
Weakness/fatigue
Skin rash
Loss of hair, which is temporary
Increased frequency of urination

Less Likely:
Headaches
Inflammation (redness and swelling) of fingers and toes
Increased sensitivity to light
Darkening of skin, nails or veins
Loss of coordination or balance
Inflammation of the intestines
Change in liver function tests which may reflect liver damage
Changes in vision (Blurring)
Rash or allergic reaction
Flu-like symptoms such as fever, chills and muscle aches
Damage to the kidney

Less likely but Serious
Confusion or memory loss
Chest pain that may mean heart damage
Infection at the catheter entry suite
Lung damage resulting in shortness of breath (may be permanent)
Blood clots

Although, rare, it is possible that treatment-related side effects could result in death.

Treatment Group B (Capecitabine, oxaliplatin before surgery, 5-flourourouracil, leucovorin and oxaliplatin after surgery)

Very Likely:
Lower blood counts, which can lead to risk of infection and bleeding
Painful redness and swelling of the hands and/or feet
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.
Loss of appetite
Mouth sores
Sore throat
Nausea and/or vomiting
Diarrhea with cramping or bleeding
Weakness/fatigue
Skin rash
Loss of hair, which is temporary
Inflammation of the intestines

Less Likely:

Headaches
Inflammation (redness and swelling) of fingers and toes
Increased sensitivity to light
Darkening of skin, nails or veins
Loss of coordination or balance
Inflammation of the colon
Liver damage, which may rarely be severe and life threatening
Changes in vision (Blurring)
Rash or allergic reaction
Flu-like symptoms such as fever, chills and muscle aches
Damage to the kidney

Less Likely, but Serious:

Confusion or memory loss
Chest pain that may mean heart damage
Infection at the catheter entry site
Change in heart beat (rapid heart beat)
Lung damage resulting in shortness of breath (which may be permanent)
Blood clots

Rare
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

Although rare, it is possible that treatment-related side-effects could result in death.

Reproductive Risks
This study may be harmful to a nursing infant or an unborn child. Sufficient medical information is not available to determine whether the study treatment administered to a pregnant woman causes significant risks to the fetus. If you are a woman able to have children and have not been surgically sterilized (tubal ligation or hysterectomy), you should have a pregnancy test before enrolling in this study. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you should become pregnant while on study, you must tell your doctor immediately.

If you are a man able to father children, the treatment you receive may risk harm to an unborn child unless you use a form of birth control approved by your doctor. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you suspect you have caused anyone to become pregnant, you must tell your doctor immediately.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY? (5/21/04)

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with rectal cancer in the future.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; (3) surgery; or (4) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other.

Another option may be to get the treatment plan described in this study at this center and other centers even if you do not take part in the study.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). Your personal information may be disclosed if required by
law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI) or its authorized representatives, Radiation Therapy Oncology Group (RTOG) representatives and other groups or organizations that have a role in this study.

**WHAT ARE THE COSTS?**

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization. Medicare should be considered a health insurance provider.

You will receive no payment for taking part in this study.

**WHAT ARE MY RIGHTS AS A PARTICIPANT?**

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

If you choose to stop participating in the study, you should first discuss this with your doctor. In order to provide important information that may add to the analysis of the study, he/she may ask your permission to submit follow-up data as it relates to the study. You may accept or refuse this request. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.
WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
(This section must be completed)

For information about your disease and research-related injury, you may contact:

_________________________  __________________________
Name                      Telephone Number

For information about this study, you may contact:

_________________________  __________________________
Name                      Telephone Number

For information about your rights as a research subject, you may contact:
(OHRP) suggests that this person not be the investigator or anyone else directly involved with
the research)

_________________________  __________________________
Name                      Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI’s Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615.

Visit the NCI’s Web sites for comprehensive clinical trials information at www.cancer.gov/clinicaltrials or for accurate cancer information including PDQ (Physician Data Query) visit www.cancer.gov/cancerinfo/pdq.

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (full study plan).

_________________________  __________________________
Patient’s Name              Signature                  Date

_________________________  __________________________
Name of Person Obtaining Consent  Signature                  Date
ABOUT USING TISSUE FOR RESEARCH

You have had or you will have a biopsy (or surgery) to see if you have cancer. Your doctor has removed or will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue and/or blood that remains for future research. If you agree, this tissue and/or blood will be kept and may be used in research to learn more about cancer and other diseases. Your tissue and/or blood may be helpful for research whether you do or do not have cancer.

The research that may be done with your tissue and/or blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

All possible methods will be used to ensure your privacy and confidentiality. Identifying information will be taken off anything associated with your tissue and/or blood before it is given to a researcher. Reports about research done with your tissue and/or blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

THINGS TO THINK ABOUT

The choice to let us keep the left over tissue and/or blood for future research is up to you. No matter what you decide to do, it will not affect your care or participation in this study.

If you decide now that your tissue and/or blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue and then any tissue that remains will no longer be used for research; or, you may request that your tissue, if any remains, be returned to you or your designee and/or that we dispose of your blood.

In the future, people who do research may need to know more about your health. While __________ (doctor/institution) may give researchers reports about your health, your doctor/institution will not give researchers your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue and/or blood is used for genetic research (about diseases that are
passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue and/or blood will be used only for research. However, the research done with your tissue may help to develop new products in the future, or your tissue may be used to establish a cell line that could be patented and licensed. If this occurs, you will not be financially compensated.

**BENEFITS**

The benefits of research using tissue and/or blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

**RISKS**

**Physical Risks**
Most patients will heal satisfactorily after having surgery or a needle biopsy to remove tissue. Risks and side effects of a biopsy/surgery can include bleeding, pain, delayed healing, possible infection, and rarely, creation of an abnormal opening or passage.

**Social-Economic Risks**
There is a very small chance that information from your health records could be incorrectly released. All possible methods will be used to protect your privacy and ensure confidentiality. Unless you have given your specific permission, your _______ (doctor/institution) will not release your personal results or information to third parties such as employers or insurers.

In the case of injury or illness resulting from participating in this research, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

**MAKING YOUR CHOICE**

If you have any questions about the research involving your tissue or about this form, please talk to your doctor or nurse, or call the institution’s research review board at _____________ (IRB’s phone number).
Please read each sentence below and think about your choice. After reading each sentence, circle “Yes” or “No”. **No matter what you decide to do, it will not affect your care or participation in this study.**

1. My tissue and/or blood may be used for the research in the current study.
   
   Yes       No

2. My tissue and/or blood may be kept for use in research to learn about, prevent, or treat cancer.
   
   Yes       No

3. My tissue and/or blood may be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer’s disease, or heart disease).
   
   Yes       No

4. Someone from ___________________ (doctor’s office/institution) may contact me in the future to ask me to take part in more research.
   
   Yes       No

**Participant statement:**
I have read and received a copy of this consent form. I have been given an opportunity discuss the information with my doctor/nurse, and all of my questions/concerns have been answered to my satisfaction. My answers above and my signature below indicate my voluntary participation in this research.

---

Patient’s Name

Signature

Date

**Witness statement:**
I have explained the information in this consent form to the patient and have answered any questions raised. I have witnessed the patient’s signature.

---

Name of Person Obtaining Consent

Signature

Date
## APPENDIX II

### KARNOFSKY PERFORMANCE SCALE

| Score | Description |
|------|-------------|
| 100  | Normal; no complaints; no evidence of disease |
| 90   | Able to carry on normal activity; minor signs or symptoms of disease |
| 80   | Normal activity with effort; some sign or symptoms of disease |
| 70   | Cares for self; unable to carry on normal activity or do active work |
| 60   | Requires occasional assistance, but is able to care for most personal needs |
| 50   | Requires considerable assistance and frequent medical care |
| 40   | Disabled; requires special care and assistance |
| 30   | Severely disabled; hospitalization is indicated, although death not imminent |
| 20   | Very sick; hospitalization necessary; active support treatment is necessary |
| 10   | Moribund; fatal processes progressing rapidly |
| 0    | Dead |

### ZUBROD PERFORMANCE SCALE

| Score | Description |
|------|-------------|
| 0    | Fully active, able to carry on all predisease activities without restriction *(Karnofsky 90-100)*. |
| 1    | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work *(Karnofsky 70-80)*. |
| 2    | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours *(Karnofsky 50-60)*. |
| 3    | Capable of only limited self-care, confined to bed or chair 50% or more of waking hours *(Karnofsky 30-40)*. |
| 4    | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair *(Karnofsky 10-20)*. |
APPENDIX III

AJCC Staging
Colon and Rectum, 6th Edition

DEFINITION OF TNM

The same classification is used for both clinical and pathologic staging.

Primary Tumor (T)

| Code | Description |
|------|-------------|
| TX   | Primary tumor cannot be assessed |
| T0   | No evidence of primary tumor |
| Tis  | Carcinoma in situ: intraepithelial or invasion of lamina propria* |
| T1   | Tumor invades submucosa |
| T2   | Tumor invades muscularis propria |
| T3   | Tumor invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues |
| T4   | Tumor directly invades other organs or structures, and/or perforates visceral peritoneum**, *** |

* Note: Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.

** Note: Direct invasion in T4 includes invasion of other segments of the colorectum by way of the serosa; for example, invasion of the sigmoid colon by a carcinoma of the cecum.

*** Note: Tumor that is adherent to other organs or structures, macroscopically, is classified T4. However, if no tumor is present in the adhesion, microscopically, the classification should be pT3. The V and L substaging should be used to identify the presence or absence of vascular or lymphatic invasion.

Regional Lymph Nodes (N)

| Code | Description |
|------|-------------|
| NX   | Regional lymph nodes cannot be assessed |
| NO   | No regional lymph node metastasis |
| N1   | Metastasis in 1 to 3 regional lymph nodes |
| N2   | Metastasis in 4 or more regional lymph nodes |

Note: A tumor nodule in the pericolectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule is classified in the pN category as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node. If the nodule has an irregular contour, it should be classified in the T category and also coded as V1 (microscopic venous invasion) or as V2 (if it was grossly evident), because there is a strong likelihood that it represents venous invasion.

Distant Metastasis (M)

| Code | Description |
|------|-------------|
| MX   | Distant metastasis cannot be assessed |
| MO   | No distant metastasis |
| M1   | Distant metastasis |
APPENDIX III

AJCC Staging
Colon and Rectum, 6th Edition
(continued)

STAGE GROUPING

| Stage   | T    | N    | M    | Dukes* |
|---------|------|------|------|--------|
|         | MAC* |      |      |        |
| Stage 0 | Tis  | N0   | M0   | -      |
| Stage I | T1   | N0   | M0   | A      |
|         | T2   | N0   | M0   | A      |
| Stage IIA | T3  | N0   | M0   | B      |
|         | IIB  | T4   | N0   | B      |
| Stage II A| T1-2| N1   | M0   | C      |
|         | IIIB | T3-4 | N1   | C      |
|         | IIIC | Any T| N2   | C      |
| Stage IV| Any T| Any N| M1   | D      |

*Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (Any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.

Note: The y prefix is to be used for those cancers that are classified after pretreatment, whereas the r prefix is to be used for those cancers that have recurred.
### Capecitabine Dosing Table Based Upon Body Surface Area Calculation

#### Arm 1

**Capecitabine Dosing Table Based Upon Body Surface Area Calculation:**

| BSA (m^2) | Total Daily Dose (mg) | AM 150 mg | AM 500mg | PM 150mg | PM 500mg |
|-----------|-----------------------|-----------|-----------|-----------|-----------|
| <1.24     | 1300                  | 1         | 1         | 1         | 1         |
| 1.25-1.36 | 1500                  | 0         | 2         | 0         | 1         |
| 1.37-1.51 | 1650                  | 1         | 2         | 0         | 1         |
| 1.52-1.64 | 1800                  | 1         | 2         | 1         | 1         |
| 1.65-1.76 | 2000                  | 0         | 2         | 0         | 2         |
| 1.77-1.91 | 2150                  | 1         | 2         | 0         | 2         |
| 1.92-2.04 | 2300                  | 1         | 2         | 1         | 2         |
| 2.05-2.17 | 2500                  | 0         | 3         | 0         | 2         |
| >2.18     | 2650                  | 1         | 3         | 0         | 2         |

**Capecitabine 25% Dose Reduction: Dosing Table Based Upon Body Surface Area Calculation**

| BSA (m^2) | Total Daily Dose (mg) | AM 150 mg | AM 500mg | PM 150mg | PM 500mg |
|-----------|-----------------------|-----------|-----------|-----------|-----------|
| <1.24     | 1000                  | 0         | 1         | 0         | 1         |
| 1.25-1.36 | 1150                  | 1         | 1         | 0         | 1         |
| 1.37-1.51 | 1300                  | 1         | 1         | 1         | 1         |
| 1.52-1.64 | 1450                  | 2         | 1         | 1         | 1         |
| 1.65-1.76 | 1500                  | 0         | 2         | 0         | 1         |
| 1.77-1.91 | 1650                  | 1         | 2         | 0         | 1         |
| 1.92-2.04 | 1800                  | 1         | 2         | 1         | 1         |
| 2.05-2.17 | 1950                  | 2         | 2         | 1         | 1         |
| >2.18     | 2000                  | 0         | 2         | 0         | 2         |

**Capecitabine 50% Dose Reduction: Dosing Table Based Upon Body Surface Area Calculation**

| BSA (m^2) | Total Daily Dose (mg) | AM 150 mg | AM 500mg | PM 150mg | PM 500mg |
|-----------|-----------------------|-----------|-----------|-----------|-----------|
| <1.24     | 650                   | 0         | 1         | 1         | 0         |
| 1.25-1.36 | 650                   | 0         | 1         | 1         | 0         |
| 1.37-1.51 | 800                   | 1         | 1         | 1         | 0         |
| 1.52-1.64 | 950                   | 1         | 1         | 2         | 0         |
| 1.65-1.76 | 1000                  | 0         | 1         | 0         | 1         |
| 1.77-1.91 | 1150                  | 1         | 1         | 0         | 1         |
| 1.92-2.04 | 1150                  | 1         | 1         | 0         | 1         |
| 2.05-2.17 | 1300                  | 1         | 1         | 1         | 1         |
| >2.18     | 1450                  | 2         | 1         | 1         | 1         |
### ARM 2

#### Dosing Table Based Upon Body Surface Area Calculation:

**Capecitabine Starting Dose**

| BSA (m^2) | Total Daily Dose (mg) | AM 150 mg | AM 500mg | PM 150mg | PM 500mg |
|-----------|-----------------------|-----------|----------|----------|----------|
| <1.24     | 2000                  | 0         | 2        | 0        | 2        |
| 1.25-1.36 | 2150                  | 1         | 2        | 0        | 2        |
| 1.37-1.51 | 2300                  | 1         | 2        | 1        | 2        |
| 1.52-1.64 | 2600                  | 2         | 2        | 2        | 2        |
| 1.65-1.76 | 2800                  | 1         | 3        | 1        | 2        |
| 1.77-1.91 | 3000                  | 0         | 3        | 0        | 3        |
| 1.92-2.04 | 3150                  | 1         | 3        | 0        | 3        |
| 2.05-2.17 | 3300                  | 1         | 3        | 1        | 3        |
| >2.18     | 3600                  | 1         | 3        | 2        | 3        |

**Capecitabine 25% Dose Reduction: Dosing Table Based Upon Body Surface Area Calculation**

| BSA (m^2) | Total Daily Dose (mg) | AM 150 mg | AM 500mg | PM 150mg | PM 500mg |
|-----------|-----------------------|-----------|----------|----------|----------|
| <1.24     | 1500                  | 0         | 2        | 0        | 1        |
| 1.25-1.36 | 1650                  | 1         | 2        | 0        | 1        |
| 1.37-1.51 | 1800                  | 1         | 2        | 1        | 1        |
| 1.52-1.64 | 1950                  | 2         | 2        | 1        | 1        |
| 1.65-1.76 | 2150                  | 1         | 2        | 0        | 2        |
| 1.77-1.91 | 2300                  | 1         | 2        | 1        | 2        |
| 1.92-2.04 | 2450                  | 2         | 2        | 1        | 2        |
| 2.05-2.17 | 2500                  | 0         | 3        | 0        | 2        |
| >2.18     | 2650                  | 1         | 3        | 0        | 2        |

**Capecitabine 50% Dose Reduction: Dosing Table Based Upon Body Surface Area Calculation**

| BSA (m^2) | Total Daily Dose (mg) | AM 150 mg | AM 500mg | PM 150mg | PM 500mg |
|-----------|-----------------------|-----------|----------|----------|----------|
| <1.24     | 1000                  | 0         | 1        | 0        | 1        |
| 1.25-1.36 | 1150                  | 1         | 1        | 0        | 1        |
| 1.37-1.51 | 1150                  | 1         | 1        | 0        | 1        |
| 1.52-1.64 | 1300                  | 1         | 1        | 1        | 1        |
| 1.65-1.76 | 1450                  | 2         | 1        | 1        | 1        |
| 1.77-1.91 | 1500                  | 0         | 2        | 0        | 1        |
| 1.92-2.04 | 1650                  | 1         | 2        | 0        | 1        |
| 2.05-2.17 | 1650                  | 1         | 2        | 0        | 1        |
| >2.18     | 1800                  | 1         | 2        | 1        | 1        |
### Appendix V (3/31/06)

**Comprehensive Adverse Events and Potential Risks List (CAEPR)**

*for Oxaliplatin (NSC 266046)*

*Bold* and *italic* text identifies expected adverse events (ASAEL), which may not need to be reported via AdEERS.

**Version 1.0; October 22, 2004**

| Body System (Category) | Reported Adverse Events (CTCAE v3.0 Term) | "Expected" Adverse Events (ASAEL – use for expedited reporting) |
|------------------------|------------------------------------------|---------------------------------------------------------------|
| **ALLERGY/IMMUNOLOGY**  |                                          |                                                               |
| Allergic reaction/hypersensitivity (including drug fever) | Allergic reaction/hypersensitivity (including drug fever) |
| **AUDITORY/EAR**        |                                          |                                                               |
| Hearing: patients without baseline audiogram and not enrolled in a monitoring program | Hearing: patients without baseline audiogram and not enrolled in a monitoring program |
| Otitis, middle ear (non-infectious) | Otitis, middle ear (non-infectious) |
| **BLOOD/BONE MARROW**   |                                          |                                                               |
| Hemoglobin              | Hemoglobin                               |                                                               |
| Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis) | Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis) |
| Leukocytes (total WBC)  | Leukocytes (total WBC)                   |                                                               |
| Lymphopenia             |                                         |                                                               |
| Neutrophils/granulocytes (ANC/AGC) | Neutrophils/granulocytes (ANC/AGC)     |
| Platelets               | Platelets                                |                                                               |
| **CARDIAC ARRHYTHMIA**  |                                          |                                                               |
| Supraventricular and nodal arrhythmia-atrial fibrillation |                                           |
| Supraventricular and nodal arrhythmia-sinus tachycardia | Supraventricular and nodal arrhythmia-sinus tachycardia |
| Supraventricular and nodal arrhythmia-supraventricular arrhythmia NOS | Supraventricular and nodal arrhythmia-supraventricular arrhythmia NOS |
| Ventricular arrhythmia-ventricular arrhythmia NOS | Ventricular arrhythmia-ventricular arrhythmia NOS |
| **CARDIAC GENERAL**     |                                          |                                                               |
| Hypertension            | Hypertension                             |                                                               |
| Hypotension             |                                         |                                                               |
| COAGULATION |  |
|-------------|---|
| DIC (disseminated intravascular coagulation) | DIC (disseminated intravascular coagulation) |
| INR (International Normalized Ratio of prothrombin time) |  |
| PTT (partial thromboplastin time) |  |
| Thrombotic microangiopathy (e.g., thrombotic thrombocytopenia purpura [TTP] or hemolytic uremic syndrome [HUS]) |  |

| CONSTITUTIONAL SYMPTOMS |  |
|-------------------------|---|
| Fatigue (asthenia, lethargy, malaise) | Fatigue (asthenia, lethargy, malaise) |
| Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L) | Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L) |
| Insomnia |  |
| Rigors/chills |  |
| Sweating |  |
| Weight gain | Weight loss |
| Weight loss |  |

| DERMATOLOGY/SKIN |  |
|------------------|---|
| Dry skin |  |
| Flushing |  |
| Hair loss/alopecia (scalp or body) | Hair loss/alopecia (scalp or body) |
| Injection site reaction/extravasation changes | Injection site reaction/extravasation changes |
| Pruritus/itching |  |
| Rash/desquamation | Rash/desquamation |
| Rash: hand-foot skin reaction | Rash: hand-foot skin reaction |
| Urticaria |  |

| ENDOCRINE |  |
|-----------|---|
| Hot flashes/flushes | Hot flashes/flushes |

| GASTROINTESTINAL |  |
|------------------|---|
| Anorexia | Anorexia |
| Ascites (non-malignant) | Ascites (non-malignant) |
| Colitis |  |
| Constipation | Constipation |
| Dehydration | Dehydration |
| Diarrhea | Diarrhea |
| Dry mouth/salivary gland (xerostomia) |  |
| Dysphagia (difficulty swallowing) |  |
| Enteritis (inflammation of the small bowel) | Enteritis (inflammation of the small bowel) |

| GASTROINTESTINAL, continued |  |
|-----------------------------|---|
| Esophagitis | Esophagitis |
| Condition                                      |
|------------------------------------------------|
| Flatulence                                    |
| Gastritis                                     |
| Heartburn/dyspepsia                           |
| Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation) |
| Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation) |
| Mucositis/stomatitis (functional/symptomatic) - oral cavity |
| Mucositis/stomatitis (functional/symptomatic) - oral cavity |
| Nausea                                        |
| Necrosis, GI - Select                         |
| Obstruction, GI (small bowel NOS)             |
| Taste alteration (dysgeusia)                  |
| Ulcer, GI - Select                            |
| Vomiting                                      |
| **HEMORRHAGE/BLEEDING**                       |
| Hemorrhage, CNS                               |
| Hemorrhage, GI - lower GI NOS                 |
| Hemorrhage, GI - rectum                       |
| Hemorrhage, GI - upper GI NOS                 |
| Hemorrhage, GU - urinary NOS                  |
| Hemorrhage, pulmonary/upper respiratory - respiratory tract NOS |
| Hemorrhage/bleeding - other (hemorrhage with thrombocytopenia) |
| Hemorrhage/bleeding - other (hemorrhage with thrombocytopenia) |
| **HEPATOBILIARY/PANCREAS**                    |
| Hepatobiliary/Pancreas - other (hepatic enlargement) |
| Liver dysfunction/failure (clinical)          |
| Pancreatitis                                  |
| **INFECTION**                                 |
| Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10e9/L, fever >=38.5 degrees C) |
| Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x 10e9/L, fever >=38.5 degrees C) |
| Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) |
| Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) |
| Infection with normal ANC or Grade 1 or 2 neutrophils |
| Infection with normal ANC or Grade 1 or 2 neutrophils |
| Infection with unknown ANC                    |
| Infection with unknown ANC                    |
| **LYMPHATICS**                                |
| Edema: head and neck                          |
| Edema: limb                                   |
### METABOLIC/LABORATORY

| Metabolic/Laboratory | Description                      |
|----------------------|----------------------------------|
| Acidosis (metabolic or respiratory) | Acidosis (metabolic or respiratory) |
| Albumin, serum-low (hypoalbuminemia) | Albumin, serum-low (hypoalbuminemia) |
| Alkaline phosphatase | Alkaline phosphatase |
| ALT, SGPT (serum glutamic pyruvic transaminase) | ALT, SGPT (serum glutamic pyruvic transaminase) |
| AST, SGOT (serum glutamic oxaloacetic transaminase) | AST, SGOT (serum glutamic oxaloacetic transaminase) |
| Bilirubin (hyperbilirubinemia) | Bilirubin (hyperbilirubinemia) |
| Calcium, serum-low (hypocalcemia) | Calcium, serum-low (hypocalcemia) |
| Creatinine | Creatinine |
| GGT (gamma-Glutamyl transpeptidase) | GGT (gamma-Glutamyl transpeptidase) |
| Glucose, serum-high (hyperglycemia) | Glucose, serum-high (hyperglycemia) |
| Glucose, serum-low (hypoglycemia) | Glucose, serum-low (hypoglycemia) |
| Magnesium, serum-low (hypomagnesemia) | Magnesium, serum-low (hypomagnesemia) |
| Phosphate, serum-low (hypophosphatemia) | Phosphate, serum-low (hypophosphatemia) |
| Potassium, serum-low (hypokalemia) | Potassium, serum-low (hypokalemia) |
| Sodium, serum-low (hyponatremia) | Sodium, serum-low (hyponatremia) |
| Uric acid, serum-high (hyperuricemia) | Uric acid, serum-high (hyperuricemia) |

### MUSCULOSKELETAL/SOFT TISSUE

| Musculoskeletal/Soft Tissue | Description                      |
|-----------------------------|----------------------------------|
| Extremity-lower (gait/walking) | Extremity-lower (gait/walking) |
| Trismus (difficulty, restriction or pain when opening mouth) | Trismus (difficulty, restriction or pain when opening mouth) |

### NEUROLOGY

| Neurology | Description                      |
|-----------|----------------------------------|
| Ataxia (incoordination) | Ataxia (incoordination) |
| CNS cerebrovascular ischemia | CNS cerebrovascular ischemia |
| Confusion | Confusion |
| Dizziness | Dizziness |
| Extrapyramidal/involuntary movement/restlessness | Extrapyramidal/involuntary movement/restlessness |
| Mood alteration - anxiety | Mood alteration - anxiety |
| Mood alteration - depression | Mood alteration - depression |
| Neurology - Other (multiple cranial nerve palsies) | Neurology - Other (multiple cranial nerve palsies) |

### NEUROLOGY, continued

| Neurology | Description                      |
|-----------|----------------------------------|
| Neuropathy: cranial (CN II vision) | Neuropathy: cranial (CN II vision) |
| Neuropathy: cranial (CN III pupil, upper eyelid, extra ocular movements) | Neuropathy: cranial (CN III pupil, upper eyelid, extra ocular movements) |
| Neuropathy: cranial (CN IV downward, | Neuropathy: cranial (CN IV downward, |

---

67
| Neuropathy: cranial (CN IX motor-pharynx, sensory-ear, pharynx, tongue) | Neuropathy: cranial (CN IX motor-pharynx, sensory-ear, pharynx, tongue) |
|-----------------------------|---------------------------------------------------------------------|
| Neuropathy: cranial (CN V motor-jaw muscles; sensory-facial) | Neuropathy: cranial (CN V motor-jaw muscles; sensory-facial) |
| Neuropathy: cranial (CN VI later deviation of eye) | Neuropathy: cranial (CN VI later deviation of eye) |
| Neuropathy: cranial (CN VII motor-face, sensory-taste) | Neuropathy: cranial (CN VII motor-face, sensory-taste) |
| Neuropathy: cranial (CN VIII hearing and balance) | Neuropathy: cranial (CN VIII hearing and balance) |
| Neuropathy: cranial (CN X motor-palate, pharynx, larynx) | Neuropathy: cranial (CN X motor-palate, pharynx, larynx) |
| Neuropathy: cranial (CN XI motor-sternomastoid and trapezius) | Neuropathy: cranial (CN XI motor-sternomastoid and trapezius) |
| Neuropathy: cranial (CN XII motor-tongue) | Neuropathy: cranial (CN XII motor-tongue) |
| Neuropathy: sensory (including acute laryngo-pharyngeal dysesthesias, hyporeflexia, Lhermitte’s sign, paresthesia) | Neuropathy: sensory (including acute laryngo-pharyngeal dysesthesias, hyporeflexia, Lhermitte’s sign, paresthesia) |

**Seizure**

**Somnolence/depressed level of consciousness**

**Speech impairment (e.g., dysphasia or aphasia)**

**Syncope (fainting)**

| OCULAR/VISUAL |
|---------------|
| Dry eye syndrome |
| Eyelid dysfunction |
| Ocular - Other (amaurosis fugax) |
| Ocular surface disease | **Ocular surface disease** |
| Optic disc edema |
| PAIN                          | PAIN-abdomen NOS                  |
|-------------------------------|----------------------------------|
| Pain-abdomen NOS             | Pain-abdomen NOS                 |
| Pain-back                     | Pain-back                        |
| Pain-bone                     | Pain-bone                        |
| Pain-chest/thorax NOS         | Pain-chest/thorax NOS            |
| Pain-eye                      | Pain-eye                         |
| Pain-head/headache            | Pain-head/headache               |
| Pain-joint                    | Pain-joint                       |
| Pain-muscle                   | Pain-muscle                      |

| PULMONARY/UPPER RESPIRATORY   |                                 |
|-------------------------------|---------------------------------|
| Bronchospasm, wheezing        | Cough                           |
| Cough                         | Cough                           |
| Dyspnea (shortness of breath) | Dyspnea (shortness of breath)   |
| Hiccoughs (hiccups, singultus)| Hiccoughs (hiccups, singultus)  |
| Nasal cavity/paranasal sinus reactions | |
| Pneumonitis/pulmonary infiltrates | Pneumonitis/pulmonary infiltrates |
| Pulmonary fibrosis (radiographic changes) | Pulmonary fibrosis (radiographic changes) |
| Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis) | |

| RENAL/GENITOURINARY           |                                 |
|-------------------------------|---------------------------------|
| Renal failure                 | Renal failure                   |
| Urinary frequency/urgency     | Urinary retention (including neurogenic bladder) |
| Urinary retention (including neurogenic bladder) | |

| SYNDROMES                     |                                 |
|-------------------------------|---------------------------------|
| Syndromes - Other (hepato-renal syndrome) | |

| VASCULAR                      |                                 |
|-------------------------------|---------------------------------|
| Phlebitis (including superficial thrombosis) | Phlebitis (including superficial thrombosis) |
| Thrombosis/thrombus/embolism  | Thrombosis/thrombus/embolism    |

1 This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The most current version can be obtained by contacting ADEERSMD@tech-res.com. Your name, the name of the investigator, the protocol, and the agent should be included in the e-mail.

Note: Oxaliplatin in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.
### RTOG 0247 CAPECITABINE/DIARRHEA DIARY

**Case Number:** ______________

**NURSE/RA:** COMPLETE TWO FORMS TO COVER CAPECITABINE TREATMENT TIME

Enter dates in day column

Record number of Capecitabine tablets per dose for each AM and PM (150mg/500mg)

**PATIENT:** Enter # bowel movements/day in excess of pretreatment # of daily bowel movement(s)

Call the office for any diarrhea

| Day of Week | # Pills 150mg / 500mg | # Bowel Movements / Treatment for Diarrhea | Day of Week | # Pills 150mg / 500mg | # Bowel Movements / Treatment for Diarrhea |
|-------------|-----------------------|------------------------------------------|-------------|-----------------------|------------------------------------------|
|             |                      | AM | PM |                      | AM | PM |
| Sun         | Sun                   |    |    | Sun                   |    |    |
| Mon         | Mon                   |    |    | Mon                   |    |    |
| Tues        | Tues                  |    |    | Tues                  |    |    |
| Wed         | Wed                   |    |    | Wed                   |    |    |
| Thurs       | Thurs                 |    |    | Thurs                 |    |    |
| Fri         | Fri                   |    |    | Fri                   |    |    |
| Sat         | Sat                   |    |    | Sat                   |    |    |
| Sun         | Sun                   |    |    | Sun                   |    |    |
| Mon         | Mon                   |    |    | Mon                   |    |    |
| Tues        | Tues                  |    |    | Tues                  |    |    |
| Wed         | Wed                   |    |    | Wed                   |    |    |
| Thurs       | Thurs                 |    |    | Thurs                 |    |    |
| Fri         | Fri                   |    |    | Fri                   |    |    |
| Sat         | Sat                   |    |    | Sat                   |    |    |

**COMMENTS___________________________________________________________
________________________________________________________________
NURSE/RA SIGNATURE ____________________________________________

PATIENT SIGNATURE (INITIALS)__________________
PATIENT EDUCATION SHEET  
(RTOG 0247)  
MANAGEMENT OF DIARRHEA DURING CHEMOTHERAPY

Patient Initials_______ Patient #_________

The patient was counseled regarding the potential side effects that may occur during treatment. This specifically addresses DIARRHEA MANAGEMENT.

DIARRHEA

You must call your doctor/nurse if you experience any diarrhea and follow the instructions below:

♦ Have a supply of loperamide (e.g., Imodium) at home and begin loperamide treatment for an increase in your usual number of daily bowel movements by more than 2 per day. **If you experience ANY diarrhea you must call your doctor/nurse at that time so that you can be given additional instructions. You should also follow the instructions below.**

Loperamide (Imodium) 2 mg tablets should be taken as follows:

♦ 2 tablets (4mg) at the first onset of diarrhea

♦ 1 tablet (2mg) every 2 hours during the day until 12 hours after last loose stool

♦ 2 tablets (4mg) every 4 hours during the night until 12 hours after the last loose stool

♦ **IF DIARRHEA DOES NOT STOP AFTER 24 HOURS OF LOPERAMIDE, STOP THE CAPECITABINE (XELODA) AND CALL YOUR TREATING PHYSICIAN/ NURSE FOR FURTHER INSTRUCTIONS**

♦ Drink at least eight –8oz glasses of fluid every day.