



E3201

Revised 3/07, Update #2
Revised 9/08, Addendum #5

Eastern Cooperative Oncology Group

Intergroup Randomized Phase III Study of Postoperative Irinotecan, 5-Fluorouracil and Leucovorin vs Oxaliplatin, 5-Fluorouracil and Leucovorin vs 5-Fluorouracil and Leucovorin for Patients with Stage II or III Rectal Cancer Receiving Either Preoperative Radiation and 5-Fluorouracil or Postoperative Radiation and 5-Fluorouracil

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Oxaliplatin (NSC 266046) (IND 57004) will be supplied by the NCI for this study.

Version Date: June 26, 2008

NCI Update Date: March 7, 2007

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*This study is supported by the NCI Cancer Trials Support Unit (CTSU). Institutions not aligned with ECOG will participate through the CTSU mechanism. (Please see Table of Contents and Appendix VII for details.)

ACTIVATION DATE

October 15, 2003

Addendum #1 incorporated prior to activation

Update #1 incorporated prior to activation

Addendum #2 – 4/04

Addendum #3 – 4/05

ENTIRE DOCUMENT REVISED

Addendum #4 – 11/05

Update #2 – 3/07

Addendum #5 – 9/08

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Rev.
11/05

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Rev. 3/07

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Institutions not aligned with ECOG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at <https://members.ctsu.org>
 - Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
 - **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
 - Data management will be performed by the ECOG. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and transmittals** must be sent to ECOG unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
 - **Data clarification forms and delinquency reports** will be sent directly to the enrolling site by ECOG. Please send data clarification form responses and delinquent data to ECOG and do not copy CTSU Data Operations. Please mail data clarification form responses and delinquent data directly to ECOG unless otherwise directed. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the ECOG data center.
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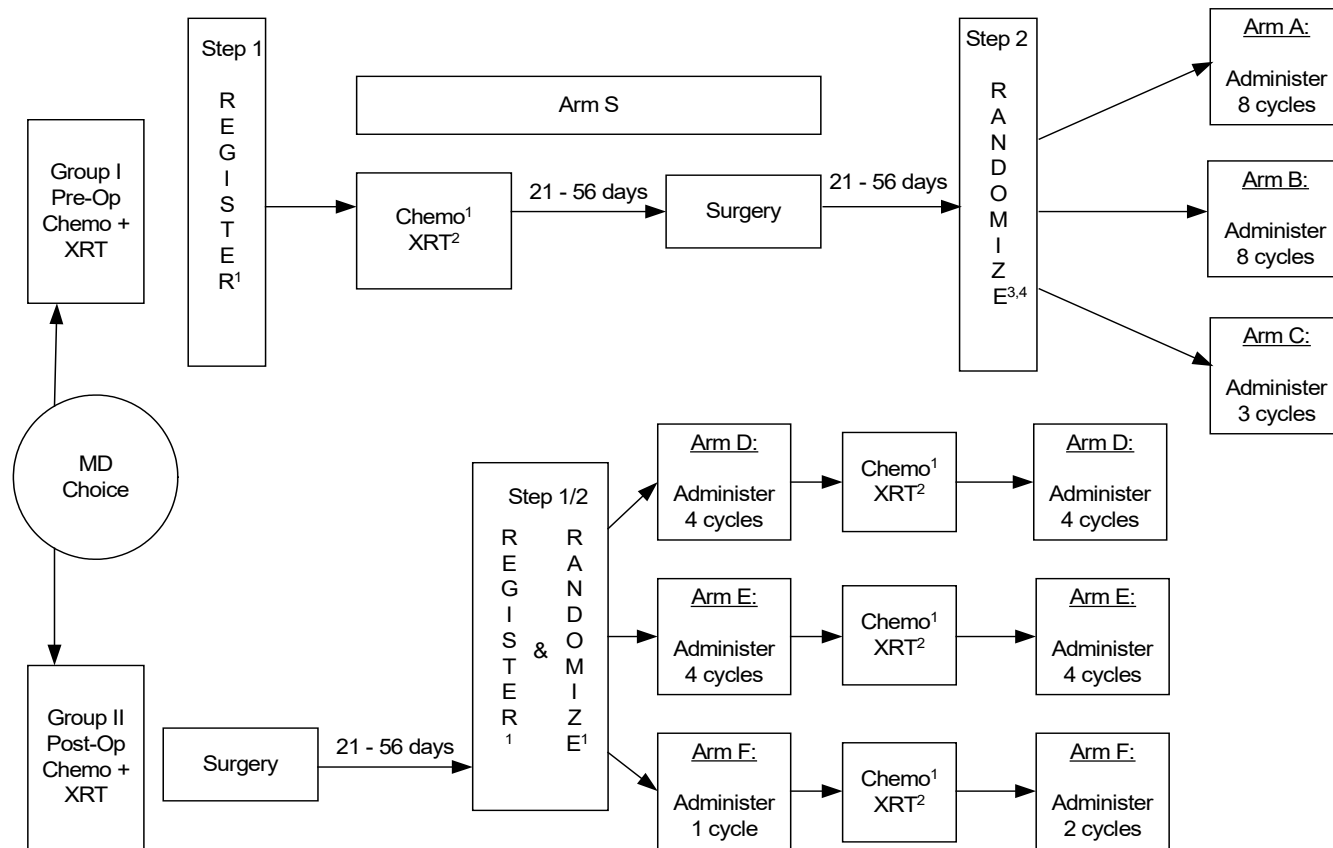
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

Rev. 3/07

To submit site registration documents:	For patient enrollments:	Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:
<p>CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone - 1-888-823-5923 Fax – 215-569-0206</p>	<p>CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 8:00 AM – 8:00 PM Eastern Time, Monday – Friday (excluding holidays)</p> <p>[For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]</p>	<p>ECOG Coordinating Center, FSTRF 900 Commonwealth Avenue Boston, MA 02215 (ATTN: DATA). Phone # 617-632-3610 Fax # 617-632-2990</p> <p>Data should be sent via postal mail (preferred); however fax is accepted.</p> <p>Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</p>
<p><u>For patient eligibility or treatment-related questions:</u> Contact the Study PI of the Coordinating Group.</p>		
<p><u>For questions unrelated to patient eligibility, treatment, or data submission</u> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</p>		
<p>The CTSU Public Web site is located at: www.ctsu.org The CTSU Registered Member Web site is located at https://members.ctsu.org</p>		

CTSU logistical information is located in Appendix VII.

Schema



All doses based on actual weight.

See Following Page for Dosing Details

1. See Section 5.1 for allowed regimens to be administered with radiation pre-op or post-op; must be declared at time of registration.
2. Patients must receive minimum radiation dose of 50.4 Gy (see section 5.5 for guidelines).
3. Patients will be stratified by ECOG performance status (0 vs 1), High risk ($T_3N_+M_0$, $T_4N_{any}M_0$) vs Low Risk ($T_{1-2}N_+M_0$, $T_3N_0M_0$) and Pre-operative chemotherapy/XRT vs Post-operative chemotherapy/XRT. (See Section 4.25)
4. Patients who have received treatment as specified in "Arm S" may join the study, if they present post-surgery. They will be registered and randomized to Group I (only) at the same time. [This group is referenced as "Group I PS".]

Arm A/Arm D*

Irinotecan: 180 mg/m², IV over 90- minutes

Leucovorin: 400 mg/m², IV over 2 hours.
5-FU: 400 mg/m², IV bolus injection,
immediately following leucovorin dose.

Continuous infusion 5-FU: 2.4 gm/m² over 46
hours by ambulatory infusion pump beginning
immediately following bolus 5-FU.

Cycle = 2 treatment days every 2 weeks.

Arm B/Arm E**

Oxaliplatin: 85 mg/m², IV over 2 hours

Leucovorin: 400 mg/m², IV over 2 hours.
5-FU: 400 mg/m², IV bolus injection,
immediately following leucovorin dose.

Continuous infusion 5-FU: 2.4 gm/m², over 46
hours by ambulatory infusion pump beginning
immediately following bolus 5-FU.

Cycle = 2 treatment days every 2 weeks.

Arm C/Arm F

Leucovorin: 500 mg/m², IV over 2 hours once
a week for 6 weeks, followed by 2 weeks rest.

5-FU: 500 mg/m², bolus IV 1 hour after the
start of the leucovorin infusion, once a week
for 6 weeks followed by 2 weeks rest.

Cycle = 8 weeks.

* See Section 5.4.1 for dose escalation

** See Section 5.4.2 for dose escalation

1. Introduction

- 1.1 The treatment for patients with resectable rectal cancer is evolving in the United States and Canada. Surgeons have increasingly offered patients preoperative combined 5-FU based chemotherapy and radiation to down-stage a patient prior to surgery, increase the possibility of a sphincter-sparing surgery, and to reduce combined modality toxicity by removing irradiated tissue at the time of resection.

Many patients, however, continue to receive surgery as their initial treatment intervention and are candidates for postoperative combined modality therapy. Although there have been a number of trials using preoperative combined modality therapy, particularly in Europe, few have been randomized and few have used conventional radiation doses. The NSABP (R03) and the Gastrointestinal Intergroup (INT0147) each designed a randomized trial of preoperative versus postoperative combined modality therapy for resectable rectal cancer in an effort to employ conventional radiation dosing, to determine whether preoperative chemotherapy and radiation improves disease-free and overall survival compared to postoperative therapy, and to evaluate local recurrence rates, sphincter preservation, down staging, and quality of life. Unfortunately, both trials were terminated prior to completion because of inadequate patient accrual. The NSABP has reported on the status of the 267 patients randomized with data one year after randomization, suggesting similar disease-free survival (83% versus 78%, $p=0.29$) with similar postoperative complications, although a larger proportion of preoperative patients had sphincter-saving surgery (1). Grade 4-5 toxicity was greater in the preoperative arm (34% versus 23%, $p=0.07$). It is evident that both pre- and postoperative strategies have been embraced in the United States, and it remains likely that a preoperative versus postoperative trial will never be completed with sufficient numbers of patients. Both approaches are now viewed as acceptable alternatives de facto.

The predominant chemotherapy regimens for rectal cancer patients include 5-FU, with or without leucovorin, and protracted venous infusion 5-FU. There also is interest in substituting oral 5-FU regimens for protracted venous infusion 5-FU. The first intergroup rectal trial (NCCTG 86-47-51) showed that protracted venous infusion of 5-FU during pelvic irradiation administered in the postoperative setting increased the time to relapse and improved survival compared to those treated with bolus 5-FU(2). Results from the second intergroup trial (INT0114), with a median follow-up of survivors at 7.4 years, suggest that overall and disease-free survival are not statistically different among the four treatment groups. All patients received two cycles of 5-FU-based chemotherapy followed by pelvic radiation with 5-FU and two additional cycles of chemotherapy. Chemotherapy was bolus 5-FU, 5-FU and leucovorin, 5-FU and levamisole, and 5-FU, leucovorin, and levamisole (3-5). The data do suggest that local recurrence is significantly less for lower risk patients ($T_{1-2} N_+ T_3 N_0$) compared to high risk ($T_3 N_+ T_4 N_{any}$) with overall survival and disease-free survival favoring the lower-risk group. Males also had a poorer outcome.

Available survival data from the first two intergroup trials include:

NCCTG 86-47-51 4-year survival (2)		
Bolus 5-FU = 60%		
PVI 5-FU = 70%		
INT 0114 (3)		
	5 Year Survival	7 Year Survival
Good Risk	76%	70%
Poor Risk	55%	45%
All Patients	64%	56%

The third intergroup trial (INT0144) is a three-arm, postoperative evaluation of 5-FU by bolus injection versus 5-FU by prolonged venous infusion prior to and following combined prolonged venous infusion plus pelvic radiation versus bolus 5-FU plus leucovorin plus levamisole prior to and following combined pelvic radiation. The study reached its accrual goal in August 2000 and will require at least three more years before analysis can begin. Therefore, pending the analysis of the third Intergroup trial, INT0144, an optimal 5-FU-based regimen has yet to be defined.

Recent advanced disease colorectal cancer trials have suggested that a regimen of irinotecan, 5-FU, and leucovorin is superior to 5-FU and leucovorin (6-7). The intergroup adjuvant colon trial (INT0089) has confirmed that 5-FU and leucovorin is the favored regimen (8-13). The recently completed colon intergroup adjuvant trial (C89803) compares irinotecan, 5-FU, and leucovorin versus 5-FU and leucovorin. The results are pending. The survival advantage of irinotecan, 5-FU, and leucovorin in the advanced disease setting justifies further evaluation of the combination, not only in the adjuvant setting for colon cancer but also for rectal cancer patients. There are limited data describing the use of post-radiation irinotecan, 5-FU and leucovorin for resected rectal cancer patients. In a study of 17 patients receiving post-radiation and post-surgery weekly irinotecan, 5-FU and leucovorin for four weeks repeated every six weeks for three cycles, there was no evidence of grade 4 neutropenia or other grade 3-4 non-hematologic toxicities (14). Recent morbidity and mortality data from advanced disease trials and the intergroup protocol (C89803) suggest that the bolus regimen of irinotecan, 5-FU and leucovorin produces a level of toxicity which would warrant dose reductions or alternative schedules (6,15). An alternative schedule includes infusion regimens of 5-FU combined with irinotecan which have been widely employed in Europe and approved by the Food and Drug Administration (7). A recent report of infusion regimens of 5-FU with irinotecan suggest a median survival of greater than 20 months for advanced colorectal cancer patients with acceptable toxicity (16).

Oxaliplatin (trans-l-1,2-diaminocyclohexane oxalatoplatinum) is a novel antineoplastic platinum derivative with a 1,2-diaminocyclohexane [DACH] carrier ligand. Although the precise mechanism of action is unknown, platinum compounds are thought to exert their cytotoxic effects through the formation of DNA adducts that block both DNA replication and transcription. Like cisplatin, oxaliplatin reacts with DNA, forming mainly platinated intra-strand links with two adjacent guanines or a guanine adjacent to an adenine (17-19). However, DACH-platinum adducts formed by oxaliplatin are apparently more effective at inhibiting DNA synthesis (19,20) and are more cytotoxic than cis-diammine-platinum adducts formed from cisplatin and carboplatin (19-21).

The safety profile of oxaliplatin was evaluated in a phase I intra-patient escalation study of 44 patients with advanced cancer, who received 116 courses of oxaliplatin through seven levels, from 45 mg/m² to 200 mg/m² every four weeks (22). Oxaliplatin was administered without pre-hydration or post-hydration. Initially, all patients experienced nausea and vomiting. As a result, systematic pretreatment with antiemetics was given to all patients receiving >90 mg/m² oxaliplatin, which reduced Grade 3 or 4 nausea and vomiting to 11%. Diarrhea was mild (primarily Grade 1 or 2 in 24% of therapy courses). Hematologic toxicity was moderate. Grade 1 or 2 thrombocytopenia was dose related and occurred in 13% of patients receiving from 135 to 150 mg/m², and 28.5% of patients receiving from 175 to 200 mg/m². Similarly, only Grade 1 or 2 neutropenia was observed, and hemoglobin levels remained unchanged. The dose-limiting side-effect of oxaliplatin therapy was a transient peripheral neuropathy. This toxicity usually appeared at doses >90 mg/m² and affected up to 75% of patients treated with 200 mg/m². The recommended phase II dose was 135 mg/m² administered over at least 1 hour every four weeks.

A review of several studies to evaluate overall safety in 682 patients who had received oxaliplatin either as a single agent or in combination with 5-FU was done to delineate the character and severity of oxaliplatin-induced neurotoxicity (23). Grade 3 neurotoxicity presenting as fine movement disturbance or moderate sensitive ataxia was observed in 12% of patients at a median cumulative dose of 900 mg/m² oxaliplatin. (Total cumulative doses of 780, 1170, and 1560 mg/m² were correlated with an incidence of 10%, 50% and 75% neurotoxicity, respectively.) The total cumulative dose of oxaliplatin was the most significant prognostic factor for the occurrence of neurotoxicity and inversely related to the likelihood of recovery from toxicity. Symptoms resulting

from Grade 1 and 2 neuropathy regressed in 82% of patients within 4 to 6 months, and disappeared entirely in 41% of patients within 6 to 8 months. In summary, all studies reported to date that the neurotoxicity resulting from oxaliplatin treatment was specific, cumulative and, unlike cisplatin-induced neuropathy, reversible in most patients.

The efficacy of oxaliplatin monotherapy in patients with advanced colorectal cancer was evaluated in five phase II trials, two with 63 previously untreated patients and three with 139 patients with metastatic disease previously treated with and mostly refractory to 5-FU (23-27). The objective response rate achieved with oxaliplatin as first-line therapy was approximately 20% while that of oxaliplatin as second-line therapy was approximately 10%.

Two randomized studies have compared the combination of oxaliplatin, 5-FU, and leucovorin to 5-FU and leucovorin alone as initial therapy for metastatic colorectal cancer. In one trial oxaliplatin was administered at 125 mg/m² every three weeks with daily x 5 5-FU plus leucovorin, and in the other oxaliplatin was administered at 85 mg/m² every two weeks with infusional 5-FU/ leucovorin on days 1-2 (28, 29). Both studies showed improved time to progression (q 2 weeks: 9.0 vs. 6.2 months, p=0.0003; q 3 weeks: 8.7 vs. 6.1 months, p=0.048) and response rates (q 2 weeks: 50.7% vs. 22.3%, p=0.0001; q 3 weeks 53% vs. 16% p<0.001) in the oxaliplatin arms. Although a trend in favor of oxaliplatin was reported, there was no statistically significant difference in overall survival between the arms.

In order to evaluate the safety and efficacy of regimens based on the following combinations: 5-FU+ leucovorin + irinotecan; 5-FU+ leucovorin + oxaliplatin; oxaliplatin + irinotecan, in newly diagnosed patients with advanced (metastatic) colorectal cancer an intergroup study, N9741, (NCCTG, ECOG, CALGB, NCIC-CTG, SWOG) was initiated. Initially, this was a 6-arm study. However, 3 arms (those administering 5-FU for 4 or 5 consecutive days) were discontinued early because of inferior efficacy or excessive toxicity. Recently, preliminary results of a planned interim analysis of the 3 remaining arms were released by the National Cancer Institute. The analysis, based on 795 patients enrolled in the study between March 1999 and April 2001, showed that patients receiving the infusional regimen (oxaliplatin with infusional 5-FU and leucovorin) had significantly longer time to disease progression (8.8 months vs 6.9 months; p = 0.0009), significantly better overall survival (18.6 months vs 14.1 months; p = 0.002) , a significantly higher response rate (38% vs 29%; p = 0.03) and lower toxicity than patients receiving irinotecan, with bolus 5-FU and leucovorin (IFL) (30, 31).

Various modifications of the combination of oxaliplatin with 5-FU/leucovorin regimens (FOLFOX 1-FOLFOX 6) have been evaluated (30-34). The more recent modifications have simplified the schedule of administration and improved patient convenience without compromising the efficacy of the regimen. Maindrault-Goebel et al. reported on a Phase II study of oxaliplatin (100 mg/m²) and leucovorin (400 mg/m²) as a 2-hour infusion on Day 1 followed by bolus (400 mg/m²) and a 46-hour infusion (2.4-3 g/m²) of 5-FU every 2 weeks (FOLFOX 6) as second line treatment for metastatic colorectal cancer (35). Sixteen of 60 patients treated had a partial response (27%) and an additional 45% had stable disease. Median progression-free survival was 5.3 months and median survival was 10.8 months. Ryan et al. evaluated biweekly oxaliplatin in combination with a modified de Gramont regimen (oxaliplatin 85 mg/m² as a 2-hour infusion on Day 1 of each 2-week cycle, immediately followed by leucovorin, 500 mg/m² as a 2-hour infusion followed by bolus FU, 400 mg/m² and a 46-hour infusion of 5-FU, total dose 2.4 mg/m²) in heavily pre-treated patients with advanced colorectal cancer. Preliminary data showed a response rate of 7% (36). Updated information reveals a response rate of 11% (5%-22%), all in patients who had received prior irinotecan. When only second-line patients are considered, the response rate was 25% (8%-43%).

1.2 Rectal Function in Patients Treated with Adjuvant Radiation Therapy

Administration of pelvic radiation therapy is associated with significant potential for both acute and long term adverse effects on rectal function. Despite this, no rectal adjuvant trial has *prospectively* undertaken a detailed evaluation of rectal function. In this clinical trial, we plan to prospectively evaluate rectal function with validated tools. Information derived in this way can be used in future

studies on interventions of treatments designed to mitigate the adverse effect of adjuvant treatment on rectal function.

In a clinical trial of postoperative adjuvant pelvic radiation therapy and bolus 5-fluorouracil for rectal cancer, 35% of the patients experienced \geq grade 2 diarrhea (37). The incidence of \geq grade 3 diarrhea was 20%. Administration of 5-FU by continuous infusion results in a higher rate of grade 3 or worse diarrhea than administration by bolus (2). In a randomized comparison of these two approaches to postoperative adjuvant therapy, grade 3 or worse diarrhea was observed in 24% of patients during radiation therapy who received concurrent 5-FU by continuous infusion compared to only 14% of patients treated with 5-FU by bolus infusion during radiation therapy. A number of randomized trials have been conducted in an effort to identify agents that prevent or decrease diarrhea during pelvic radiation therapy. Three trials have assessed the value of salicylate preparations (38-40). Two studies suggested a beneficial effect (38-40) and one NCCTG study suggested a large harmful effect. Two double blind clinical trials evaluated oral sucralfate (41,42). In one trial, sucralfate was associated with a decrease in diarrhea (41). In the other trial, performed by the NCCTG, sucralfate was not associated with a decrease in diarrhea, and some gastrointestinal symptoms were exacerbated by the use of this agent (42). A trial evaluating cholestyramine provided evidence that this agent can decrease diarrhea, but only at the expense of unacceptable gastrointestinal side effects (43). Taken together, evidence from these studies indicates that acute diarrhea is a significant clinical problem in patients receiving pelvic radiation therapy. These studies also indicate that there is no class of agents that *consistently* demonstrates the ability to prevent diarrhea in these patients with an acceptable toxicity profile.

Long term adverse effects on rectal function as a result of combined postoperative chemotherapy and radiation therapy were studied by Kollmorgen and colleagues from the Mayo Clinic (44). Forty-one patients who had received this treatment were contacted and questioned about their bowel function, as were 59 patients who had not received this treatment. Highly statistically significant adverse effects on bowel function were observed in the irradiated group across a broad spectrum of 11 different parameters. For example, 46% of the irradiated patients experienced nocturnal bowel movements, compared to only 14% of the non-irradiated patients ($P<0.001$). Fifty-six percent of the irradiated patients experienced at least occasional incontinence, compared to only 7% of non-irradiated patients ($P<0.001$). Protective clothing was used by 41% of irradiated patients and 10% of non-irradiated patients ($P<0.001$). Because interviewers were not blinded, and because the patients were not randomized to receive or not receive pelvic irradiation, the results of this study must be interpreted with caution.

Lundby and colleagues evaluated rectal function 11 years after completion of a randomized clinical trial comparing adjuvant postoperative pelvic radiation therapy (50 Gy in 25 fractions, with a two week break after 30 Gy) with observation (45). 103 of the 494 patients originally entered onto the trial were alive without recurrence at the time of the evaluation. The study design called for patients to be contacted by phone for a structured interview regarding their bowel function. Eight patients were excluded because of dementia or deafness. Two could not be contacted. The remaining 93 patients, 49 in the radiation group and 44 in the control group, were included in the evaluation of rectal function. Individuals interviewing patients were blinded as to the treatment received at the beginning of the interview. Blinding was maintained in 89% of the interviews. Findings of this study are strikingly similar to those observed in the Mayo Clinic study. For example, 49% of irradiated patients experienced fecal incontinence, compared to only 5% of control patients ($P<0.001$). Protective clothing was used by 26% of the irradiated patients compared to none of the control patients ($P<0.001$). Because of the randomized nature of the original treatment allocation and because of the fact that interviewers, in the vast majority of cases, remained blinded as to the treatment received by the patients, it is unlikely that bias can account for these results. This study, therefore, provides strong corroboration of the Mayo Clinic study and indicates that a very high proportion of patients experience clinically significant, long term rectal toxicity following postoperative adjuvant pelvic radiation therapy for rectal cancer.

A review of the literature on the measurement of bowel function uncovered no standard uniform approach or measurement scale. A number of studies report assessing “bowel function” but remain primarily concerned with the number of stools per day or use a varied assortment of questionnaire formats (46-52).

Prospective assessment of rectal function will be an integral part of this clinical trial, in view of the extensive body of research providing unequivocal evidence of both acute and long term adverse effects on rectal function in patients receiving pelvic radiation therapy. A simple bowel function questionnaire has been developed for assessment of several measures of rectal function, such as stool frequency, continence, “clustering” (the need to have a second bowel movement, 30 minutes after defecation), and the ability to defer defecation 15 minutes. The questionnaire is based on the Mayo Clinic study mentioned above, in which bowel function was assessed in a group of patients with resected rectal cancer who either had or had not received adjuvant pelvic RT (44). As indicated previously, findings from this study suggest that this questionnaire is able to discriminate between patients that have received and not received pelvic radiation therapy. For each of the eight measures of bowel function addressed by the questionnaire, a highly significant difference was noted between the group of patients who had received prior RT and those who had not (44). Further evidence of the ability of this questionnaire to discriminate between groups of patients may be found in the NCCTG study of sucralfate, which demonstrated statistically significant worse outcome in the sucralfate group with regard to fecal incontinence, need for protective clothing, and overall gastrointestinal symptoms (42). Use of this questionnaire will provide more detailed information on long-term bowel function than would be provided by common toxicity criteria alone.

The primary construct we are targeting with the questionnaire is problems with bowel function as perceived by the patient. This construct is more relevant and precise than asking for a simple incidence measure of various bowel function parameters. If the patient perceives that bowel function is a problem, then it is a problem (46, 53). Hence it is important to capture this patient-reported outcome as an indicator of treatment efficacy.

Face validity of the bowel function questionnaire derives from a content analysis of the literature and the framework used in the application of the original questionnaire (44, 50-60). We will carry out further psychometric evaluation of the bowel function questionnaire in this study. Specifically, we will assess the reliability and validity of the bowel function questionnaire according to standard methods (47) and analogous to specific methodology used to validate a tool for measuring constipation in cancer patients (46).

A function questionnaire with a more general quality-of-life (QOL) measure is known as the Uniscale (48). The Uniscale is a single-item visual analogue tool intended to measure overall QOL, which has been used successfully in a number of NCCTG trials. These studies have demonstrated that this global measure of quality of life is reliable and valid, and also has some advantages over more complex instruments (49). Discriminant validity will be examined by correlating toxicity incidence with individual items of the bowel function questionnaire.

We will also use the FACT Diarrhea Subscale, a subscale of FACT-G, to assess bowel function in this study. The FACT Diarrhea Subscale is a simple eleven item instrument which covers a range of problems encountered by patients who experience diarrhea related to cancer treatment. A key difference between the FACT Diarrhea Subscale and the bowel function questionnaire is that the FACT Diarrhea Subscale uses a Likert scale, while the bowel function questionnaire uses a dichotomous scale for most questions. A general description of the extensive measures that have been undertaken to validate the FACT quality of life scales has been reported by Cella and colleagues (61).

It generally takes patients less than 5 minutes to complete the short twelve-item bowel function questionnaire. We believe this is an efficient means to obtain more detailed bowel function data. The extra effort should not be overly burdensome to either the patients in terms of time or the trial in terms of cost. The Uniscale has been added to the end of the bowel function questionnaire for

the convenience of the patient. Similarly, it will take less than five minutes to complete the FACT Diarrhea Subscale. Hence, in total the FACT, Uniscale and bowel function questionnaires require less than ten minutes for the patient to complete the combined 24 items

1.3 Correlative Studies

Numerous studies of molecular prognostic and predictive markers have been reported (62-88), but none of the markers has reached routine clinical usage because their value is not proven (89-91). As a result of successful clinical trials (92), the current standard of care for rectal cancer patients in stage II and III is pre- or post-operative chemoradiation. Identification of high- and low-risk patients within the stage groupings would be helpful.

In addition, predictive markers for response or resistance to chemoradiation have broad implications for treatment of patients with rectal carcinoma. Therapy results in morbidity and mortality in some patients, and cancer can progress despite therapy. Therefore, markers that predict survival are needed (62).

The sensitivity and resistance of cancers to chemoradiation are complex characteristics affected by pharmacology, pharmacokinetics, tumor biology, radiation biology, and tumor cell phenotypes and genotypes. Recent advances in molecular biology have directed attention at genetic pathways involved in control of the cell cycle and apoptosis which are affected by therapeutic agents (93-95). In vitro studies suggested that the p53 pathway is important: responses to most agents, including anti-metabolites such as 5-FU, the mainstay of chemotherapy for colorectal cancer, and radiation, were in large part dependent on wild-type p53 (96). Cells with abnormal mismatch repair showed resistance to a wide variety of chemotherapeutic agents and radiation (97-98). In addition, genes that encode enzymes involved in metabolism of chemotherapeutic agents and repair of their DNA adducts may affect drug efficacy and also serve as predictive markers for sensitivity and resistance to the agents (123). Few studies, however, have addressed markers in clinical trials of chemoradiation.

In patients who undergo resection of a rectal carcinoma with curative intent, it is the presence of undetected residual disease which is responsible for recurrence and ultimately death of the patient (99). These occult metastases are the target of pre-operative neoadjuvant and post-operative adjuvant chemoradiation in rectal cancer (100,101). Patients who have occult metastasis may benefit if the adjuvant chemoradiation is effective, but those patients who lack occult metastasis derive no benefit and are nonetheless subjected to the toxicity of treatment (102). Ideally, markers for risk-adapted therapy would identify the patients at high risk and low risk, thereby helping to guide treatment decisions.

Improved prediction of outcome by identification of the high-risk minority and the low-risk majority of patients would be helpful in both groups of rectal cancer patients to identify appropriate candidates for chemoradiation and those who do not need therapy because of inherently high survival rates.

Dr. Hamilton's laboratory was the first to report that 18q allelic loss was an unfavorable prognostic marker in stage II colorectal cancer (103), a finding that was confirmed in numerous subsequent studies (62, 65, 71, 73, 75, 78, 79). In a collaborative study with the ECOG of stage III colon cancer, Dr. Hamilton's laboratory reported that retention of chromosome 18q alleles in microsatellite-stable cancers and mutation of the transforming growth factor beta type II receptor gene (TGF beta RII) in cancers with high levels of microsatellite instability were favorable markers for disease-free and overall survival. Therefore, we will evaluate the molecular predictive markers identified in our and others' previous studies (chromosome 18q allelic loss, p53 gene mutation and microsatellite instability) in order to evaluate the relative strengths of the markers.

The cooperative groups and others have conducted a series of retrospective trials correlating expression of key targets of 5-FU-based therapy with response to therapy in the adjuvant setting. In rectal cancer, a retrospective analysis demonstrated decreased survival for those patients with high thymidylate synthetase (TS) expression, although the patients who received the most benefit from chemotherapy had high TS expression (104). Other investigators have confirmed that high

TS correlates with worse survival. However, more recent analyses for metastatic colorectal cancer suggest that low TS mRNA expression in tumor tissue is associated with a much higher response to therapy compared to those patients who have high TS mRNA expression. Preliminary data suggest that patients who have rectal tumor resection after preoperative 5-FU and radiation therapy not only will demonstrate tumor downstaging, but polymorphisms of the repeat sequences in the enhancer region of thymidylate synthase gene promoter may predict tumor downstaging (105, 106). In addition, recent analyses suggest colorectal cancer responding to 5-FU have low gene expression levels of dihydropyrimidine dehydrogenase (DPD) and thymidine phosphorylase (TP) (88). We will evaluate expression of these three enzymes (TS, DPD and TP) as potential markers.

This protocol includes therapy with oxaliplatin in Arm B and Arm E. Excision repair cross-complementing 1 (ERCC1), ERCC2 and XPF are enzymes involved in nucleotide excision repair, and their activity could affect the ability of tumor cells to remove platinum adducts from their DNA and influence the efficacy of the drug. Colorectal cancer patients with low levels of ERCC1 expression in their tumor have been reported to have improved survival after oxaliplatin therapy (123). We will evaluate expression of these three genes (ERCC1, ERCC2 and XPF) as potential markers.

1.4 Gender and Ethnicities Statement

This study is open to both men and women and to all racial/ethnic groups. The patient enrollment pattern is expected to be similar to that of typical ECOG colorectal cancer studies. According to the most recent ECOG experience, there is no evidence for outcome to be affected by either race or gender. Thus, the study will not have separate accrual targets for different subgroups. We will, however, conduct subset analyses to assess gender and racial/ethnic effects when possible.

2. Objectives

- 2.1 To compare the overall survival of patients treated with irinotecan, 5-FU and leucovorin versus those treated with oxaliplatin, leucovorin and 5-FU versus those treated with leucovorin and 5-FU for patients with stage II and III rectal cancer.
- 2.2 Secondary endpoints will include sphincter preservation, tolerance of treatment and patterns of failure.
- 2.3 To prospectively assess rectal function using the Patient Bowel Function/Uniscale questionnaire and the FACT Diarrhea Subscale in patients treated with an adjuvant program of pelvic radiation therapy and chemotherapy.
- 2.4 To correlate TS, DPD and TP expression (key targets for 5-FU); retention of chromosome 18q alleles and MSI with TGFβ1RII mutation (markers for 5-FU efficacy); ERCC1, ERCC2 and XPF expression (participants in repair of adducts from oxaliplatin); and p53 gene mutation in tumor tissue specimens with treatment efficacy.
- 2.5 To correlate tumor molecular prognostic markers (chromosome 18q allelic loss and MSI) with survival.
- 2.6 To determine physician preference in regard to the radiation-chemotherapy sequence in the Intergroup.

3. Selection of Patients

NOTE: All questions regarding eligibility should be directed to the ECOG Coordinating Center at (617) 632-3610.

NOTE: Patients who have received treatment as specified in "Arm S" of the protocol—specifically having undergone concurrent chemotherapy/radiation (refer to Section 5.1 for allowed regimens of chemotherapy and Section 5.5 for radiation guidelines) followed by surgery—and present post-

surgery may join/participate in this trial. These patients will be assigned to Group I (only). Hereinafter, this group will be referenced as "Group I PS" (post surgery). Group I PS is required to satisfy the eligibility criteria defined in Section 3.2 (**except 3.25**) and Section 3.3 at the time of registration, since registration and randomization are performed at the same time.

3.1 Group I (Pre-operative) Registration

- 3.1.1 Patients must have histologically proven adenocarcinoma of the rectum with no distant metastases. Clinical staging is required (T₃N₀M₀, T₄N₀M₀, T_{any}N₁₋₃M₀). See Appendix V for staging criteria.
- 3.1.2 Patients must not have evidence of tumor outside of the pelvis including liver metastases, peritoneal seeding, or metastatic inguinal lymphadenopathy.
- 3.1.3 Patients must have ECOG performance status 0-1.
- 3.1.4 The distal border of the tumor must be at or below the peritoneal reflection, defined as within 12 centimeters of anal verge by proctoscopic examination. In addition, patients who have had a portion of their tumors confirmed to be below the peritoneal reflection at the time of surgery are eligible regardless of the distance determined by endoscopy.
- 3.1.5 Transmural penetration of tumor through the muscularis propria must be demonstrated by CT scan, endo-rectal ultrasound or MRI.
- 3.1.6 Tumors must be defined prospectively by the surgeon as clinically resectable or not.
 - 3.1.6.1 Clinically resectable tumors will be defined by the surgeon as not fixed and completely resectable with negative margins based on the routine examination of the non-anesthetized patient.
 - 3.1.6.2 Before pre-op treatment, the surgeon should estimate and record the type of resection anticipated: APR, LAR or LAR/coloanal anastomosis.
- 3.1.7 The tumor may be clinically fixed or initially not completely resectable, clinical stage T₄ N₀₋₂ M₀ based on the presence of at least one of the following criteria:
 - 3.1.7.1 Clinically fixed tumors on rectal examination with tumor adherent to the pelvic sidewall or sacrum.
 - 3.1.7.2 Hydronephrosis on CT scan or IVP or ureteric or bladder invasion as documented by cystoscopy and cytology or biopsy, or invasion into prostate.
 - 3.1.7.3 Vaginal or uterine involvement.
- 3.1.8 Patients must not have received prior chemotherapy or pelvic irradiation therapy.
- 3.1.9 Patients must not have a previous or concurrent malignancy, with the exception of:
 - 3.1.9.1 Nonmelanoma skin cancer or *in situ* cervical cancer.
 - 3.1.9.2 Treated non-pelvic cancer from which the patient has been continuously disease-free more than five years.
- 3.1.10 Patients must not have an active inflammatory bowel disease or other serious medical illness which might limit the ability of the patient to receive protocol therapy.
- 3.1.11 Patients must be ≥ 18 years of age.
- 3.1.12 Female patients must not be pregnant or breast-feeding because of the potentially teratogenic and abortifacient effects of this regimen and there is no information on the excretion of the agents or other metabolites into breast milk. All females of childbearing potential must have a blood or urine test within 2 weeks prior to registration to rule out pregnancy.

- 3.1.13 Sexually-active women of childbearing potential and sexually active males are strongly advised to use an accepted and effective method of contraception.

3.2 Group II (Post-operative) Registration

NOTE: Group II patients are required to satisfy the eligibility criteria defined in Sections 3.2 and 3.3 at the time of registration since registration and randomization are performed at the same time.

- 3.2.1 Patients must have had histologically proven adenocarcinoma of the rectum with no distant metastases. Pathologic staging is required (T₃N₀M₀, T₄N₀M₀, T_{any}N₁₋₃M₀). See Appendix V for staging criteria.
- 3.2.2 Patients must not have evidence of tumor outside of the pelvis including liver metastases, peritoneal seeding, or metastatic inguinal lymphadenopathy.
- 3.2.3 Patients must have ECOG performance status 0-1.
- 3.2.4 The distal border of the tumor must have been at or below the peritoneal reflection, defined as within 12 centimeters of anal verge by proctoscopic examination. In addition, patients who have had a portion of their tumors confirmed to be below the peritoneal reflection at the time of the surgery are eligible regardless of the distance determined by endoscopy.
- 3.2.5 Patients must not have received prior chemotherapy or pelvic irradiation therapy.
- 3.2.6 Patients must not have a previous or concurrent malignancy, with the exception of:
- 3.2.6.1 Non-melanoma skin cancer or *in situ* cervical cancer.
- 3.2.6.2 Treated non-pelvic cancer from which the patient has been continuously disease-free more than five years.
- 3.2.7 Patients must not have an active inflammatory bowel disease or other serious medical illness which might limit the ability of the patient to receive protocol therapy.
- 3.2.8 Patients must be ≥ 18 years of age.
- 3.2.9 Female patients must not be pregnant or breast-feeding because of the potentially teratogenic and abortifacient effects of this regimen and there is no information on the excretion of the agents or their metabolites into breast milk. All females of childbearing potential must have a blood or urine test within 2 weeks prior to registration to rule out pregnancy.
- 3.2.10 Sexually active women of childbearing potential and sexually active males are strongly advised to use an accepted and effective method of contraception.

3.3 Randomization (Groups I and II)

- 3.3.1 Patients must have a completely resected tumor and be within 21 - 56 days from the date of surgery.
- 3.3.2 Patients who received combination chemotherapy/radiation prior to randomization (Group I) must have had a minimum radiation dose of 50.4 Gy.
- 3.3.3 Patients must have ECOG performance status 0-1.
- 3.3.4 Patients must have adequate renal function (creatinine $\leq 1.5 \times$ ULN) obtained ≤ 4 weeks prior to randomization.
- 3.3.5 Patients must have adequate hepatic function (bilirubin $\leq 1.5 \times$ ULN, SGOT (AST) $\leq 3 \times$ ULN) obtained ≤ 4 weeks prior to randomization).
- 3.3.6 Patients must have absolute neutrophil count $\geq 1500/\text{mm}^3$ and platelet count $\geq 100,000/\text{mm}^3$ ≤ 4 weeks prior to randomization.

- 3.3.7 Patients must not have an active inflammatory bowel disease or other serious medical illness which might limit the ability of the patient to receive protocol therapy.

4. Registration and Randomization Procedures

Submitting Regulatory Documents

Before an ECOG Institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX: (215) 569-0206

Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form.
2. Copy of IRB Informed Consent Document.

NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. A. CTSU IRB Certification Form.

Or

- B. HHS 310 Form.

Or

- C. IRB Approval Letter

NOTE: The above submissions must include the following details:

- Indicate all sites approved for the protocol under an assurance number.
- OHRP assurance number of reviewing IRB
- Full protocol title and number
- Version Date
- Type of review (full board vs. expedited)
- Date of review.
- Signature of IRB official

The CTSU encourages you to link to the following RSS2.0 webpage so that more information on RSS2.0 as well as the submission forms can be accessed http://www.ctsu.org/rss2_page.asp. If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail CTSUContact@westat.com. Monday through Friday, 9:00am - 6:00pm.

Patients must not start protocol treatment prior to registration.

Treatment should start within three working days after registration.

Institutions may register eligible patients to this study via the ECOG webpage 24 hours a day, 7 days a week, using the Web-based Patient Registration Program (<https://webreg.ecog.org>). If you need assistance or have questions, please telephone the Central Randomization Desk at the ECOG Coordinating Center at (617) 632-2022, Monday through Friday 9:00am – 5:00pm Eastern Time. Please note that a password is required to use this program. The following information will be requested:

4.1 Registration

NOTE: The choice of pre-operative versus post-operative chemotherapy/XRT is at the treating physician's discretion. However, the physician must declare the selected regimen at the time of registration. (See Section 5.0)

4.1.1 Protocol Number

4.1.2 Investigator Identification

4.1.2.1 Institution and affiliate name

4.1.2.2 Investigator's name

4.1.3 Patient Identification

4.1.3.1 Patient's initials and chart number

4.1.3.2 Patient's Social Security number

4.1.3.3 Patient demographics

4.1.3.3.1 Sex

4.1.3.3.2 Birth date (mm/yyyy)

4.1.3.3.3 Race

4.1.3.3.4 Ethnicity

4.1.3.3.5 Nine-digit ZIP code

4.1.3.3.6 Method of payment

4.1.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.0. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG Coordinating Center.

4.1.5 Additional Requirements

4.1.5.1 Patient must provide signed and dated written informed consent.

4.1.5.2 Physician will select and declare the regimen of chemotherapy/XRT. (See Section 5.0)

4.1.5.3 For Group I only, physician must also identify the surgical procedure to be performed. (see Section 5.7 Surgery)

4.1.5.4 The pathology materials should be submitted for correlative studies as outlined in Section 10.

4.1.5.5 [Deleted in Update #2]

4.1.6 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the instructions in the E3201 Forms Packet. Document the reason for not starting protocol treatment on one

of the baseline forms. Also report the date and type of the first non-protocol treatment that the patient receives and first progression.

4.2 Randomization

NOTE: Randomization must occur between 21 and 56 days from the date of surgery.

NOTE: Group II patients will be registered and randomized at the same time.

Institutions may register eligible patients to this study via the ECOG webpage 24 hours a day, 7 days a week, using the Web-based Patient Registration Program (<https://webreg.ecog.org>). If you need assistance or have questions, please telephone the Central Randomization Desk at the ECOG Coordinating Center 617-632-2022. Please note that a password is required to use this program. The following information will be requested:

4.2.1 Protocol Number

4.2.2 Investigator Identification

4.2.2.1 Institution name and/or affiliate

4.2.2.2 Investigator's name

4.2.3 Patient Identification

4.2.3.1 Patient's initials and chart number

4.2.3.2 Patient's Social Security Number

4.2.3.3 Patient Demographics

4.2.3.3.1 Sex

4.2.3.3.2 Birthdate (MM/YYYY)

4.2.3.3.3 Race

4.2.3.3.4 Ethnicity

4.2.3.3.5 Nine-digit zip code

4.2.3.3.6 Method of payment

4.2.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.3. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG Coordinating Center.

4.2.5 Stratification Factors

4.2.5.1 ECOG Performance Status 0 vs. 1.

4.2.5.2 Pre-operative chemotherapy/XRT vs Post-operative chemotherapy/XRT

4.2.5.3 High risk(T_3 N+ M_0 , T_4 N_{any} M_0) vs low risk (T_{1-2} N+ M_0 , T_3 N₀ M_0)

4.2.6 Additional Requirements

4.2.6.1 The samples for laboratory studies should be submitted as outlined in section 10.0.

4.2.6.2 For Group I and Group II, physician must indicate the surgical procedure performed. (See Section 5.7 Surgery)

4.2.7 Instructions for Patients Who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the forms packet

referenced in the Records to be Kept section (see Section 12.0). Document the reason for not starting protocol treatment on one of the baseline forms. Also report the date and type of the first non-protocol treatment that the patient receives.

5. Treatment Plan

Group I patients will receive concurrent chemotherapy (Section 5.1) and radiation (Section 5.5) prior to surgery. Twenty-one (21) to 56 days post-surgery, patients will be randomized to receive irinotecan/leucovorin/5-FU, oxaliplatin/leucovorin/5-FU or leucovorin/5-FU (Section 5.2).

Group 1 PS patients are registered and randomized 21 to 56 days following surgery. At randomization, patients will receive one of the following: irinotecan/leucovorin/5-FU, oxaliplatin/leucovorin/ 5-FU or leucovorin/5-FU (Section 5.2.).

Group II patients will be registered and randomized 21 to 56 days following surgery. Upon randomization, patients will receive an initial treatment cycle of irinotecan/leucovorin/5-FU, oxaliplatin/leucovorin/5-FU or leucovorin/5-FU. Concurrent chemotherapy (Section 5.1) and radiation therapy (Section 5.5) will then be administered followed by further cycles of irinotecan/leucovorin/ 5-FU, oxaliplatin/leucovorin/5-FU or leucovorin/5-FU.

5.1 Chemotherapy Regimens Allowed During Radiation Therapy

NOTE: All doses are based on actual weight

Patients will receive concurrent radiation and chemotherapy, which will consist of one of the following regimens, either pre-operatively or post-operatively. Please note that the radiation plus capecitabine regimen is open only to those patients enrolled on NSABP R-04. The radiation regimen is defined in Section 5.5.

Physicians must select and report the chosen chemotherapy regimen at the time of registration. The regimens allowed are:

XRT + continuous infusion 5-FU
FU 225 mg/m² over 24 hours 7 days/week during XRT

NOTE: Patients entered on R-04 may have been randomized to protracted venous infusion (PVI) 5-FU. Treatment with XRT and PVI 5-FU must therefore follow R-04 specifications.

XRT + 5-FU/LV
5-FU 400 mg/m² + Leucovorin 20 mg/m² for 4 days during Weeks 1 and 5 of XRT

XRT + Capecitabine
825 mg/m² PO BID throughout course of XRT (beginning 2 hours before start of XRT and ending with the last dose of XRT). **This regimen is allowed only if patient is enrolled on NSABP R-04**

5.2 Administration Schedule

NOTE: All doses are based on actual weight. Postoperative chemotherapy should begin within 8 weeks after surgery.

5.2.1 Group 1 (Preoperative Chemotherapy/XRT)

Upon registration, patients are to receive concurrent chemotherapy (Section 5.1) and radiotherapy (Section 5.5) prior to surgery. Patients will then be randomized to one of the following three treatments. Post-operative chemotherapy should begin 21 to 56 days after surgery. (Post-operative chemotherapy should begin 21 to 56 days after surgery for Group 1 PS, also.)

5.2.1.1 Arm A

Irinotecan	180 mg/m ² , IV over 90 minutes
Leucovorin	400 mg/m ² , IV over 2 hours
5-FU	400 mg/m ² , IV bolus injection immediately following leucovorin dose
5-FU	2.4 gm/m ² over 46 hours, by ambulatory infusion pump, immediately following bolus 5-FU.

A cycle is comprised of a 2-day treatment period administered every 2 weeks. Eight (8) cycles will be administered.

NOTE: Dose escalation is allowed; see section 5.4.2.

5.2.1.2 Arm B

Oxaliplatin	85 mg/m ² , IV over 120 minutes
Leucovorin	400 mg/m ² , IV over 2 hours
5-FU	400 mg/m ² , IV bolus injection immediately following leucovorin dose.
5-FU	2.4 gm/m ² over 46 hours, by ambulatory infusion pump, immediately following bolus 5-FU.

A cycle is comprised of a 2-day treatment period administered every 2 weeks. Eight (8) cycles will be administered.

NOTE: Dose escalation is allowed; see section 5.4.3.

5.2.1.3 Arm C

Leucovorin	500 mg/m ² , IV over 2 hours once a week for 6 weeks
5-FU	500 mg/m ² , IV bolus injection 1 hour after the start of the leucovorin infusion, once a week for 6 weeks

A cycle is comprised of 6 weeks of treatment followed by 2 weeks of rest. Three (3) cycles will be administered.

5.2.2 Group II (Post-operative Chemotherapy/XRT)

Patients are to be registered and randomized 21 to 56 days after surgery. Upon registration, patients will be randomized to one of the following three treatments. Concurrent chemotherapy (Section 5.1) and radiation therapy (Section 5.5) will then be administered followed by further courses of the chemotherapy assigned at randomization.

5.2.2.1 Arm D

Irinotecan	180 mg/m ² , IV over 90 minutes
Leucovorin	400 mg/m ² , IV over 2 hours
5-FU	400 mg/m ² , IV bolus injection immediately following each leucovorin dose
5-FU	2.4 gm/m ² over 46 hours by ambulatory infusion pump immediately following bolus 5-FU.

A cycle is comprised of a 2-day treatment administered every 2 weeks. Four cycles will be administered followed by concurrent pelvic XRT + chemotherapy, followed by an additional 4 cycles of irinotecan/leucovorin/5-FU.

NOTE: Dose escalation is allowed; see section 5.4.2.

NOTE: Concurrent pelvic XTR + chemotherapy should begin within 4 weeks of the completion of the first 4 cycles of chemotherapy. Four to 6 weeks after the completion of concurrent pelvic XTR + chemotherapy, the second 4 cycles of chemotherapy will be administered.

5.2.2.2 Arm E

Oxaliplatin 85 mg/m², IV over 120 minutes

Leucovorin 400 mg/m², IV over 2 hours

5-FU 400 mg/m², IV bolus injection immediately following leucovorin dose.

5-FU 2.4 gm/m² over 46 hours, by ambulatory infusion pump, immediately following bolus 5-FU.

A cycle is comprised of a 2-day treatment period administered every 2 weeks. Four cycles will be administered followed by concurrent pelvic XRT + chemotherapy, followed by an additional 4 cycles of oxaliplatin/leucovorin/5-FU.

NOTE: Dose escalation is allowed; see section 5.4.3.

NOTE: Concurrent pelvic XTR + chemotherapy should begin within 4 weeks of the completion of the first 4 cycles of chemotherapy. Four to 6 weeks after the completion of concurrent pelvic XTR + chemotherapy, the second 4 cycles of chemotherapy will be administered.

5.2.2.3 Arm F

Leucovorin 500 mg/m², IV over 2 hours once a week for 6 weeks

5-FU 500 mg/m², IV bolus injection one hour after the start of the leucovorin infusion, once a week for 6 weeks

A cycle is comprised of 6 weeks of treatment followed by 2 weeks of rest. One cycle will be administered followed by concurrent pelvic XRT + chemotherapy followed by an additional 2 cycles of leucovorin/5-FU.

NOTE: Concurrent pelvic XTR + chemotherapy should begin within 4 weeks of the completion of the first cycle of chemotherapy. Four to 6 weeks after the completion of concurrent pelvic XTR + chemotherapy, the final 2 cycles of chemotherapy will be administered.

5.3 Dose Specifics

5.3.1 Dose Specifics (Arms A and D) –Groups I, I PS, and II

5.3.1.1 Irinotecan

The starting dose of irinotecan will be 180 mg/m² (infused over 90 minutes) given once every 2 weeks.

For the first 2 cycles of irinotecan, patients should remain in the treatment area for a minimum of one hour following completion of irinotecan infusion in case acute abdominal cramping develops.

5.3.1.2 Leucovorin

The dose of leucovorin will remain fixed at 400 mg/m², administered over two hours and may be given during the irinotecan infusion.

5.3.1.3 5-Fluorouracil

The starting dose of 5-FU will be 400 mg/m², given as an intravenous bolus injection immediately following leucovorin dose.

The starting dose of continuous infusion 5-FU is 2.4 grams administered over 46 hours using an ambulatory infusion pump to begin immediately following bolus 5-FU.

5.3.2 Dose Specifics (Arms B and E) – Groups I, I PS and II

5.3.2.1 Oxalplatin

The starting dose of oxaliplatin will be 85 mg/m² (infused over 2 hours) given once every two weeks.

5.3.2.2 Leucovorin

The dose of leucovorin will remain fixed at 400 mg/m² and administered over 2 hours

5.3.2.3 5-Fluorouracil

The starting dose of 5-FU will be 400 mg/m², given as an intravenous bolus injection immediately following leucovorin dose.

The starting dose of continuous infusion 5-FU is 2.4 grams administered over 46 hours using an ambulatory infusion pump to begin immediately following bolus 5-FU.

5.3.3 Dose Specifics (Arms C and F) – Groups I, I PS and II

5.3.3.1 Leucovorin

500 mg/m² diluted in 250 cc of normal saline and administered IV as a 2 hour infusion weekly for six consecutive weeks followed by a two week rest period.

5.3.3.2 5-FU

500 mg/m² administered bolus IV one hour after the start of the leucovorin infusion, weekly for six weeks followed by two weeks rest.

5.4 Dose Modifications

NOTE: All toxicities should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) (version 3.0).

5.4.1 Dose Modifications for Combined Chemotherapy and Radiation - Group I (Pre-Op) and Group II (Post-Op)

NOTE: Dose Modifications for Radiation Toxicity: Refer to Section 5.58.

NOTE: All patients who are randomized on NSABP R-04 and receive capecitabine or continuous infusion 5-FU must follow dose mods as written in R-04

NOTE: If toxicities have not resolved within 3 weeks, the patient's protocol treatment will be discontinued.

Patients must have WBC \geq 3500/ μ l and platelet count \geq 100,000/ μ l prior to initiation of combined XRT-continuous infusion 5-FU. Dose modification should be based upon worst grade of toxicity experienced.

5.4.1.1 Concurrent XRT and Continuous Infusion 5-FU

5.4.1.1.1 Hematologic Toxicities

WBC (/ μ l)	Platelets (/ μ l)	Modification
< 2000	< 50,000	Hold until WBC \geq 2000 and PLT \geq 50,000; resume at full dose

5.4.1.1.2 Stomatitis or Diarrhea

Grade	Toxicities/Symptoms	Modification
1		Continue current dose level
≥ 2	Mucositis, stomatitis or esophagitis	Hold** until \leq grade 1 and decrease dose by 50 mg/m ² /d
≥ 3	Diarrheas \geq 7 stools/day above baseline	Hold** until \leq grade 1; resume at same dose

** In the event of a dose "hold", the central venous catheter should be flushed daily to prevent catheter occlusion.

5.4.1.2 Concurrent XRT and Bolus 5-FU/Leucovorin

If radiation therapy is delayed, the chemotherapy should be similarly delayed so that chemotherapy is always given during the first and fifth week of radiation therapy. Different drug modifications will be made depending on whether the toxicity is the maximum seen during the interval between the two doses of chemotherapy or the toxicity at the time of delivery of the second dose of chemotherapy (with week 5 radiation therapy).

Maximum toxicity during interval between courses of 5-FU given during radiation therapy:

5.4.1.2.1 Hematologic Nadirs

WBC (/ μ l)	Platelets (/ μ l)	Modification
1000-2500	25,000-75,000	Reduce by 20%
< 1000	< 25,000	Reduce by 30%

5.4.1.2.2 Stomatitis or Diarrhea

Grade	Toxicities/Symptoms	Modification
≥ 1		Continue current dose level
2	Stomatitis	Reduce by 20%
3	Diarrhea Stomatitis	Reduce by 20% Reduce by 30%
4	Diarrhea/Stomatitis	Reduce by 30%

Toxicity at time of second dose of chemotherapy during radiation therapy:

5.4.1.2.3 Hematologic Toxicities

WBC (/ μ l)	Platelets (/ μ l)	Modification
< 3500	< 75,000	Do not administer 2 nd course

5.4.1.2.4 Stomatitis or Diarrhea

Grade	Toxicities/Symptoms	Modification
2-4	Stomatitis	Do not administer 2 nd course
2*-4	Diarrhea	Delay chemotherapy with radiation therapy delay until diarrhea returns to Grade 1. Reinitiate XRT and chemotherapy with appropriate 5-FU dose reductions after diarrhea resolution.

* Grade 2 diarrhea with loose, watery bowel movements.

5.4.2 Dose Modifications – Arms A and D (Groups I & II)

The final dose modification according to the following tables should be made based upon the worst grade of toxicity experienced. Note that the leucovorin dose remains constant and without modification. IF patients require dose reductions lower than level -2, protocol therapy will be discontinued.

	Irinotecan (mg/m ²)	Leucovorin (mg/m ²)	Bolus 5-FU (mg/m ²)	Infusion 5-FU (mg/m ²)
Level +1	180	400	400	3
Starting Dose**	180	400	400	2.4
Level -1	150	400	320	2
Level -2	90	400	200	2*

* In case of hand-foot syndrome, the dose of infusional 5-FU, only, may be further reduced 20% as needed.

** All patients will start cycle 1 with doses list in the "starting dose" row.

Dose escalation to “dose level +1” should be performed if the following conditions are met: the full course of cycle 1 must have been associated with no greater than grade 1 diarrhea and/or neutropenia and cycle 1 did not require omission of a dose or dose reduction. Any dose reduction is continued for all subsequent cycles. Dose re-escalation on Arms A and D is not allowed following a dose reduction.

5.4.2.1 Neutropenia and Other Hematologic Toxicities

Grade	ANC1 (/mm ³)		Platelets ¹ (/mm ³)	Modification
1	≥ 1500	Or	≥ 75,00	Continue current dose level
2	≥ 1000 - <1500	Or	≥ 50,000- <75,000	Hold until ≤ grade 1 and decrease dose level
≥ 3	<1000	Or	<50,000	Hold until ≤ grade 1 and decrease 2 dose levels

¹ Within 24 hours of day of treatment

5.4.2.2 Diarrhea

Grade	Without colostomy ¹	With colostomy ¹	Modification ²
1	Increase of < 4 stools/day over baseline	Mild increase in loose, watery colostomy output compared with pretreatment	Continue current dose level
2	Increase of 4-6 stools per day from baseline or nocturnal stools	Moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	Hold until ≤ grade 1 and decrease 1 dose level
3	Increase of 7 or more stools per day from baseline or incontinence or need for parenteral support	Severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	Hold until ≤ grade 1 and decrease 1 dose level
4	Physiologic consequences requiring intensive care or hemodynamic collapse	Physiologic consequences, requiring intensive care; or hemodynamic collapse	Hold until ≤ grade 1 and decrease 2 dose levels

¹ Within 24 hours of day of treatment

² Any dose reduction is continued for all subsequent cycles. Dose re-escalation on Arms A and D is not allowed following a dose reduction.

See Section 5.4.5 for the treatment of diarrhea.

5.4.2.3 All Other Toxicities

All other toxicities should be managed by grade according to the modifications described for diarrhea in section 5.4.2.2.

5.4.2.4 Adjustments to Treatment Schedule Following the 'Withhold' of Treatment for Toxicity

In order to maintain dose intensity, the schedule of treatment should be adjusted for any treatment days that are withheld, such that no dose is ever omitted from the schedule.

5.4.3 Dose Modifications – Arms B and E (Groups I andII)

The final dose modification according to the following tables should be based upon the worst grade of toxicity experienced. If patients require dose reductions lower than level-2, protocol therapy will be discontinued. Any dose reduction is continued for all subsequent cycles. Dose re-escalation on Arms B and E is not allowed following a dose reduction. Note that leucovorin dose remains constant and without modification.

	Oxalplatin (mg.m ²)	Leucovorin (mg/m ²)	Bolus 5-FU (mg/m ²)	Infusional 5-FU (gm/m ²)
Level +1	100	400	400	3
Starting Dose**	85	400	400	2.4
Level –1	65	400	320	2
Level –2	50	400	200	2*

* In case of hand foot syndrome, the dose of infusional 5-FU may be further reduced by 20% as needed.

** All patients will start cycle 1 with doses listed in the "Starting Dose" row.

Dose escalation to level +1 is allowed following cycle 1, provided the following criteria are met:

- 1) Cycle was tolerated with diarrhea, neutropenia and thrombocytopenia no worse than grade 1
- 2) The start of cycle 2 did not require a delay.

5.4.3.1 Neutropenia and Other Hematologic Toxicities

Grade	ANC1 (/mm ³)		Platelets ¹ (/mm ³)	Modification
1	≥ 1500	Or	≥ 75,00	Continue current dose level
2	≥ 1000 - <1500	Or	≥ 50,000- <75,000	Hold until ≤ grade 1 and decrease dose level
≥ 3	<1000	Or	<50,000	Hold until ≤ grade 1 and decrease 2 dose levels

¹ Within 24 hours of day of treatment

5.4.3.2 Diarrhea

Grade	Without colostomy ¹	With colostomy ¹	Modification ²
1	Increase of < 4 stools/day over baseline	Mild increase in loose, watery colostomy output compared with pretreatment	Continue current dose level
2	Increase of 4-6 stools per day from baseline or nocturnal stools	Moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	Hold until \leq grade 1 and decrease 1 dose level
3	Increase of 7 or more stools per day from baseline or incontinence or need for parenteral support	Severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	Hold until \leq grade 1 and decrease 1 dose level
4	Physiologic consequences requiring intensive care or hemodynamic collapse	Physiologic consequences, requiring intensive care; or hemodynamic collapse	Hold until \leq grade 1 and decrease 2 dose levels

¹ Within 24 hours of day of treatment

See Section 5.4.5 for the treatment of diarrhea.

5.4.3.3 Dose Modifications for Neurologic Toxicity of Oxaliplatin

Toxicity (Grade)	Duration of Toxicity	Duration of Toxicity	Persistent Between Doses ²
	1-7 Days	> 7 Days	
Paresthesias/dysesthesias ¹ of short duration that resolve and do not interfere with function (Grade 1)	No change	No change	No change
Paresthesias/dysesthesias ¹ interfering with function, but not activities of daily living (ADL) (Grade 2)	No change	No change	Reduce oxaliplatin 1 dose level
Paresthesias/dysesthesias ¹ with pain or with functional impairment that also interferes with ADL (Grade 3)	1 st time: reduce oxaliplatin 1 dose level 2 nd time: reduce oxaliplatin another dose level	1 st time: reduce oxaliplatin 1 dose level 2 nd time: reduce oxaliplatin another dose level	Discontinue protocol therapy
Persistent Paresthesias/dysesthesias ¹ that is disabling or life-threatening (Grade 4)	Discontinue protocol therapy	Discontinue protocol therapy	Discontinue protocol therapy
Pharyngo-laryngeal dysesthesias			
Grade 1 (mild)	No change	Increase duration of infusion to 6 hours	Increase duration of infusion to 6 hours
Grade 2 (moderate) and Grade 3 (severe). Management of grade 2-3 pharyngo-laryngeal dysesthesias occurs while treatment is being administered	-Stop oxaliplatin infusion -Administer benzodiazepine and give patient reassurance. -At the discretion of the investigator, the infusion can be restarted at 1/3 the original rate of infusion	Discontinue oxaliplatin permanently	Discontinue oxaliplatin permanently

¹ May be cold-induced

² Not resolved by the beginning of the next cycle.

NOTE: See Appendix VI for a comparative table outlining the differentiation of platinum hypersensitivity from toxicity unique to oxaliplatin and pharmacologic dysesthesias.

5.4.3.4 Hemolytic Uremic Syndrome

There have been several reports of hemolytic uremic syndrome (HUS) associated with oxaliplatin use. The hemolytic uremic syndrome should be suspected in individuals who experience the following unexplained severe hemolysis, hemoglobinemia, and renal failure as demonstrated by an increase in serum creatinine.

Oxaliplatin should be discontinued permanently for any suspected occurrence of hemolytic uremic syndrome.

Patients suspected of experiencing HUS must have the following laboratory analyses conducted:

Creatinine, BUN
Urinalysis with microscopic evaluation
CBC with differential and platelets
PT/PTT
Fibrinogen, Fibrinogen Degradation Products (FDP)
Anti-thrombin III (ATIII)
von Willebrand Factor (VWF)
Anti-nuclear antibodies (ANA)
Rheumatoid Factor (RhF)
C3, C4, CH50
Anti-platelet antibodies
Platelet associated IgG
Circulating immune complexes

5.4.3.5 Pulmonary Fibrosis

There have been reports of pulmonary fibrosis associated with oxaliplatin use. Patients receiving oxaliplatin should be instructed to promptly report any respiratory difficulties

Pulmonary toxicities of grade 3 or worse will require that oxaliplatin be withheld until resolved to grade 1 or less. Signs and symptoms associated with pulmonary fibrosis (cough, dyspnea, rales, hypoxia and tachypnea) should be investigated to rule out pulmonary fibrosis as their cause. The investigation for pulmonary fibrosis should include (but not be limited to): chest radiography, oxygen saturation by pulse oximetry or arterial blood gas evaluation and pulmonary function testing to include DLCO.

The diagnosis of pulmonary fibrosis will result in the discontinuation of oxaliplatin. These patients may continue to receive fluorouracil and leucovorin.

5.4.3.6 All Other Toxicities

All other toxicities should be managed by grade according to the modifications described for diarrhea in section 5.4.3.2.

5.4.3.7 Adjustments to Treatment Schedule Following the 'Withhold' of Treatment for Toxicity

In order to maintain dose intensity, the schedule of treatment should be adjusted for any treatment days that are withheld, such that no dose is ever omitted from the schedule.

5.4.4 Dose Modifications- Arms C and F (Groups I & II)

The final dose modification according to the following tables should be made based upon the worst grade of toxicity experienced. Note that the leucovorin dose remains constant and without modification.

5.4.4.1 Neutropenia and Other Hematologic Toxicities

Grade	ANC1 (/mm ³)		Platelets ¹ (/mm ³)	Modification ²
1	≥ 1500	Or	≥ 75,000	Continue current dose level
2	≥ 1000 - <1500	Or	≥ 50,000- <75,000	Hold until ≤ grade 1 then resume 5-FU at a 100mg/m ² dose reduction to complete the cycle. ^{3,4}
≥ 3	<1000	Or	<50,000	Hold for at least 3 weeks from last dose and < grade 1 then resume 5-FU at a 100mg/m ² dose reduction to complete the cycle. ^{3,4}

¹ Within 24 hours of day of treatment

² Leucovorin dose remains fixed at 500mg/m².

³ If occurs after week 4 of any cycle, begin the rest period.

⁴ 5-FU dose re-escalation in subsequent cycles will be allowed at 100mg/m² increments per cycle.

5.4.4.2 Diarrhea, Vomiting, Stomatitis

Grade ¹	Modification ²
1	Hold until resolved, then resume 5-FU at a 100mg/m ² dose reduction to complete the cycle. ^{3,4}
2	Hold for at least 2 weeks AND until resolved, then resume the 5-FU at a 100mg/m ² dose reduction to complete the cycle. ^{3,4}
3 and 4	Discontinue protocol therapy and initiate appropriate supportive care.

¹ Within 24 hours of day of treatment

² Leucovorin dose remains fixed at 500mg/m².

³ If occurs after week 4 of any cycle, begin the rest period.

⁴ 5-FU dose re-escalation in subsequent cycles will be allowed at 100mg/m² increments per cycle.

See Section 5.4.5 for diarrhea control

5.4.4.3 All other toxicities

All other toxicities should be managed by grade according to the modifications described for hematologic toxicity in Section 5.4.4.

5.4.5 Management of Gastrointestinal Toxicity (All Patients)

Patients will be instructed to begin taking loperamide at the earliest signs of a poorly formed or loose 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 the patient is diarrhea-free for at least 12 hours. Patients may take loperamide 4 mg (2 capsules) every four hours during the night. If there is no relief within 24-36 hours, add deodorized Tincture of Opium 4 drops in 1/4 to 1/2 cup of bland liquid or juice every 4 hours around the clock. In addition, begin oral fluoroquinolone and continue for 7 days.

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If diarrhea persists for greater than 48 hours, parenteral hydration is recommended (including hospitalization for such). Oral fluoroquinolone treatment also should be initiated for patients who develop an ANC $\leq 500\text{mm}^3$ (even in the absence of fever or diarrhea) or a fever that occurs with diarrhea (even without neutropenia). Antibiotics should continue until resolution of diarrhea. (Refer to Appendix IX, Diarrhea Management Instructions.)

Diarrhea or abdominal cramping that occurs during or within one hour after receiving irinotecan can be treated with atropine (0.25 to 1 mg IV as indicated). Patients having recurrent problems with cholinergic symptoms may receive atropine prophylactically (SC or IV). Additional antidiarrheal measures may be used at the discretion of the treating physician.

Patients who experience diarrhea during treatment may benefit from dietary modification and/or consultation with a clinical dietitian. Examples of foods which may exacerbate diarrhea include milk, ice cream, whole bran bread and cereal, nuts, seeds, fried or fatty foods, fresh and dried fruit, prune juice, raw vegetables, popcorn, potato chips, chocolate, coffee, teas, alcoholic beverages and cooked fruits and vegetables with seeds or skins such as berries, corn and tomatoes. Foods which may mitigate problems with diarrhea include fish, poultry and meat that is cooked, broiled or roasted, bananas, apple sauce, peeled apples, white bread, macaroni and noodles, baked, boiled or mashed potatoes, cooked vegetables that are mild, such as asparagus tips, green and waxed beans, carrots, spinach, squash, mild processed cheese, eggs and smooth peanut butter.

5.4.6 Dose Modification for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by (1) the patient's BSA as calculated from actual weight or (2) actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with administering chemotherapy dose based on actual body weight should not enroll obese patients.

5.4.7 Interruption of Chemotherapy for Reasons Other Than Toxicity

Closure of Colostomy: The time for closure of the colostomy will be at the discretion of the surgeon and should be arranged to minimize time off chemotherapy. Closure of colostomy following completion of chemotherapy is encouraged. The total number of cycles should be retained.

5.5 Radiation Therapy

All patients will receive a total of 50.4 Gy external beam radiation therapy at 1.8 Gy per fraction per day for 28 fractions over a total of 5 1/2 weeks. Pelvic fields will receive 45 Gy in 25 fractions, followed by a boost of 5.4 Gy in 3 fractions. Intraoperative radiation therapy and/or brachytherapy are strictly prohibited.

The Quality Assurance Review Center (QARC) will perform a Final Review at the completion of radiation therapy. Please see sections 5.5.11, 12.3 and Appendix IV for the quality assurance documentation requirements.

Standard and conformal techniques will be allowed in this study. Institutions using conformal techniques must complete a 3D benchmark. The benchmark materials may be obtained from the QARC website (www.QARC.org) and must be submitted to QARC prior to final review.

5.5.1 Patient Positioning and Setup/Treatment Planning and Verification

Multiple fields technique (usually either 3 fields with a posterior and 2 lateral fields with wedges or 4 fields with anterior, posterior and 2 lateral fields) is mandatory. Custom shielding is mandatory to exclude as much small bowel as possible. Prone position is recommended, and “belly-drop” devices should be considered. It is recommended that the buttocks be taped apart to decrease self-bolus effect. It is also recommended that patients be treated with a full bladder. They should be instructed to void 1 hour before XRT and immediately drink 16 ounces of a non-caffeinated beverage and then not void until after treatment is complete for that day. All fields must be treated daily.

As part of the treatment planning process, all patients will undergo simulation for all fields to be treated with a machine that duplicates the geometry of the actual treatment machine. Conventional simulation or the use of CT based simulation linked to software that allows “virtual simulation” are both allowed as long as the simulation process provides for duplication of the geometry of the actual treatment machine. It is recommended that oral gastrointestinal contrast material be given between 1 and 2 hours prior to simulation to facilitate definition of the small bowel, so that as much as possible of this normal structure can be shielded. At the time of simulation, barium or other contrast materials should be placed in the rectum. The anal verge should be marked with a radio-opaque marker.

5.5.2 Target Volume – Initial Fields

5.5.2.1 Preoperatively Irradiated Patients

The target volume will include the entire tumor and nodal groups at risk for metastatic disease. This will include the internal iliac and pre-sacral lymph nodes. The external iliac nodes will be included when tumors extend to the uterus, cervix, vagina, bladder or prostate. Exclusion of as much bowel as possible through the use of custom shielding is required.

5.5.2.2 Postoperatively Irradiated Patients

The target volume will include the entire preoperative tumor and nodal groups at risk for metastatic disease. Determination of the preoperative tumor volume will be based on findings from preoperative and intraoperative evaluations, including preoperative endoscopy studies, preoperative imaging studies (such as CT scans or barium enema), the operative note and the pathology report. Clips placed by the surgeon to mark the tumor bed may also be used for determining the preoperative tumor volume. This will include the internal iliac and pre-sacral lymph nodes. The external iliac nodes will be included for tumors that extended to the uterus, vagina, bladder or prostate. Exclusion of as much bowel as possible through the use of custom shielding is required.

5.5.3 PA and AP Fields

5.5.3.1 PA and AP Fields in Preoperatively Irradiated Patients

The superior border of the fields will extend at least 3 cm superior to the tumor, and will be no lower than L5-S1 interspace. The inferior border will be at least 2 cm distal to the tumor. The lateral border of the fields will be at least 1.5 cm lateral to the greater sciatic notch on each side. Customized blocking is recommended for all fields. Blocks will provide at least 3 cm margin around the tumor. Superiorly, the blocks will be on or lateral to the sacroiliac joints. Inferiorly, the blocks will be on or lateral to a line connecting the ischial tuberosities to the field edge at the widest

separation of the pelvis at the level of the greater sciatic notch. As outlined in Section 5.5.1, AP fields need not be used in patients treated with PA and lateral fields.

5.5.3.2 PA and AP Fields in Postoperatively Irradiated Patients

5.5.3.2.1 PA and AP Fields for Postoperatively Irradiated Patients Who Have Had An Anterior Resection

The superior border of the fields will extend at least 3 cm superior to the tumor bed, and will be no lower than L5-S1 interspace. The inferior border will be at least 2 cm distal to the tumor bed. The lateral border of the fields will be at least 1.5 cm lateral to the greater sciatic notch on each side. Customized blocking is recommended for all fields. Blocks will provide at least 3 cm margin around the tumor bed. Superiorly, the blocks will be on or lateral to the sacroiliac joints. Inferiorly, the blocks will be on or lateral to a line connecting the ischial tuberosities to the field edge at the widest separation of the pelvis at the level of the greater sciatic notch. As outlined in Section 5.5.1, AP fields need not be used in patients treated with PA and lateral fields.

5.5.3.2.2 PA and AP Fields For Postoperatively Irradiated Patients Who Have Had An Abdominal Perineal Resection

The superior border of the fields will extend at least 3 cm superior to the tumor bed, and will be no lower than L5-S1 interspace. The inferior border will include the entire perineal scar. It is recommended that the perineal scar be identified with radio-opaque markers prior to simulation to assist with identification and inclusion in the RT field. The lateral border of the fields will be at least 1.5 cm lateral to the greater sciatic notch on each side. Customized blocking is recommended for all fields. Blocks will provide at least 3 cm margin around the tumor bed. Superiorly, the blocks will be on or lateral to the sacroiliac joints. Inferiorly, the blocks will be on or lateral to a line connecting the ischial tuberosities to the field edge at the widest separation of the pelvis at the level of the greater sciatic notch.

5.5.4 Lateral Fields

5.5.4.1 Lateral Fields For Preoperatively Irradiated Patients

The superior and inferior borders of the lateral fields will be the same as the AP-PA fields. The posterior border/blocking will provide for a margin of at least 1.5 cm on the anterior sacrum. The anterior border/blocking will extend at least 2.5 cm anterior to the tumor and will also include the internal iliac nodes. In most patients, this will mean that the anterior border is such that the anterior half to one-third of the femoral heads lie anterior to the anterior border of the lateral RT field. In patients at risk for external iliac lymph node involvement, because of involvement of the bladder, prostate, vagina, cervix or uterus, the field will extend to the anterior symphysis pubis, to allow for inclusion of the external iliac lymph nodes.

5.5.4.2 Lateral Fields For Postoperatively Irradiated Patients

5.5.4.2.1 Lateral Fields For Postoperatively Irradiated Patients Who Have Had An Anterior Resection:

The superior and inferior borders of the lateral fields will be the same as the AP-PA fields. The posterior border/blocking will provide for a margin of at least 1.5 cm on the anterior sacrum. The anterior border/blocking will extend at least 2.5 cm anterior to the tumor bed and will also include the internal iliac nodes. In most patients, this will mean that the anterior border is such that the anterior half to one-third of the femoral heads lie anterior to the anterior border of the lateral RT field. In patients at risk for external iliac lymph node involvement, because of involvement of the bladder, prostate, vagina, cervix or uterus, the field will extend to the anterior symphysis pubis, to allow for inclusion of the external iliac lymph nodes.

5.5.4.2.2 Lateral Fields For Postoperatively Irradiated Patients Who Have Had An Abdominal Perineal Resection

The superior and inferior borders of the lateral fields will be the same as the AP-PA fields. The inferior border and the posterior border will include the entire perineal scar. It is recommended that the perineal scar be identified with radio-opaque markers prior to simulation to assist with identification and inclusion in the RT field. The posterior border/blocking will also provide for a margin of at least 1.5 cm on the anterior sacrum. The anterior border/blocking will extend at least 2.5 cm anterior to the tumor bed and will also include the internal iliac nodes. In most patients, this will mean that the anterior border is such that the anterior half to one-third of the femoral heads lie anterior to the anterior border of the lateral RT field. In patients at risk for external iliac lymph node involvement, because of involvement of the bladder, prostate, vagina, cervix or uterus, the field will extend to the anterior symphysis pubis, to allow for inclusion of the external iliac lymph nodes.

5.5.5 Target Volume-Boost Fields

After a dose of 45 Gy is delivered to the pelvic field, the fields will be reduced to include the primary tumor (or tumor bed, for postoperatively irradiated patients) with a minimum 2 cm margin in all directions. Exclusion with custom shielding of as much of small bowel (defined by oral contrast) as possible is strongly encouraged. The boost fields will be given a dose of 5.4 Gy at 1.8 Gy/fraction. The total cumulative dose delivered within the boost fields will be to a total dose of 50.4 Gy in 28 fractions. Patients may be treated with opposed fields or a multiple field technique during the boost phase of treatment.

5.5.6 Equipment

5.5.6.1 Modality: X-rays with nominal energy of 4 MV or greater. The minimum allowable treatment distance is 80 cm SAD. Co-60 is not allowed on this study.

5.5.6.2 Calibration: The calibration of therapy machines used in this protocol shall be verified by the Radiological Physics Center (RPC).

5.5.7 Target Dose

5.5.7.1 Prescription Point: The prescription point is at or near the isocenter.

5.5.7.2 Dose Definition: Dose is specified in cGy to muscle.

5.5.7.3 Tissue Heterogeneity: Density corrections are not required, however, inhomogeneity correction for air or bone attenuation may be applied. This is optional and would typically be in the setting of CT-based treatment planning where radiation dose distributions and treatment calculations are automatically generated based upon the CT densities of the treatment-planning scan.

5.5.7.4 Prescribed Dose and Fractionation: Initial fields will be given 45 Gy at 1.8 Gy per day. The boost fields will receive 5.4 Gy at 1.8 Gy per day.

5.5.7.5 Dose Uniformity: The dose variation in the PTV will be +7% and -5% of the prescription point dose. This applies to all photon treatment techniques. Wedges, compensators, and other methods of generating a uniform dose distribution are encouraged.

5.5.7.6 Therapy Interruptions: Interruptions that are required because of RT or chemotherapy-related toxicity or major holidays shall not result in protocol violation. Interruptions that are due to a major intervening illness (for example, myocardial infarction) shall not result in protocol violation. Interruptions for other reasons that prolong treatment by 5-8 days shall constitute a minor protocol deviation, and interruptions for other reasons that prolong treatment by 9 or more treatment days shall constitute a major protocol deviation. Because it is not possible to anticipate every interruption that may be required during a course of RT, the principle radiation therapy investigator will be given discretion to *not* assess a protocol violation for interruptions for toxicity other than those described in section 5.5.8.1, if such interruption is felt to be in the best interest of the patient.

5.5.8 Radiation Toxicity

5.5.8.1 Chemoradiation will be interrupted for Grade 3 acute skin, hematologic or GU toxicity or diarrhea, as defined in the Common Toxicity Criteria (version 2.0).

5.5.8.2 In the event of such an interruption, chemoradiation can resume when there is recovery to Grade 2 or less toxicity. (See Section 5.4 for chemotherapy dose modifications.)

5.5.9 Normal Tissue Sparing

As previously described, every effort must be made to limit the dose to the small bowel. It is expected that portions of the bladder will receive full dose.

5.5.10 Dose Calculation and Reporting

If conformal techniques are used to treat patients on this study, a 3D benchmark needs to be completed and submitted to QARC.

5.5.10.1 Prescription Point: The monitor units required to deliver the prescribed dose to the prescription point shall be calculated and submitted.

- 5.5.10.2 Dose Uniformity: The maximum and minimum doses in the PTV shall be calculated and reported. These may be extracted from isodose distributions, calculated separately or derived from DVH's.
- 5.5.10.3 Reference Point: The daily dose reference point calculated on this study is the isocenter. The total dose to this point shall be calculated and reported.
- 5.5.10.4 Isodose Distribution: For 2-D plans a color isodose plot of the dose distribution in a transverse plane through the prescription point (isocenter) shall be submitted. The prescription point and the outlines of the planning target volume and critical organs shall be shown. Isodose values must be clearly labeled. The effects of shielding blocks shall be included.

For volume based treatment planning, a color hard copy isodose distribution for the total dose plan in the axial, sagittal, and coronal planes, which includes the isocenter of the planning target volume (PTV) must be submitted. If sagittal and coronal planes are not available, then five axial distributions may be submitted (central axis, two superior and two inferior planes). These dose distributions must include the following:

A sufficient number of isodose contours should be shown to determine that the dose distribution conforms to the protocol guidelines. These isodoses should be superimposed over treatment planning CT or MR images. However, if such hard copy presents difficulty, similar plots without the gray scale image are acceptable if enough critical contours are identifiable to verify the dose distribution to target volumes and critical normal structures. Specifically, include those volumes for which there are dose volume histograms.

5.5.11 QA Documentation

Data should be forwarded to:

Quality Assurance Review Center
272 West Exchange Street, Suite 101
Providence, Rhode Island 02903-1025
Telephone 401-454-4301
FAX 401-454-4683

- 5.5.11.1 For standard planning techniques, submit the following within 1 week of the completion of radiotherapy.

NOTE: Materials listed below for Group I PS must be submitted within 1 week of randomization.

- Copy of Appendix IV: Checklist For Submission of Radiation Oncology QA Materials
- Prescription Sheet for Entire Treatment
- Completed Daily Treatment Record
- Preoperative imaging studies: CT with contrast and barium enema (if available).
- Copies of the planning CT and/or the diagnostic imaging utilized in defining the gross target volume.
- Copies of simulator films and /or digitally reconstructed radiographs (DRR's) for each field.
- Copies of verification (portal) films (or hard copy of real time portal images) for each field.

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- Photographs of the patient in the treatment position with the fields marked.
- Copies of worksheets and/or printouts used for calculations of monitor units and for calculating the dose to normal structures.
- Color copies of isodose distributions to demonstrate that the dose variation is within specification. The target volume, and the prescription point must be clearly shown. (See Section 5.5.10.4)

5.5.11.2 For 3D conformal treatment planning submit the following within 1 week of the completion of radiotherapy.

NOTE: Materials listed below for Group I PS must be submitted within 1 week of randomization.

- Copy of Appendix IV: Checklist For Submission of Radiation Oncology • QA Materials
- Prescription Sheet for Entire Treatment
- Partial Daily Treatment Record
- Preoperative imaging studies: CT with contrast and barium enema (if available).
- Copies of the planning CT and/or the diagnostic imaging utilized in defining the gross target volume.
- Copies of simulator films and /or digitally reconstructed radiographs (DRR's) for each field.
- Copies of verification (portal) films (or hard copy of real time portal images) for each field.
- Photographs of the patient in the treatment position with the fields marked.
- Copies of worksheets and/or printouts used for calculations of monitor units and for calculating the dose to normal structures.
- Complete description of each portal, including energy, gantry, couch, and collimator position, wedge description (if used), and equivalent field size.
- One set of orthogonal anterior/posterior and lateral films for isocenter localization for each group of concurrently treated beams. If portals being submitted contain an orthogonal set, this is sufficient.
- Beam's Eye Views (BEV's) for all fields and showing the PTV and critical structures. BEV hard copies must be in color to enable reviewers to identify structures.
- A room view display of all fields should be submitted.
- Dose volume histograms for the total treatment of the PTV and normal critical structures.
- Color hard copy isodose distributions for the total dose plan in the axial, sagittal, and coronal planes, which includes the isocenter of the planning target volume. The target volume, critical structures, and the prescription point must be clearly shown. (See Section 5.5.10.4)

5.5.11.3 Questions regarding the dose calculations or documentation should be directed to:

ECOG Protocol Dosimetrist
Quality Assurance Review Center
272 West Exchange Street, Suite 101
Providence, RI 02903-1025

5.5.11.4 Questions regarding the radiotherapy section of this protocol should be directed to:

James Martenson Jr., MD
Charlton Building, Desk R
Mayo Clinic/Rochester
Rochester MN 55905
Phone: 507-284-4561
Fax: 507-284-0079

5.5.12 Definitions of Deviations in Protocol Performance:

Prescription Dose:

Minor Deviation: The dose to the prescription point differs from that in the protocol by between 6% and 10%.

Major Deviation: The dose to the prescription point differs from that in the protocol by more than 10%.

Dose Uniformity:

Minor Deviation: The variation of dose in one of the target volumes exceeds +7% and –5% of the dose to the planning target volume.

Treatment Interruptions:

Minor Deviation: Total duration of treatment more than 5-8 days longer than protocol specifications (excluding interruptions for major holidays, toxicity or major intervening illness, as per section 5.5.7.6).

Major Deviation: Total duration of treatment more than 8 days longer than protocol specifications (excluding interruptions for major holidays, toxicity or major intervening illness, as per section 5.5.7.6).

Volume:

Minor Deviation: Margins less than specified or fields excessively large as deemed by the study.

Major Deviation: Transection of tumor (GTV) or potentially.

5.6 Assessment of Bowel Function

5.6.1 Assessment of Bowel Function in Preoperatively Irradiated Patients (Group I)

Bowel function will be measured in preoperatively irradiated patients, using the Patient Bowel Function/Uniscale Questionnaire and the FACT Diarrhea Subscale, completed at the following time-points:

1. Prior to radiation therapy (baseline)
2. During the last week of radiation therapy
3. Immediately prior to surgery
4. 18 ± 2 months following completion of radiation therapy

If a patient is not assessed due to a non-functioning rectum, please report this to the ECOG data center, using the QOL Assessment Compliance Form. **This information is only to be collected in patients with a functioning rectum, i.e. do not collect it in patients with a colostomy, permanent or temporary.**

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5.6.1.1 Assessment of Bowel Function in Preoperatively Irradiated Patients (Group IPS)

Patients who joined study post-surgery (Group II) will complete the Patient Bowel Function /Uniscale Questionnaire and the FACT Diarrhea Subscale at the following time-points:

1. Time of registration/randomization (baseline)
2. 18 ± 2 months following completion of radiation therapy

This information is only to be collected in patients with a functioning rectum, i.e. do not collect it in patients with a colostomy, permanent or temporary. If a patient is not assessed due to a non-functioning rectum, please report this to the ECOG data center, using the QOL Assessment Compliance Form.

5.6.2 Assessment of Bowel Function in Postoperatively Irradiated Patients (Group I PS)

Bowel function will be measured in postoperatively irradiated patients, using the Patient Bowel Function/Uniscale Questionnaire and the FACT Diarrhea Subscale completed at the following time-points:

1. Prior to surgery (if possible)
2. Prior to beginning adjuvant postoperative chemotherapy (baseline)
3. Immediately prior to starting radiation therapy (RT)
4. During the last week of RT
5. 18 ± 2 months following completion of RT

This information is only to be collected in patients with a functioning rectum, i.e. do not collect it in patients with a colostomy, permanent or temporary. If a patient is not assessed due to a non-functioning rectum, please report this to the ECOG data center, using the QOL Assessment Compliance Form.

5.6.3 Administration Instructions

5.6.3.1 The FACT Diarrhea Subscale (FACT-D) is available in Spanish; the Patient Bowel Function/Uniscale Questionnaire is not. Patients who do not speak English or who prefer Spanish to English, may be offered a Spanish version of the FACT-D.

5.6.3.2 Instructions at the top of the questionnaires should be read to the patient. Assure patient's understanding and ask him/her to complete every item without overlooking any items.

5.6.3.3 If patients are unable to complete the forms independently because language, literacy, or physical condition is a barrier, the form should be administered by a trained staff member. Note on the Assessment Compliance Form the degree of assistance required and the mode of administration: interview or self-administration.

5.6.3.4 It is very important to review the questionnaires after the patient has completed them to be sure that all questions have been answered and that only one answer has been marked for each question. If the patient has marked more than one answer for a question, ask the patient which answer best reflects how he/she is feeling. If the patient skipped a question, inform the patient and ask him/her to answer the question. Always give the patient the option to refuse and indicate on the measure itself, next to the question that was not answered, that the patient did not want to answer the question.

- 5.6.3.5 If the patient misses an appointment or is too sick to complete the questionnaires, they can be mailed to the patient or sent home with him/her. A telephone interview can be conducted when the patient is looking at his/her copy of the forms. Please note on the Assessment Compliance Form that a telephone interview was conducted. Questionnaire data should be collected within one week of the missed assessment.
- 5.6.3.6 While it is preferable for the patient to complete the questionnaires, it is acceptable for them to be completed with the assistance of a family member/companion, health care provider or via a phone call to the patient by a health care provider or research associate. The 18-month questionnaires may be obtained at the time of a follow-up visit, may be mailed in by the patient or completed via a phone call, as described above.
- 5.6.3.7 If the patient fails to complete an assessment for any reason, he/she should still be asked to complete the remaining scheduled assessments.
- 5.6.3.8 The Assessment Compliance Form should be completed and attached to the questionnaires each time they are scheduled to be completed. Mail the form to the ECOG Coordinating Center (Reference Records to be Kept, Section 12.0)

5.7 Surgery

Prior to randomization (for patients registered prior to surgery), patients will be evaluated and cleared by the surgeon to determine if their medical condition will tolerate the planned operation.

The surgeon should determine whether or not the tumor is fixed or mobile, resectable or not, and, if resectable, which operation will be performed should the patient go directly to the operating room (LAR, APR, LAR/coloanal anastomosis).

Patients with any symptoms suggesting an obstruction should have a diverting colostomy placed prior to beginning preoperative therapy.

5.7.1 Surgery Schedule

Surgical resection should occur between 21-56 days (3 - 8 weeks) after the patient completes preoperative 5-FU and radiation therapy.

5.7.2 General Operative Evaluation

All patients will be explored at least for palliative intent even if there is no clinical evidence of tumor regression, because palliation is superior if tumor is resected, providing there is no clinical evidence of metastatic disease. An exam under anesthesia should be performed and evaluation of tumor size and location reported. At the time of surgery, the procedure should begin with close inspection of the liver and peritoneal surfaces for any evidence of metastatic disease. Any suspicious areas should be biopsied prior to beginning resection of the primary tumor. If any of the biopsies are positive, the patient will be considered to have extensive disease and the surgeon will select the procedure to be performed.

5.7.3 Surgical Resection

If the preoperative evaluation demonstrates extrapelvic metastatic disease, a palliative procedure may be selected by the operating surgeon to provide the maximal control of symptoms for the greatest duration of the patient's anticipated survival. In almost all cases, this will be an LAR or APR.

The choice of the operative procedure (APR, LAR or LAR/coloanal anastomosis) is at the discretion of the surgeon. It is strongly recommended that the entire mesorectum be removed and that the distal rectal margin of 2 cm be obtained for sphincter preserving procedures. The surgical procedure will be determined by the extent of the tumor prior to preoperative therapy. Adjacent organs involved with tumor at the time of pre-registration evaluation should be resected even if there is no evidence of residual tumor in those tissues at the time of surgery.

The pathologist will ink the specimen for evaluation of the radial margin.

Following the resection of the tumor specimen, when feasible, biopsies will be taken from the adjacent tissues near the resection margin and sent separately for evaluation of the surgical bed for residual tumor.

When APR is performed, some form of closure of the perineum will be performed unless contraindicated.

If the patient has a diverting colostomy, it should not be closed until after the completion of chemotherapy. During this time, the patient should be seen monthly by the surgeon and the anastomosis digitally dilated. Patients should be followed for at least four weeks after surgery.

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5.8 Adverse Event Reporting Requirements

5.8.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (please refer to the E3201 Forms Packet for the list of forms with directions for routine adverse event reporting). Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. The following sections provide information about expedited reporting.

5.8.2 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event; 3) the phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study arm includes both investigational and commercial agents, the following rules apply.

Concurrent administration: When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.

Steps to determine if an adverse event is to be reported in an expedited manner:

Step 1: *Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.* The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: *Grade the event using the NCI CTCAE.*

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event.* Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected*, for expedited reporting purposes only, when either the type of event or the severity of the event is **NOT** listed in:

- **Arm A, C, D, F, and S** – the drug package insert or protocol
- **Arm B and E** – the current NCI Agent-Specific Adverse Event List for the investigational agent or package insert/protocol for the commercial agents

NOTE: The NCI Agent-Specific Adverse Event List (ASAE) is included in Section 5.9 of the protocol. The ASAE is a list of events that should be considered 'expected' for adverse event reporting purposes. The ASAE is presented in the third column of the Comprehensive Adverse Event and Potential Risks List (CAEPR) and identified with **bold** and *italicized* text.

Step 5: *Review the "Additional instructions, requirements, and exceptions for protocol E3201" table in section 5.8.6 and footnote b in Section 5.8.7 for protocol and/or ECOG specific requirements for expedited reporting of specific adverse events that require special monitoring.*

NOTE: For general questions regarding expedited reporting requirements, please contact the NCI Medical Help Desk: 301-897-7497.

5.8.3 Reporting methods

Arm A, B, C, D, E, F, and S – This study requires that expedited adverse event reporting use the NCI's Adverse Expedited Reporting System (AdEERS). The NCI's guidelines for AdEERS can be found at <http://ctep.cancer.gov>. For questions regarding the use of the AdEERS application, please contact the NCI Technical Help Desk: 301-840-8202.

An AdEERS report must be submitted to ECOG and the appropriate regulatory agencies by one of the following methods:

Electronically submit the report via the AdEERS Web-based application located at <http://ctep.cancer.gov>

or

Fax the completed NCI Adverse Event Expedited Report – Single Agent or Multiple Agents paper template located at <http://ctep.cancer.gov> to ECOG (617-632-2990), Attention: AE. In addition, fax the completed AdEERS report to the NCI (301-230-0159) for Arms B and E and to the FDA (800-332-0178) for Arms A, C, D, F, and S.

NOTE: Paper copies of AdEERS reports will only be accepted if the AdEERS system is down. Once the system is restored, a report submitted on a paper template must be entered into the AdEERS system by the original submitter of the report at the site.

Any supporting or follow up documentation must be faxed to ECOG (617-632-2990), Attention: AE. In addition, supporting or follow up documentation must be faxed to the NCI (301) 230-0159 for Arms B and E and the FDA (800)-332-0178) for Arms A, C, D, F, and S.

5.8.4 When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Section 5.8.6). Please complete a 24-Hour Notification Report via the NCI AdEERS website (<http://ctep.cancer.gov/reporting/adeers.html>) within 24 hours of learning of the event. The full AdEERS report must be completed and submitted via AdEERS within 5 calendar days.

If the AdEERS system is down, a 24-hour notification call must be made to ECOG (617-632-3610) and to NCI (301-897-7497). Once the system is restored, a 24-hour Notification Report must be entered into the AdEERS system by the original submitter of the report at the site.

When an adverse event requires expedited reporting, submit a full AdEERS report within the timeframes outlined in Sections 5.8.6 and 5.8.7.

NOTE: Adverse events that meet the reporting requirements in Sections 5.8.6 or 5.8.7 and occur within 30 days of the last dose of protocol treatment must be reported on an expedited adverse event report form (using AdEERS). For any adverse events that occur more than 30 days after the last dose of treatment, only those that have an attribution of possibly, probably, or definitely AND meet the reporting requirements in Sections 5.8.6 or 5.8.7 must be reported on an expedited adverse event report form (using AdEERS).

5.8.5 Other recipients of adverse event reports

ECOG will forward AdEERS reports to the appropriate regulatory agencies and pharmaceutical company, if applicable.

Adverse events determined to be reportable must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.8.6 Expedited reporting for investigational agents

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days¹ of the Last Dose of Investigational Agent (Oxaliplatin) in this Study (Arm B and E) OR Within 30 Days of the Last Dose of Any Protocol Treatment.

Attribution	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 ²	Grades 4 & 5 ²
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	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
¹ Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows: AdEERS 24-hour notification followed by complete report within 5 calendar days for: <ul style="list-style-type: none"> Grade 4 and Grade 5 unexpected events AdEERS 10 calendar day report: <ul style="list-style-type: none"> 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 additional information below under section entitled "Additional instructions, requirements, and exceptions for protocol E3201"									

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NOTE: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines:**

- **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 disability/incapacity, congenital anomaly, or birth defect** 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 provided during trial registration on all reports.

* Hospitalizations are defined as lasting 24 hours or longer and these events must be reported via AdEERS.

Additional instructions, requirements and exceptions for protocol E3201

1. Additional Instructions:

- With respect to determining the specific day by which the event must be reported, the day the reporter learns of the adverse event constitutes "Day 0"
- For grade 2 and 3 unexpected events, AdEERS reporting is only required if the event is related to the investigational agent(s); it is not required if the event is related only to the commercial agent(s) included in the protocol treatment.

NOTE: For grade 3 unexpected events with hospitalization lasting ≥ 24 hours (or prolonged hospitalization), an AdEERS report is required even if the event is unrelated to the investigational agent(s).

- For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via AdEERS, please contact the NCI Medical Help Desk at 301-897-7497 or adeersmd@tech-res.com.

2. ECOG and Protocol Specific expedited reporting requirements:

The adverse events listed below also require expedited reporting for this trial:

ECOG specific expedited reporting requirements:

- **Hospitalizations:** Any grade 1 or 2 adverse event with precipitates a hospitalization lasting ≥ 24 hours (or prolongs hospitalization) must be reported via AdEERS within 10 calendar days of learning of the event regardless of the attribution and designation as expected or unexpected.

3. Protocol specific expedited reporting exceptions:

For study arms B and E, the adverse events listed below **do not** require expedited reporting via AdEERS, **including hospitalization for these events:**

- Grade 1-4 Constipation, Ileus, or Bowel obstruction
- Grade 1-4 Dehydration
- Grade 1-4 Diarrhea with and without colostomy and associated electrolyte imbalances
- Grade 1-4 Mucositis, esophagitis, stomatitis/pharyngitis, dysphagia
- Grade 1-4 Nausea or vomiting
- Grade 1-4 Febrile neutropenia
- Grade 1-4 Fever without neutropenia
- Grade 1-4 Infection with or without neutropenia or infection with unknown ANC
- Grade 1-3 Hand/foot skin reaction
- Grade 1-4 Pain- including abdominal pain/cramping
- Grade 1-4 Sensory neuropathy
- Grade 1-4 SGOT/SGPT
- Grade 1-4 Thrombosis/Embolism- including pulmonary embolism
- Grade 1-4 Fatigue (lethargy, malaise, asthenia)
- Grade 1-4 Neutrophils, leukocytes, hemoglobin, platelets
- Grade 1-3 Cardiac Ischemia/infarction

5.8.7 Expedited reporting for commercial agents

Commercial reporting requirements are provided below. The commercial agents used in arms A, C, D, F and S of this study Irinotecan, Leucovorin, 5-FU, Capecitabine (only for those in NSABP protocol R-04).

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only – Arms A, C, D, F, and S.					
Attribution	Grade 4		Grade 5 ^a		ECOG and Protocol-Specific Requirements
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely			7 calendar days	7 calendar days	See footnote (b) for special requirements.
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	
7 Calendar Days: Indicates a full AdEERS report is to be submitted within 7 calendar days of learning of the event.					
a This includes all deaths within 30 days of the last dose of treatment regardless of attribution. NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.					
b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:					
Serious Events: Any event following treatment that results in <u><i>persistent or significant disabilities/incapacities, congenital anomalies, or birth defects</i></u> must be reported via AdEERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via AdEERS, please contact the NCI Medical Help Desk at 301-897-7497.					

5.8.8 Reporting secondary AML/MDS/ALL

All cases of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and acute lymphocytic leukemia (ALL) that occur in patients on NCI-sponsored trials following their chemotherapy for cancer must be reported to ECOG. Submit the following information within 30 days of an AML/MDS/ALL diagnosis occurring after treatment for cancer on NCI-sponsored trials:

- a completed NCI/CTEP Secondary AML/MDS/ALL Report Form (*do not use AdEERS*);
- a copy of the pathology report confirming the AML/MDS/ALL; and
- a copy of the cytogenetics report (if available).

ECOG will forward copies to the Investigational Drug Branch (IDB) of the NCI Cancer Therapy Evaluation Program (CTEP).

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the NCI/CTEP Secondary AML/MDS/ALL Report Form must be submitted for the most recent trial. ECOG must be provided with a copy of the report even if ECOG was not the patient's most recent trial.

5.8.9 Reporting of other second primary cancers

All cases of new primary cancers that occur on ECOG protocols during or after protocol must be reported to ECOG, according to the follow up schedule outlined in the E3201 Forms Packet, on the ECOG Second Primary Form within 30 days of diagnosis, regardless of relationship to protocol treatment. This form is not for use for reporting recurrence or development of metastatic disease. A copy of the pathology report should be sent, if available.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted, including the NCI AML/MDS/ALL form and ECOG Second Primary Form.

Submit AML/MDS/ALL and Second Primary information to:

ECOG Coordinating Center
FSTRF
900 Commonwealth Avenue
Boston, MA 02215

[Deleted NOTE in Update #2]

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5.9 **Comprehensive Adverse Events and Potential Risks List (CAEPR) for Oxaliplatin (NSC 266046)**

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single, complete list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' <http://ctep.cancer.gov/reporting/adeers.html> for further clarification. *Frequency is provided based on 869 patients.* Below is the CAEPR for Oxaliplatin.

Version 2.0, December 10, 2007¹

Adverse Events with Possible Relationship to Oxaliplatin (CTCAE v3.0 Term) [n=869 patients]			Agent Specific Adverse Event List' (ASAEL)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
ALLERGY/IMMUNOLOGY			
	Allergic reaction/hypersensitivity (including drug fever)		<i>Allergic reaction/hypersensitivity (including drug fever)</i>
	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)		<i>Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)</i>
AUDITORY/EAR			
	Hearing: patients without baseline audiogram and not enrolled in a monitoring program		<i>Hearing: patients without baseline audiogram and not enrolled in a monitoring program</i>
	Otitis, middle ear (non-infectious)		<i>Otitis, middle ear (non-infectious)</i>
BLOOD/BONE MARROW			
Hemoglobin			<i>Hemoglobin</i>
	Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)		<i>Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis)</i>
	Leukocytes (total WBC)		<i>Leukocytes (total WBC)</i>
	Lymphopenia		<i>Lymphopenia</i>
Neutrophils/granulocytes (ANC/AGC)			<i>Neutrophils/granulocytes (ANC/AGC)</i>
Platelets			<i>Platelets</i>

CARDIAC ARRHYTHMIA			
	Supraventricular and nodal arrhythmia: Atrial fibrillation		
	Supraventricular and nodal arrhythmia: Sinus tachycardia		<i>Supraventricular and nodal arrhythmia: Sinus tachycardia</i>
	Supraventricular and nodal arrhythmia: Supraventricular arrhythmia NOS		<i>Supraventricular and nodal arrhythmia: Supraventricular arrhythmia NOS</i>
	Ventricular arrhythmia: Ventricular arrhythmia NOS		<i>Ventricular arrhythmia: Ventricular arrhythmia NOS</i>
CARDIAC GENERAL			
	Hypertension		<i>Hypertension</i>
	Hypotension		<i>Hypotension</i>
COAGULATION			
	DIC (disseminated intravascular coagulation)		<i>DIC (disseminated intravascular coagulation)</i>
	INR (International Normalized Ratio of prothrombin time)		<i>INR (International Normalized Ratio of prothrombin time)</i>
	PTT (Partial Thromboplastin Time)		<i>PTT (Partial Thromboplastin Time)</i>
		Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])	
CONSTITUTIONAL SYMPTOMS			
Fatigue (asthenia, lethargy, malaise)			<i>Fatigue (asthenia, lethargy, malaise)</i>
	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)		<i>Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)</i>
	Insomnia		<i>Insomnia</i>
	Rigors/chills		<i>Rigors/chills</i>
	Sweating (diaphoresis)		<i>Sweating (diaphoresis)</i>
	Weight gain		<i>Weight gain</i>
	Weight loss		<i>Weight loss</i>
DERMATOLOGY/SKIN			
	Dry skin		<i>Dry skin</i>
	Flushing		<i>Flushing</i>
	Hair loss/alopecia (scalp or body)		<i>Hair loss/alopecia (scalp or body)</i>
	Injection site reaction/extravasation changes		<i>Injection site reaction/extravasation changes</i>
	Pruritus/itching		<i>Pruritus/itching</i>
	Rash/desquamation		<i>Rash/desquamation</i>
	Rash: hand-foot skin reaction		<i>Rash: hand-foot skin reaction</i>
	Urticaria (hives, welts, wheals)		<i>Urticaria (hives, welts, wheals)</i>
ENDOCRINE			
	Hot flashes/flushes		<i>Hot flashes/flushes</i>
GASTROINTESTINAL			
	Anorexia		<i>Anorexia</i>
	Ascites (non-malignant)		<i>Ascites (non-malignant)</i>
	Colitis		<i>Colitis</i>
	Constipation		<i>Constipation</i>
	Dehydration		<i>Dehydration</i>
Diarrhea			<i>Diarrhea</i>
	Dry mouth/salivary gland (xerostomia)		<i>Dry mouth/salivary gland (xerostomia)</i>

	Dysphagia (difficulty swallowing)		<i>Dysphagia (difficulty swallowing)</i>
	Enteritis (inflammation of the small bowel)		<i>Enteritis (inflammation of the small bowel)</i>
	Esophagitis		<i>Esophagitis</i>
	Flatulence		<i>Flatulence</i>
	Gastritis (including bile reflux gastritis)		<i>Gastritis (including bile reflux gastritis)</i>
	Heartburn/dyspepsia		<i>Heartburn/dyspepsia</i>
	Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)		<i>Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)</i>
	Mucositis/stomatitis (functional/symptomatic): oral cavity		<i>Mucositis/stomatitis (functional/symptomatic): oral cavity</i>
Nausea			<i>Nausea</i>
	Necrosis, GI - Select		<i>Necrosis, GI - Select</i>
		Gastrointestinal - Other (pneumatosis intestinalis)	
	Obstruction, GI: small bowel NOS		<i>Obstruction, GI: small bowel NOS</i>
	Taste alteration (dysgeusia)		<i>Taste alteration (dysgeusia)</i>
	Ulcer, GI - Select		<i>Ulcer, GI - Select</i>
Vomiting			<i>Vomiting</i>
HEMORRHAGE/BLEEDING			
	Hemorrhage, CNS		<i>Hemorrhage, CNS</i>
	Hemorrhage, GI: Select		<i>Hemorrhage, GI: Select</i>
	Hemorrhage, GU: Select		<i>Hemorrhage, GU: Select</i>
	Hemorrhage, pulmonary/upper respiratory: respiratory tract NOS		<i>Hemorrhage, pulmonary/upper respiratory: respiratory tract NOS</i>
	Hemorrhage/bleeding - Other (hemorrhage with thrombocytopenia)		<i>Hemorrhage/bleeding - Other (hemorrhage with thrombocytopenia)</i>
HEPATOBIILIARY/PANCREAS			
		Cholecystitis	
	Hepatobiliary/Pancreas - Other (Hepatic enlargement)		<i>Hepatobiliary/Pancreas - Other (Hepatic enlargement)</i>
	Hepatobiliary/Pancreas - Other (Veno-occlusive disease)		<i>Hepatobiliary/Pancreas - Other (veno-occlusive disease)</i>
	Liver dysfunction/failure (clinical)		<i>Liver dysfunction/failure (clinical)</i>
	Pancreatitis		<i>Pancreatitis</i>
INFECTION			
	Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)(ANC <1.0 x 10e9/L, fever >=38.5 degrees C)		<i>Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)(ANC <1.0 x 10e9/L, fever >=38.5 degrees C)</i>
	Infection with Grade 3 or 4 neutrophils - Select		<i>Infection with Grade 3 or 4 neutrophils - Select</i>
	Infection with normal ANC or Grade 1 or 2 neutrophils - Select		<i>Infection with normal ANC or Grade 1 or 2 neutrophils - Select</i>
	Infection with unknown ANC - Select		<i>Infection with unknown ANC - Select</i>
LYMPHATICS			
	Edema: head and neck		<i>Edema: head and neck</i>
	Edema: limb		<i>Edema: limb</i>

METABOLIC/LABORATORY			
	Acidosis (metabolic or respiratory)		<i>Acidosis (metabolic or respiratory)</i>
	Albumin, serum-low (hypoalbuminemia)		<i>Albumin, serum-low (hypoalbuminemia)</i>
	Alkaline phosphatase		<i>Alkaline phosphatase</i>
ALT, SGPT (serum glutamic pyruvic transaminase)			<i>ALT, SGPT (serum glutamic pyruvic transaminase)</i>
	AST, SGOT (serum glutamic oxaloacetic transaminase)		<i>AST, SGOT (serum glutamic oxaloacetic transaminase)</i>
	Bilirubin (hyperbilirubinemia)		<i>Bilirubin (hyperbilirubinemia)</i>
	Calcium, serum-low (hypocalcemia)		<i>Calcium, serum-low (hypocalcemia)</i>
	Creatinine		<i>Creatinine</i>
	GGT (gamma-glutamyl transpeptidase)		<i>GGT (gamma-glutamyl transpeptidase)</i>
	Glucose, serum-high (hyperglycemia)		<i>Glucose, serum-high (hyperglycemia)</i>
	Glucose, serum-low (hypoglycemia)		<i>Glucose, serum-low (hypoglycemia)</i>
	Magnesium, serum-low (hypomagnesemia)		<i>Magnesium, serum-low (hypomagnesemia)</i>
	Phosphate, serum-low (hypophosphatemia)		<i>Phosphate, serum-low (hypophosphatemia)</i>
	Potassium, serum-low (hypokalemia)		<i>Potassium, serum-low (hypokalemia)</i>
	Sodium, serum-low (hyponatremia)		<i>Sodium, serum-low (hyponatremia)</i>
	Uric acid, serum-high (hyperuricemia)		<i>Uric acid, serum-high (hyperuricemia)</i>
MUSCULOSKELETAL/SOFT TISSUE			
	Extremity-lower (gait/walking)		<i>Extremity-lower (gait/walking)</i>
	Trismus (difficulty, restriction or pain when opening mouth)		<i>Trismus (difficulty, restriction or pain when opening mouth)</i>
NEUROLOGY			
	Ataxia (incoordination)		<i>Ataxia (incoordination)</i>
	CNS cerebrovascular ischemia		<i>CNS cerebrovascular ischemia</i>
	Confusion		<i>Confusion</i>
	Dizziness		<i>Dizziness</i>
	Extrapyramidal/involuntary movement/restlessness		<i>Extrapyramidal/involuntary movement/restlessness</i>
	Mood alteration: Anxiety		<i>Mood alteration: Anxiety</i>
	Mood alteration: Depression		<i>Mood alteration: Depression</i>
	Neuropathy: cranial - Select		<i>Neuropathy: cranial - Select</i>
	Neuropathy: motor		<i>Neuropathy: motor</i>
	Neurology - Other: (multiple cranial nerve palsies)		<i>Neurology Other (multiple cranial nerve palsies)</i>
Neuropathy: sensory			<i>Neuropathy: sensory</i>

	Seizure		Seizure
	Somnolence/depressed level of consciousness		Somnolence/depressed level of consciousness
	Speech impairment (e.g. dysphagia or aphasia)		Speech impairment (e.g. dysphagia or aphasia)
	Syncope (fainting)		
OCULAR/VISUAL			
	Dry eye syndrome		Dry eye syndrome
	Eyelid dysfunction		Eyelid dysfunction
	Ocular surface disease		Ocular surface disease
	Ocular/Visual - Other (Cold-induced transient visual abnormalities)		Ocular/Visual - Other (cold-induced transient visual abnormalities)
	Ocular/Visual - Other (Amaurosis fugax)		Ocular/Visual - Other (Amaurosis fugax)
	Optic disc edema		Optic disc edema
PAIN			
	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 - Head/headache		Pain - Head/headache
	Pain - Joint		Pain - Joint
	Pain - Muscle		Pain - Muscle
PULMONARY/UPPER RESPIRATORY			
	Adult respiratory distress syndrome (ARDS)		Adult respiratory distress syndrome (ARDS)
	Bronchospasm, wheezing		Bronchospasm, wheezing
	Cough		Cough
	Dyspnea (shortness of breath)		Dyspnea (shortness of breath)
	Hiccoughs (hiccups, singultus)		Hiccoughs (hiccups, singultus)
	Hypoxia		
	Nasal cavity/paranasal sinus reactions		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)		Voice changes/dysarthria (e.g. hoarseness, loss or alteration in voice, laryngitis)
RENAL/GENITOURINARY			
	Renal failure		Renal failure
	Urinary frequency/urgency		Urinary frequency/urgency
	Urinary retention (including neurogenic bladder)		Urinary retention (including neurogenic bladder)
SYNDROMES			
	Syndromes - Other (Hepato-renal syndrome)		Syndromes - Other (Hepato-renal syndrome)
VASCULAR			
	Phlebitis (including superficial thrombosis)		Phlebitis (including superficial thrombosis)
	Thrombosis/thrombus/embolism		Thrombosis/thrombus/embolism
	Thrombosis/thrombus/embolism (vascular access-related)		

¹This 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 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.

Also reported on oxaliplatin trials but with the relationship to oxaliplatin still undetermined:

GASTROINTESTINAL - GI perforation

METABOLIC/LABORATORY - amylase; lipase

MUSCULOSKELETAL/SOFT TISSUE - generalized muscle weakness

SYNDROMES - tumor lysis syndrome

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.

5.10 Supportive Care (Chemotherapy Toxicity)

All supportive measures consistent with optimal patient care will be given throughout the study.

Loperamide (Imodium): Patients will be instructed to begin taking loperamide at the earliest signs of a poorly formed or loose 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 the patient is diarrhea-free for at least 12 hours. Patients may take loperamide 4 mg (2 capsules) every four hours during the night. (Refer to Appendix IX, Diarrhea Management Instructions.)

Atropine: Diarrhea or abdominal cramping that occurs during or within one hour after receiving irinotecan can be treated with atropine (0.25 to 1 mg IV as indicated). Patients having recurrent problems with cholinergic symptoms may receive atropine prophylactically (sc or IV). Additional antidiarrheal measures may be used at the discretion of the treating physician.

Antiemetics: Patients may receive dexamethasone 10 mg IV as a pretreatment antiemetic before irinotecan doses, unless there is a relative or absolute contraindication to corticosteroids (i.e., diabetes, known sensitivity to corticosteroids, severe muscle weakness or myalgias, etc.). Other antiemetics may be used in addition to the suggested regimen, if clinically indicated. As the majority of patients on previous trials have not experienced significant nausea, antiemetics other than decadron are recommended only for those patients who demonstrate nausea and/or vomiting despite treatment with decadron.

Routine use of antiemetics prior to treatment with standard dose 5-FU and leucovorin is rarely indicated. It is recommended that patients not be given routine antiemetics for the standard arms of the study (Arms C and F) and that antiemetics be prescribed by the treating physician as clinically indicated if a patient develops nausea and/or vomiting.

Oxaliplatin is emetogenic. All patients receiving oxaliplatin (Arms B and E) should be pre-medicated with an acceptable anti-emetic regimen.

Antibiotics (for patients with persistent diarrhea): Begin oral fluoroquinolone and continue for 7 days. If diarrhea persists for greater than 48 hours, parenteral hydration is recommended (including hospitalization for such). Oral fluoroquinolone treatment also should be initiated for patients who develop an ANC ≤ 500 /mm³ (even in the absence of fever or diarrhea) or a fever that occurs with diarrhea (even without neutropenia). Antibiotics should continue until resolution of diarrhea. (15)

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Anticoagulants: Patients who are taking Coumadin may participate in this study; however, it is recommended the prothrombin time be monitored carefully (at least weekly). Subcutaneous heparin is permitted.

Hypersensitivity: Platinum hypersensitivity can cause dyspnea, bronchospasm, itching and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, antihistamines, and epinephrine; bronchodilators and vasopressors may be required. Platinum hypersensitivity is an extremely rare event and should be treated promptly.

Oxaliplatin hypersensitivity occurs in approximately 0.5% of patients receiving this investigational agent. See Appendix VI for the "Comparison of the Symptoms and Treatment of Pharyngo-Laryngodysesthesias and Platinum Hypersensitivity Reactions.

Pharyngo-laryngodysesthesias: Oxaliplatin may cause discomfort in the larynx or pharynx associated with dyspnea, anxiety, swallowing difficulty and is exacerbated by cold. Appropriate therapy includes use of anxiolytics, cold avoidance and monitoring. See Appendix VI for the "Comparison of the Symptoms and Treatment of Pharyngo-Laryngodysesthesias and Platinum Hypersensitivity Reactions."

5.11 Duration of Therapy

Patients will continue to be monitored for toxicity but will discontinue protocol therapy in the following situations:

- 5.11.1 Patient experiences unacceptable toxicity, in spite of dose modifications as outlined in Section 5.4.
- 5.11.2 If the patient requests discontinuation of therapy.
- 5.11.3 If the patient's attending physician believes that it is in the patient's best interest to stop therapy.
- 5.11.4 Disease recurrence while on therapy.
- 5.11.5 Severe hypersensitivity reaction.
- 5.11.6 If a patient is removed from study treatment, that patient should be evaluated for continuing radiation therapy +/- standard chemotherapy or surgery at the discretion of the treating physician.

5.12 Duration of Follow-up

All patients, including those who discontinue protocol therapy early, will be followed for response until progression and for survival until 10 years from the date of registration. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

6.1 Local, Regional Recurrence

The development of a local or regional recurrence of rectal cancer.

6.2 Distant Recurrence

The development of a distant recurrence of rectal cancer.

6.3 Disease-Free Survival

Date of randomization to the date of the first treatment failure (recurrence or death before recurrence).

6.4 Survival

Date of Randomization to date of death

NOTE: Recurrence must be documented by biopsy and/or evidence of disease on radiologic studies. Abnormal blood studies alone (e.g., elevated transaminases or alkaline phosphatase) are not sufficient evidence of relapse. Whenever possible, histologic proof of recurrence should be obtained.

7. Study Parameters

NOTE: Section 7.1 refers to therapeutic parameters required of the institutions for patient monitoring. Section 7.2 pertains to the requested sample submissions for the correlative studies described in Section 10.0.

7.1 Therapeutic Parameters

7.1.1 Group I (Patients Treated with Preoperative Radiation Therapy)

1. Prestudy CXR and/or scans should be done \leq 4 weeks prior to definitive surgery.
2. Prestudy CBC (with differential and platelet count) should be done \leq 4 weeks before randomization.
3. All required prestudy chemistries, as outlined in Section 3.0, should be done \leq 4 weeks before randomization.

Evaluation	Prior to Registration	Weekly during XRT	Post – Chemo/XRT Pre-Op	Post-Op/ Pre-Chemo	Prior to Each Chemo Cycle (Post-Op)	Every 3 Months after chemo x 8	Every 6 months. Years 3-5 after treatment	18 \pm 2 months after completion of XRT	Yearly After Surgery
History and Physical	X	X	X		X	X	X		
Performance Status	X	X	X			X	X		
CBC ¹	X	X			X ^{1,3}				
Creatinine, SGOT, (AST), Bilirubin	X		X		X				
CEA	X		X	X		X	X		
Pregnancy Test ²	X								
CT, Transrectal MRI or Endo-rectal Ultrasound ⁴	X								
Colonoscopy or Barium Enema	X ⁷								X ⁵
Fact-Diarrhea Subscale Questionnaire ⁶	X ⁶	X ⁶	X ⁶					X ⁶	
Patient Bowel Function/Uniscale Questionnaire	X ⁶	X ⁶	X ⁶					X ⁶	

¹ CBCs (with differential and platelet count) which includes WBC, ANC, Platelets and Hgb required for protocol therapy must be done < 24 hours prior to the treatment cycle.

² Required for premenopausal women who have not been surgically sterilized. All females of childbearing potential should undergo GYN pelvic exam and Pap smear before receiving protocol therapy.

³ Patients will be monitored for toxicity weekly during the first cycle of postoperative chemotherapy.

⁴ CT-scan, transrectal MRI or endo-rectal ultrasound may be used.

⁵ One year after surgery then *recommended* every 3 years.

⁶ Using the specified tool, bowel function will be measured 4 times: prior to radiation therapy (baseline), during the last week of RT, immediately prior to surgery and 18 \pm 2 months following completion of RT. Bowel function of Group I PS will be measured 2 times: at registration/randomization (baseline) and 18 \pm 2 months following completion of RT. This information is only to be collected in patients with a functioning rectum, i.e. do not collect it in patients with a colostomy. Please refer to Section 5.6.

⁷ Does not need to be repeated if performed pre-op or intra-op.

7.1.2 Group II (Patients Treated with Postoperative Radiation Therapy)

1. Prestudy CXR and/or scans should be done ≤ 4 weeks prior to definitive surgery.
2. Prestudy CBC (with differential and platelet count) should be done ≤ 4 weeks before randomization.
3. All required prestudy chemistries, as outlined in Section 3.0, should be done ≤ 4 weeks before randomization.

Evaluation	Prior to Registration	Weekly during XRT	Post – Chemo/XRT Pre-Op	Post-Op/ Pre-Chemo	Prior to Each Chemo Cycle (Post-Op)	Every 3 Months after chemo x 8	Every 6 months. Years 3-5 after treatment	18 \pm 2 months after completion of XRT	Yearly After Surgery
History and Physical	X	X	X		X	X	X		
Performance Status	X	X	X			X	X		
CBC ¹	X	X			X ^{1,3}				
Creatinine, SGOT, (AST), Bilirubin	X		X		X				
CEA	X		X	X		X	X		
Pregnancy Test ²	X								
CT, Transrectal MRI or Endo-rectal Ultrasound ⁴	X								
Colonoscopy or Barium Enema	X ⁷								X ⁵
Fact-Diarrhea Subscale Questionnaire ⁶	X ⁶	X ⁶	X ⁶					X ⁶	
Patient Bowel Function/Uniscale Questionnaire	X ⁶	X ⁶	X ⁶					X ⁶	

¹ CBCs (with differential and platelet count) which includes WBC, ANC, Platelets and Hgb required for protocol therapy must be done < 24 hours prior to the treatment cycle.

² Required for premenopausal women who have not been surgically sterilized. All females of childbearing potential should undergo GYN pelvic exam and Pap smear before receiving protocol therapy.

³ Patients will be monitored for toxicity weekly during the first cycle of postoperative chemotherapy.

⁴ CT-scan, transrectal MRI or endo-rectal ultrasound may be used.

⁵ One year after surgery then *recommended* every 3 years.

⁶ Using the specified tool, bowel function will be measured 4 times: prior to radiation therapy (baseline), during the last week of RT, immediately prior to surgery and 18 \pm 2 months following completion of RT. Bowel function of Group I PS will be measured 2 times: at registration/randomization (baseline) and 18 \pm 2 months following completion of RT. This information is only to be collected in patients with a functioning rectum, i.e. do not collect it in patients with a colostomy. Please refer to Section 5.6.

⁷ Does not need to be repeated if performed pre-op or intra-op.

7.2 Biological Material Submissions

7.2.1 Pathology samples have been requested for the correlative studies described in Section 11.0. Collection and submission of correlative samples should be limited to those patients who have agreed to participate in the correlative studies. Samples should be submitted as outlined in Section 10.0.

Rev. 3/07 7.2.2 ECOG's diagnostic review project for secondary AML/MDS ended December 1, 2005. Submission of diagnostic slides upon diagnosis of secondary AML/MDS for central diagnostic review and classification is no longer required.

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	Pre-Treatment Biopsy ¹	Surgical Resection ²
Tumor Tissue Block ³	X	X
Mucosa Tissue Block ³		X

¹ To be submitted from patients receiving preoperative treatment (Group I).

² Group I PS and Group II (pre-registration surgical resection) materials are to be submitted within one month of registration. Group I (post-registration surgical resection) materials are to be submitted within one month of surgery.

³ If paraffin-embedded blocks cannot be provided, please contact the PCO regarding the appropriate alternative sample submission.

8. Drug Formulation and Procurement

8.1 Irinotecan - For more information, please refer to the package insert.

8.1.1 Other Names

Camptothecin-11, CPT-11, Camptosar®

8.1.2 Classification

Topoisomerase I inhibitor.

8.1.3 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 the inhibited topoisomerase I during the course of DNA and RNA synthesis. Irinotecan is an inactive prodrug and must be metabolized *in vivo* by carboxyesterases to the active compound SN-38.

8.1.4 Storage and Stability

Undiluted vials are stored at room temperature (15-30EC), and protected from light. Irinotecan diluted with 5% dextrose is stable at refrigerated temperatures for 48 hours when protected from light.

8.1.5 Dose Specifics

Arms A and D: 180 mg/m² IV over 90 minutes. Repeat every 2 weeks.

8.1.6 Preparation

Irinotecan must be diluted before infusion. The recommended dilutant for short intravenous administration of irinotecan is 500 mL of dextrose 5% or a concentration range between 0.12 to 2.8 mg/mL. Stability is less in normal saline. The diluted solution should be inspected visually for particulate matter.

8.1.7 Administration

IV over 90 minutes

8.1.8 Availability

Irinotecan is a commercially marketed product which has been approved by the FDA for the treatment of metastatic carcinoma of the colon or rectum and metastatic carcinoma of the colon or rectum where disease has recurred or progressed following initial fluorouracil-based therapy. However, its use in patients with advanced (stage II or III) rectal cancer is not currently approved by the FDA. When used as directed by this protocol, irinotecan is classified as an "unapproved use of an approved agent" and, by definition, considered as an investigational agent. However, while it is not an indication currently approved by the FDA, the use of irinotecan in this protocol is exempt from the requirements of an IND, as described under Title 21 CFR 312.2(b).

Commercially available in 100 mg single dose 5 mL vials and 40 mg single dose 2 mL vials containing 20 mg/mL.

8.1.9 Incompatibilities

Solutions other than dextrose 5% or normal saline should not be used for dilution. Other compatibility information is not available.

8.1.10 Drug Interactions

Dexamethasone when administered concurrently with irinotecan causes increased lymphopenia and hyperglycemia.

Laxative use should be curtailed during irinotecan administration and in the immediate days following irinotecan administration.

Simultaneous administration of prochlorperazine and irinotecan has increased the incidence of akathisia.

Diuretic use with irinotecan may exacerbate dehydration induced by diarrhea and chemotherapy-induced nausea and vomiting.

St. John's wort decreases the AUC of SN-38 presumably by induction of CYP3A4 activity.

Ketoconazole via inhibition of CYP3A4 significantly increase exposure of the active metabolite SN-38, which could result in exaggerated toxicity. Consideration of dose reduction in patients on ketoconazole and other agents known to inhibit CYP3A4 should be considered for irinotecan.

8.1.11 Side Effects

Hematologic: Leukopenia, neutropenia, anemia, thrombocytopenia, neutropenic fever, hemorrhage

Gastrointestinal: Diarrhea, nausea and vomiting, anorexia, abdominal pain, flatulence, stomatitis, dyspepsia, dehydration

Hepatic: Elevated transaminases

Cardiovascular: Vasodilation, hypotension, myocardial infarction, stroke, edema

Neurologic: Dizziness, confusion, somnolence, insomnia, back pain

Respiratory: Pulmonary embolism

Dermatologic: Alopecia, rash

Other: Asthenia, thrombophlebitis, sweating, weight loss, chills

8.1.12 Nursing/Patient Implications

Premedicate with dexamethasone in anticipation of mild to moderate nausea and vomiting. When used in combination with 5-fluorouracil and leucovorin the nausea and vomiting will likely be worse.

Fatalities have been reported with thromboembolic events and neutropenic sepsis in patients receiving 5-fluorouracil, leucovorin and irinotecan.

Monitor for diarrhea. For diarrhea occurring during or immediately after the infusion of irinotecan, atropine 0.25 to 1mg can be administered IV or SC (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. Loperamide dosing should continue at 2 mg q 2h (4 mg q 4h at night) until 12 hours after the first formed stool. (NOTE: this loperamide regimen is in excess of the labeled "maximum" dose of 16 mg/day.)

Monitor CBC, platelets, and liver function tests.

Dose modifications per the protocol or the package insert should be followed for hematologic and gastrointestinal toxicity.

Administration of a oral quinolone antibiotic may decrease the risk of neutropenic sepsis in patients receiving 5-fluorouracil/leucovorin and irinotecan.

Advise patient of likely post-treatment neutropenia and instruct in appropriate neutropenic precautions.

Advise patient of possible alopecia and inform patient of various cosmetic strategies. (See Section 5.10).

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8.1.13 References

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Mathijssen RHJ, Verweij J, DeBruijn P et al: Effects of St. John's Wort on irinotecan metabolism. *J Natl Cancer Inst* 2002; 94(16):1247-1249.

Noda K, Nishiwaki Y, Kawahara M et al: Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002; 346(2):85-91.

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Saltz LB. Cox JV. Blanke C. Rosen LS. Fehrenbacher L. Moore MJ. Maroun JA. Ackland SP. Locker PK. Pirotta N. Elfring GL. Miller LL. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *New England Journal of Medicine*. 2000;343(13):905-14.

Kehrer DF. Mathijssen RH. Verweij J. de Bruijn P. Sparreboom A. Modulation of irinotecan metabolism by ketoconazole. *Journal of Clinical Oncology*. 2002; 20(14):3122-9.

Rev. 4/05	<p>8.2 <u>Oxaliplatin (266046)</u> - For more information, please refer to the package insert.</p>
	<p>8.2.1 <u>Chemical Name</u> cis -[(1R,2R)-1,2-cyclohexanediamine- N,N'] [oxalate(2-)- 0,0'] platinum.</p>
	<p>8.2.2 <u>Other Names</u> Trans-1-diaminocyclohexane oxalatoplatinum Cis-[oxalato (trans-1- ,2-diaminocyclohexane) platinum(II)] /-OHP Eloxatin™ Eloxatine™ Dacplat™ 5R96669</p>
	<p>8.2.3 <u>Classification</u> Platinum Derivative</p>
	<p>8.2.4 <u>CAS Registry Number</u> 63121-00-6</p>
	<p>8.2.5 <u>Molecular Formula/Weight</u> $C_8H_{14}N_2O_4$ Pt 397.3</p>
Rev. 4/05	<p>8.2.6 <u>Approximate Solubility</u> Oxaliplatin is slightly soluble in water at 6 mg/mL, very slightly soluble in methanol, and practically insoluble in ethanol and acetone.</p>
	<p>8.2.7 <u>Mode of Action</u> Oxaliplatin is biotransformed to a reactive species which complex with (crosslink) DNA, amino acids, proteins, and other macromolecules and cause tumor cell death by preventing cellular replication and transcription and stimulating cells to undergo apoptosis.</p>
	<p>8.2.8 <u>Description</u> Oxaliplatin is a novel antineoplastic platinum derivative with an oxalato ligand as group and a 1 ,2-diaminocyclohexane (DACH) carrier.</p>
Rev. 4/05	<p>8.2.9 <u>How Supplied</u> Oxaliplatin is available in two distinct dosage forms:</p> <ul style="list-style-type: none"> • <u>Oxaliplatin for injection (lyophilized sterile powder)</u> is a preservative-free, lyophilized powder as a white to off-white cake or powder contained in clear vials, sealed with an elastomeric stopper and a flip-off cover. It is available in 50 mg and 100 mg vials containing 450 mg and 900 mg of lactose monohydrate, respectively. • <u>Oxaliplatin injection (sterile solution)</u> is a preservative-free, aqueous solution containing 5 mg of oxaliplatin per mL in water for injection. It is available in 50 mg and 100 mg vials containing 50 mg in 10 mL of water for injection and 100 mg in 20 mL of water for injection, respectively. The primary package is a clear glass (Type I) vial sealed with an elastomeric stopper and flip-off cover. <p><u>Both formulations must be further diluted in D5W before administration.</u></p>

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8.2.10 Preparation

- Oxaliplatin for injection: Reconstitute the lyophilized powder by adding 10 mL (for the 50 mg vials) or 20 mL (for the 100 mg vials) of Water for Injection or Dextrose 5% in Water to yield a 5 mg/mL solution. After reconstitution in the original vial, withdraw the required amount of reconstituted solution from the vial(s) and then dilute with 250 mL to 500 mL Dextrose 5% in Water to give an oxaliplatin concentration of not less than 0.2 mg/mL. **Do not reconstitute or dilute oxaliplatin with a sodium chloride solution.**
- Oxaliplatin injection: Withdraw the calculated dose of the 5 mg/mL solution from the vial(s) and then dilute with 250 mL to 500 mL Dextrose 5% in Water to give an oxaliplatin concentration between 0.2 mg/mL and 2.0 mg/mL. **Do not reconstitute or dilute oxaliplatin with a sodium chloride solution.**

Do not use administration needles or intravenous infusion sets containing aluminum items (risk of degradation of oxaliplatin upon contact with aluminum) for the preparation or administration of either the oxaliplatin for injection or the oxaliplatin injection.

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8.2.11 Incompatibilities (Both Formulations)

Do not mix or administer with saline or other chloride containing solutions. Oxaliplatin is unstable in the presence of chloride.

The infusion line should be flushed with D5W prior to administration of any concomitant medication.

Oxaliplatin is unstable under alkaline conditions. Do not mix with alkaline drugs or solutions (in particular 5-fluorouracil basic solution, trometamol and folinic products containing trometamol as an excipient). When oxaliplatin is administered with 5-fluorouracil, the oxaliplatin infusion should precede that of 5-fluorouracil. Ensure the infusion lines are adequately flushed with 5% Dextrose between administration of the two drugs.

When oxaliplatin is administered with folinic acid, separate infusion bags and lines must be used, with Y-tubing to connect the two lines prior to the single injection site. Under these conditions of administration, the two products have been shown to be chemically compatible.

Do not use components containing aluminum for the preparation or administration of oxaliplatin. There is a risk of drug degradation when in contact with aluminum.

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8.2.12 Storage/Stability

8.2.12.1 Intact Vials

- Oxaliplatin for injection: Store between 15°C and 30°C (59°F-86°F). Do not exceed 30°C. Stable for 3 years under these conditions.
- Oxaliplatin injection: Store between 20°C and 25°C (68°F-77°F) with excursion permissible between 15°C and 30°C (59°F-86°F). Do not freeze. For long-term storage, protect product from light (keep vial in outer carton). Stable for 3 years under these conditions.

8.2.12.2 Reconstituted and Diluted Solutions

- Reconstituted solution (oxaliplatin for injection only): After reconstitution in the original vial, the reconstituted solution may be stored up to 24 hours under refrigeration (2°-8°C /36°-46°F).

- Both formulations, after final dilution in 250-500 mL of 5% Dextrose in Water, are stable for 6 hours at room temperature (20°C to 25°C; 68°F - 77°F) or up to 24 hours under refrigeration (2°C to 8°C; 36°F-46°F).

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8.2.13 Dose Specifics

Oxaliplatin will be administered to patients registered on Arms B and E. Dose is 85 mg/m² IV infusion over 2 hours, given once every 2 weeks. Use actual, rather than ideal, body weight to calculate dose. If ascites is present, however, use estimated "dry" body weight.

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8.2.14 Route of Administration

Intravenous.

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8.2.15 Availability

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Investigational agent to be obtained from Division of Cancer Treatment and Diagnosis, NCI. Oxaliplatin is supplied to the NCI under a Cooperative Research and Development Agreement (CRADA) between Sanofi-Aventis and the NCI, DCTD.

Drug Ordering: Oxaliplatin (NSC #266046) may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained - see general information). The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF) and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution. Completed Clinical Drug Requests (NIH-986) should be submitted to the PMB by fax (301) 480-4612 or mailed to the Pharmaceutical Management Branch, CTEP, DCTDC, NCI, 9000 Rockville Pike, EPN, Rm. 707, Bethesda, M.D. 20892. The NCI Clinical Drug Request form is available on the NCI home page (www.cancer.gov) or by calling the PMB at (301) 496-5725.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 301-496-5725 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time.

Drug Returns: All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators must return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (<http://ctep.info.nih.gov>) or by calling the PMB at (301) 496-5725.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page (www.cancer.gov) or by calling the PMB at (301) 496-5725.

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8.2.16 Reported Adverse Events and Potential Risks

Please refer to the Oxaliplatin CAEPR in Section 5.9.

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8.2.17 Potential Drug Interactions (Both Formulations)

In vitro, oxaliplatin is not metabolized by, nor does it inhibit, human cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP3A4, CYP2D6, or CYP2E1. Metabolically mediated drug-drug interactions of oxaliplatin on co-administered drugs cleared by these CYP isoforms are not anticipated in humans.

No significant pharmacokinetic interactions between oxaliplatin and 5-fluorouracil, irinotecan, topotecan, or gemcitabine have been observed in patients.

Since platinum-containing compounds are eliminated primarily through the kidney, oxaliplatin clearance may be decreased by co-administration of potentially nephrotoxic compounds, although this has not been specifically studied.

In vitro, platinum was not displaced from plasma proteins by the following medications: erythromycin, salicylate, sodium valproate, granisetron, and paclitaxel. No plasma protein binding displacement interaction are anticipated in humans.

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8.2.18 Contraindications

Oxaliplatin should not be administered to patients with a known allergy to other platinum compounds.

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8.2.19 Nursing/Patient Implications

- Premedicate with antiemetics (5 HT3 antagonist and steroid) to prevent severe nausea and vomiting.
- Monitor for diarrhea and treat symptomatically.
- Monitor for neuropathies (paresthesias of hands, feet and toes and pharynx and occasionally cramps), if they occur, tend to be brief (less than one week) during the first course but longer with subsequent courses. Advise patients to avoid cold exposure and against touching cold objects. Sensory neuropathies develop with continued treatment. Ask patient if changes in ambulation, swallowing, breathing or fine motor activity have been noted.
- Prolonging the oxaliplatin infusion time to 6 hours may alleviate acute neurologic toxicities.
- Monitor for respiratory changes such as shortness of breath.

WARNING: The hemolytic uremic syndrome should be suspected in individuals who experience the following: unexplained severe hemolysis, hemoglobinemia and renal failure, as demonstrated by an increase in serum creatinine. (See section 8.2.16).

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8.2.20 References

Investigator's Brochure: Oxaliplatin. Sanofi Winthrop 1996

Prescribing Information: Oxaliplatin (Eloxatin) Sanofi- Sythelabo Inc., November 2004

8.3 5-Fluorouracil - For more information, please refer to the package insert.

8.3.1 Other Names

5-FU, Adrucil, Efudex

8.3.2 Classification

Antimetabolite.

8.3.3 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 and thus interfering in the synthesis of DNA. It also interferes with RNA synthesis.

8.3.4 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.

8.3.5 Dose Specifics

Arms A, B, D, E: 400 mg/m² then 2.4 gm/m² over 46 hours.

Arms C and F: 500 mg/m² over 1 hour.

8.3.6 Administration

Arms A, B, D, E: IV bolus followed by continuous infusion.

Arms C and F: IV bolus.

8.3.7 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.

8.3.8 Side Effects

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 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.

Ophthalmic: Eye irritation, nasal discharge, watering of eyes, blurred vision.

Hepatic: Hepatitis with hepatic infusion.

8.3.9 Nursing/Patient Implications

Monitor CBC, platelet counts.

Administer antiemetics as indicated.

Monitor for diarrhea. Encourage fluids and treat symptomatically - may be dose limiting.

Assess for stomatitis - oral care recommendations as indicated.

Monitor for neurologic symptoms (headache, ataxia).

Patients on continuous infusions may need instruction regarding central IV catheters and portable IV or IA infusion devices.

Inform patient of potential alopecia.

8.3.10 References

Hansen R, Quebbeman E, Ausman R, *et al.* Continuous systemic 5-fluorouracil in advanced colorectal cancer: Results in 91 patients. *J Surg Oncol* 1989; 40:177-181.

Freeman NJ, Costanza ME. 5-Fluorouracil-associated cardiotoxicity. *Cancer* 1988; 61:36-45.

8.4 Leucovorin - For more information, please refer to the package insert.

8.4.1 Other Names

Leucovorin Calcium, Wellcovorin, citrovorum factor, folinic acid, 5-formyl tetrahydrofolate, LV, LCV.

8.4.2 Classification

Tetrahydrofolic acid derivative.

8.4.3 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.

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.

8.4.4 Storage and Stability

All dosage forms are stored 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.

8.4.5 Dose Specifics

Arms A, B, D, E: 400 mg/m² IV over 2 hours.

Arms C and F: 500 mg/m² IV over 2 hours.

8.4.6 Preparation

The 50 and 100 mg vials for injection are reconstituted with 5 and 10 ml of sterile 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. Due to the increased preservative content with the higher doses of bacteriostatic water, only sterile water should be used for reconstitution of leucovorin doses greater than 10 mg/m² (i.e. doses utilized in this protocol).

8.4.7 Administration

Intravenous infusion over 2 hours.

8.4.8 Compatibilites

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.

8.4.9 Availability

Commercially available in parenteral formulations (50 mg, 100 mg and 350 mg vial).

8.4.10 Side Effects

Hematologic: Thrombocytosis.

Dermatologic: Skin rash.

Gastrointestinal: Nausea, upset stomach, diarrhea.

Allergic: Skin rash, hives, pruritus.

Pulmonary: Wheezing (possibly allergic in origin).

Other: Headache; may potentiate the toxic effects of fluoropyrimidine therapy, resulting in increased hematologic and gastrointestinal (diarrhea, stomatitis) adverse effects.

8.4.11 Nursing/Patient Implications

Observe for sensitization reactions.

When given with fluoropyrimidines, monitor closely for diarrhea and stomatitis.

8.4.12 References

Arbuck SG. Overview of clinical trials using 5-fluorouracil and leucovorin for the treatment of colorectal cancer. Cancer 1989; 63: 1036-1044.

Bleyer WA. New vistas for leucovorin in cancer chemotherapy. Cancer 1989; 63: 995-1007.

Grem JL. 5-Fluorouracil plus leucovorin in cancer therapy. In: Cancer: Practices and Principles of Oncology Updates. Devita VT, Hellman S, Rosenberg SA, editors. 1988; 2(7): 1-12.

8.5 Capecitabine - For more information, please refer to the package insert. Only available for patients on NSABP R-04.

8.5.1 Other Names

Xeloda

8.5.2 Classification

Orally administered prodrug of Fluorouracil which is an antimetabolite

8.5.3 Mode of Action

Capecitabine is a prodrug, which is readily absorbed intact from the GI tract, then converted in the liver by carboxyesterase to 5-deoxy-5-fluorocytidine, and ultimately to 5-fluorouracil by thymidylate synthetase. This enzymatic conversion occurs in all tissues, but is higher in colorectal tumors due to increased intratumoral levels of thymidylate synthetase. Capecitabine produces plasma concentrations of fluorouracil comparable to equivalent doses of intravenous fluorouracil administered by continuous infusion.

8.5.4 Storage and Stability

Store tablets at controlled room temperature. The drug is stable as per the manufacturer's expiration date.

8.5.5 Dose Specifics

As per protocol. Recommended daily dosage is 825 mg/ m² divided into two doses.

8.5.6 Preparation

Orally administered drug. Needs no preparation other than dispensing the proper amount of medication for that dosing period.

8.5.7 Administration

Drug is administered orally with food in two divided daily doses. Dose should be taken with water.

8.5.8 Compatibilities

Drug – Drug Interactions:

Folic Acid may increase fluorouracil concentrations and may increase the toxicity.

8.5.9 Availability

Commercially available as 150 mg and 500 mg tablets, in bottles of 120 and 240 mg respectively. Only available for patients on NSABP R-04.

8.5.10 Side Effects

Gastrointestinal: Nausea, vomiting, diarrhea, mucositis, stomatitis. abdominal pain, cachexia, anorexia. Diarrhea can be life threatening and is dose limiting

Dermatological: Hand – Foot Syndrome (dose limiting), photosensitivity, radiation recall

Cardiovascular: Angina, Cardiac Sudden death (reported with fluorouracil)

Hematologic: Neutopenia, thrombocytopenia, anemia, lymphopenia

Immune System: Susceptibility to infections

Musculoskeletal: Myalgias

Hepatobiliary: Hyperbilirubinemia

8.5.11 Nursing/Patient Implications

Monitor CBC

Assess for hand-foot syndrome, oropharyngeal lesions

Reinforce importance of taking medication as instructed. Various patient aids are provided by manufacturer to assist patient and caregivers

Assess for diarrhea. Instruct patient to report any symptoms immediately

Reinforce any dosage changes/ reductions which are ordered due to side effects

8.5.12 References

Xeloda product information

Kerr, R Capcitabine/ irinotecan Combinations in Colorectal Cancer. Oncology (supplement) 2002, 16: 27-29

Freeman NJ, Costanza ME. 5- Fluorouracil associated cardiotoxicity. Cancer 1988 61: 36-45

Budman DR Mropol NJ Reigner B, et al: Preliminary studies of a novel fluoropyrimidine carbamate: Capecitabine . J Clin Oncol 16: 1795-1802 1998

Gradishar WJ: Clinical status of capecitabine in the treatment of breast cancer. Oncology 15 (1) supplement: 69-72 2001

Prepared by Gary Mead 5/2002

9. Statistical Considerations

9.1 Clinical Endpoints

The main endpoint of this trial is overall survival (OS). We expect OS to be 75% at three years for the control arm (5-FU/LV, Arms C [Group 1]/F [Group 2]) and the study is designed to target a hazard ratio of 1.3 (75% vs 80% OS at 3 years; 62% vs 69% at 5 years) in either of the experimental arms, Irinotecan/5-FU/LV (Arms A [Group 1]/D [Group 2]) or Oxaliplatin/5-FU/LV (Arms B [Group 1]/E [Group 2]).

With all major cooperative groups participating in this study, we expect to achieve an accrual rate in the range of 600 patients per year (200 patients per arm per year). With the expected accrual and failure rates given above, the study will have over 82% power to detect a hazard ratio of 1.3 for OS between either experimental arm and control with 3,000 total eligible patients (600 eligible patients per year for 5 years) and follow-up of 1.5 years after closure to accrual. With an expected ineligibility rate of 5%, this trial may enter 3,150 total registrations. This design incorporates 7 interim analyses and one final analysis at 6.5 years post activation for overall survival. One interim analysis will occur every six months corresponding to scheduled ECOG Data Monitoring Committee (DMC) meetings, once the trial achieves 25% expected information (142 total failures, at roughly 36 months post activation). Analyses will use stratified log rank tests (stratified on the factors listed in section 4.26) with an overall 0.0167 (=0.05/3) one-side type I error. Full information will occur at 564 total deaths. The O'Brien-Fleming group sequential boundary will be used to adjust for the sequential testing and the use function methodology of Lan and DeMets will be employed to adjust the boundaries if the actual interim analyses do not correspond with the projected information times given here. Group sequential O'Brien-Fleming boundaries for the first three interim analyses will be truncated at 0.00033. Simulation studies conducted by the ECOG Statistical Center and others (Friedlin, Korn and George) (108) suggest that overall test size is inflated by a negligible factor from the truncation, but there may be a small gain in terms of expected stopping time.

Assuming one of the experimental arms is no different from the control arm and the other experimental arm is active, power for a true hazard ratio of 1.30 to compare the two experimental arms using a two-sided 0.0167 level test is 74% (power is 82% for a hazard ratio of 1.33). If both of the experimental arms are active (at least 80% OS at 3 years), the power to detect a hazard ratio of 1.30 between experimental arms, using a two-sided 0.0167 level test is 64% (power is 80% for a hazard ratio of 1.37). Power to compare the experimental arms will also be higher with longer follow-up.

This study will be monitored for early stopping in favor of the null hypothesis using repeated confidence interval methodology similar to that described by Jennison and Turnbull (109). At each interim analysis nominal one-sided (1-alpha) confidence intervals on the overall survival hazard ratios comparing the experimental arms to control will be computed, where alpha is the nominal one-sided significance level of the use function boundary at the information fraction at the particular analysis time. If the confidence intervals do not contain the target alternative of 1.3, the ECOG DMC may consider closing an experimental arm or stopping the trial early for overall lack of a treatment difference. Conversely, if an experimental arm is found to be statistically superior to the control arm at a particular interim analysis before accrual is completed, the ECOG DMC may consider closing the control arm to further accrual.

Patient follow-up will be completed per section 7.0. All patients will be followed at least yearly for survival for a period of 10 years post registration.

9.2 Laboratory Correlates

Objectives 2.4 and 2.5 seek to determine the prognostic and predictive significance of TS and other key targets of 5-FU, ERCC1 and other enzymes involved in repair of oxaliplatin adducts and molecular markers (18q allelic loss, MSI and p53 gene mutation) for overall survival in

rectal cancer. We base power calculations for these endpoints on our previous ECOG experience in adjuvant colon cancer with TS and 18q allelic loss. Results in adjuvant colon cancer have shown that roughly 80% of cases showed high levels of expression (2+/3+) and 20% of patients showed no or low levels of expression (0/1+). Also, we observed an absolute 10% difference in OS at 5 years in the colon series, with highly expressing patients exhibiting worse survival. Using these figures, we anticipate having at least 85% power to detect an 8% absolute difference in OS at 5 years in this study (from 63% in the highly expressing group to 71% in the low/no expression group; a 35% increase in median overall survival). Calculations are based on the accrual and follow-up assumptions given in the previous section and a two-sided 0.05 level logrank test for overall survival, assuming 85% of the patients contribute evaluable samples to the correlative component of the trial. If the split between low and high expression groups is more evenly distributed (50% in each group) then the power will be higher to compare these groups, greater than 95%. We expect that the other targets of 5-FU will have power similar to that described above for TS.

For molecular marker analysis we use 18q allelic loss to estimate power and expect that other molecular markers will have similar power. In our previous adjuvant colon correlative study we found that roughly 50% of samples showed 18q loss of heterozygosity (LOH) and 50% showed no loss, with an absolute difference in overall survival at 5 years of 19% (69% for no loss group versus 50% in the LOH group). Assuming that the rectal cases in this study will exhibit similar patterns of LOH, we anticipate that there will be greater than 95% power to detect a smaller difference, 63% versus 73% at 5 years, again assuming that 85% of the samples will be available for this analysis. If the 18q LOH split is different from 50:50, say 25% of cases with LOH and 75% of cases with no loss, then the power will still be high, greater than 95%. With 50% of cases showing LOH, there will be 83% power to detect an absolute difference as small as 30% in overall survival (63% versus 70% at 5 years).

9.3 Bowel Function and Quality of Life Endpoints

9.3.1 Quality of Life (QOL) Data Analysis

Analytical processing of the patient bowel function questionnaire (PBF), Uniscale, and FACT Diarrhea Subscale (FACT-D) will be comparable. We will calculate summary scores for the PBF and FACT-D as prescribed by the tool authors. The PBF will provide a score representing the number of problems experienced by the patient with bowel functioning as well as with individual aspects of bowel function. The FACT-D produces a single total score transformed onto a 0-100 point range. The Uniscale is a single-item score from 0-100.

Each of the endpoints mentioned in the previous paragraph will be compared across the two treatment groups. The main statistical comparison across treatment arms will be the change score from baseline to last assessment (18 month post treatment) in each group. The summated scores from the PBF, FACT-D, and Uniscale will be compared via ANOVA and two-sample t-tests (two-sample tests will be performed at a two-sided significance level of $0.05/3=0.0167$). Supplementary analyses will include analysis of covariance modeling of the differences between groups over time in each of the QOL endpoints while holding constant the various demographic and treatment covariates. The proportion of patients that report problems with different aspects of bowel function will be compared across groups using equality of binomial proportions testing. Further analysis will involve an examination of the clinical significance for changes over time by calculating the percentage of patients in each treatment group that report an improvement of more than 10 points on the 0-100 point scale for any QOL endpoint (110-112). These percentages will be compared via chi-square testing. All testing will be done using a two-tailed overall 5% Type I error rate (0.0167 level for each of three pairwise comparisons).

Concurrent validity of the QOL measures will be ascertained by calculating the difference in scores between the Uniscale, PBF, and FACT-D values for each patient

followed by a number of approaches. First, simple correlational data will be obtained via the use of Spearman's rho correlation coefficient with validity being determined to have been established if the monthly correlation coefficients are all within the range of 0.5 to 0.75 (113). Simple paired comparison procedures (t-tests, Wilcoxon procedures) will be used based on the results of normality testing (114) and the measurement comparison procedures of Bland and Altman (115). Equality of trends over time analysis will be carried out by calculating the slope of the QOL scores over time and testing for equality of slopes across the two measures and by subsequently testing for a zero slope for the trend of different scores over time. Finally, area under the curve analysis will be completed by calculating the difference of the area under the curves for the two measures and using the same simple univariate tests for measures of central tendency specified above.

9.3.2 Power considerations for QOL data

A two-sample t-test with 1000 patients per group provides over 90% power to detect a difference of 20% times the standard deviation. This effect size has been classified as small and minimally clinically significant by various authors. Hence, we will have sufficient power to detect all clinically significant differences between individual treatment groups. With 1000 patients per group, we will have over 90% power to detect differences of 10% in the rate of bowel function problems reported between groups by standard equality of binomial proportions testing.

9.3.3 Handling of Missing QOL Data

Several approaches to missing data will be employed including alternatives that carry forward the mean, minimum, maximum, last value, and zero value (in the case of death) for the purposes of verifying that the results for treatment comparisons are consistent relative to various assumptions and impact of the randomness of the missing data (117, 116). Previous experience with imputation in clinical trials has demonstrated that the use of various imputation methods compared to complete cases analysis provides evidence of the degree of robustness of the results relative to the assumptions of the analytical procedure (118). We do not expect the amount of missing data to exceed 20% and therefore the results should remain relatively resistant to missing data. We will examine the data for any influence that would be likely to cause data to be missing for any other reason than simple random chance. In other words, we will explore the dataset for evidence to suggest that any concomitant influence may cause the data to not be missing completely at random. (117, 116, 119)

9.4 Ethnicity/Racial Breakdown by Gender

Expected accrual: 50 per month (600 per year). Accrual goal is 3000 eligible patients.

Ethnic Category	Gender		
	Males	Females	Total
Hispanic or Latino	21	34	55
Not Hispanic or Latino	1950	995	2945
Ethnic Category: Total of all subjects	1971	1029	3000
Racial Category			
American Indian or Alaskan Native	11	8	19
Asian	77	43	120
Black or African American	95	80	175
Native Hawaiian or other Pacific Islander	10	6	16
White	1778	892	2670
Racial Category: Total of all subjects	1971	1029	3000

Estimates are based on past protocols E1297, E4290, S9304, R9401.

10. Pathology Review

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NOTE: ECOG's diagnostic review project for secondary AML/MDS ended December 1, 2005. Submission of secondary slides upon diagnosis of secondary AML/MDS for central diagnostic review and classification is no longer required. Submit materials requested for correlative studies per patient consent.

10.1 The clinical investigator and the submitting pathologist are responsible for submitting representative diagnostic materials for correlative studies. When a patient is registered to receive protocol therapy, the submitting pathologist and clinical research associate should refer to Appendix II (Pathology Submission Guidelines) which provides the following:

10.1.1 Instruction Sheet from ECOG Pathology Coordinating Office providing details for the Submission of Pathology Materials.

10.1.2 Memorandum to the submitting pathologist from Stanley Hamilton, M.D., chair, ECOG Pathology Committee, providing details for the Submission of Pathology Materials.

10.1.3 A list of required materials.

10.1.4 An ECOG Pathology Material Submission Form (#638).

10.2 The materials required for this protocol are:

10.2.1 ECOG Pathology Material Submission Form (#638), Parts A & B completed. Please identify the clinical status of the submitted material (i.e., pretreatment as opposed to remission and relapse).

10.2.2 A copy of the surgical pathology report.

It is imperative that the number of lymph nodes retrieved in the surgical specimen is mentioned within the surgical pathology report. In addition to the surgical pathology report, if immunologic studies have been performed at the home institution, it is necessary that these be forwarded as well.

10.2.3 Sample Submission

For Correlative Study

Analysis of 18q allelic loss status and MSI status requires evaluation of DNA from tumor tissue and control non-neoplastic tissue, preferably mucosa, in routine formalin-fixed, paraffin-embedded histologic sections. Immuno-histochemistry requires tissue sections on positively charged slides.

The requested specimens are:

- In patients receiving pre-operative treatment (Group I): formalin-fixed, paraffin-embedded block from pre-treatment biopsy tissue including cancer
- In all patients: from surgical resection specimen
 - One block containing tumor tissue
 - One block containing mucosa tissue

NOTE: If tissue blocks cannot be submitted, contact the PCO regarding the appropriate alternative sample submission. Contact information is provided in Section 10.3.2.

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[Deleted in Update #2]

NOTE: If pathology materials cannot be submitted, please indicate the reason on the ECOG Pathology Material Submission Form (#638) and include a letter of explanation.

NOTE: A copy of the completed submission form will be sent to the Coordinating Center by the Pathology Coordinating Office.

10.3 Shipping Procedures

10.3.1 Submission Schedule

10.3.1.1 Pretreatment biopsy materials (Group I) and surgical resections (Group II) are to be submitted within one month after registration

10.3.1.2 On study surgical resections (Group I) are to be submitted within one month following the surgery.

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[Deleted in Update #2]

10.3.2 Submit materials to:

ECOG Pathology Coordinating Office
Robert H. Lurie Comprehensive Cancer Center
of Northwestern University Medical School
Olson Pavilion - Room 8501
710 North Fairbanks Court
Chicago, IL 60611
Tel: (312) 503-3384
FAX: (312) 503-3385

The ECOG Pathology Coordinating Office will forward the appropriate pathology materials to Dr. Stanley Hamilton's laboratory at MD Anderson Cancer Center for microdissection, DNA extraction and molecular analysis, and to Dr. Robert Diasio's laboratory at the University of Alabama at Birmingham for RNA extraction and immunohistochemistry.

10.4 Processing and Routing by the Pathology Coordinating Office

10.4.1 For the correlative studies (defined in section 11.0), the PCO will section the blocks and forward the appropriate materials to Dr Hamilton and Dr. Rashid for analysis.

Section Number	Processing	Purpose
1	H&E-stained slide	Documentation of block status upon receipt at PCO
2	H&E-stained slide	Microdissection guidance at MDACC
3-12	unstained slides	DNA extraction for marker analysis at MDACC
13-17	unstained slides	For future analysis of TS, TPD, etc.
18	1 unstained slide	Archive at PCO
19	H&E-stained slide	Documentation of block status completion of sectioning at PCO

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10.4.2 [Deleted in Update #2]

10.5 Banking

The residuals tissue blocks and/or slides collected for the correlative studies described in Section 10.0 will be retained at the ECOG Central Tissue Repository for possible future use in GI Intergroup approved studies. Any residual blocks will be available for purposes of individual patient management upon specific written request. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

11. Correlative Studies

11.1 Marker Analysis

The correlative studies will evaluate chromosome 18q allelic loss, microsatellite instability including mutation of the gene for transforming growth factor beta 1 type II receptor (TGFβ1RII), p53 gene mutation, and expression of thymidylate synthase (TS), dipyrimidine dehydrogenase (DPD), thymidine phosphorylase (TP), excision repair cross-complementing 1 (ERCC1), ERCC2 and XPF genes. The correlative studies are summarized in the following table:

Marker	Method	Results format	Laboratory
Chromosome 18q allelic loss	PCR and automated sequencing of D18S69, D18S64, D18S55, D18S61, D18S58 in tumor and control DNA	Shift, no shift + loss, no shift + no loss, or unsatisfactory for each marker Complete loss, partial loss, no loss, or unsatisfactory for each tumor	Molecular Diagnostics Laboratory, M.D. Anderson Cancer Center
MSI including TGFβ1RII gene mutation	PCR and automated sequencing of BAT25, BAT26, D2S123, D5S346, D17S250 & TGFβ1RII in tumor and control DNA	Shift or no shift for each marker MSI-H + TGFβ1RII mutation, MSI-H + no TGFβ1RII mutation, MSI-L or MSS from 11 markers (18q and MSI sets) for each tumor	Molecular Diagnostics Laboratory, M.D. Anderson Cancer Center
p53 gene mutation	PCR amplification and automated sequencing of exons 5-8	Mutation or no mutation	Molecular Diagnostics Laboratory, M.D. Anderson Cancer Center
TS, DPD, TP expression	Kinetic quantitative RT-PCR Immunohistochemistry with Roche antibody kits	Crossing point values with algorithm for RT-PCR Semi-quantitative scoring of intensity (0-4+) and proportion of cells (0-100%) for score of 0-400 for immunohistochemistry	Laboratory of Dr. Robert Diasio, University of Alabama-Birmingham
ERCC1, ERCC2 and XPF expression	Kinetic quantitative RT-PCR Quantitative RT-PCR	Crossing point values with algorithm for RT-PCR	Laboratory of Dr. Robert Diasio, University of Alabama-Birmingham

Five polymorphic dinucleotide markers on 18q (D18S69, D18S64, D18S55, D18S61 and D18S58 from centromere to telomere) and the National Cancer Institute Consensus MSI Panel of two mononucleotide markers (BAT25, BAT26) and three dinucleotide markers (D2S123, D5S346 and D17S250) and the mononucleotide marker in transforming growth factor beta type II receptor are amplified in DNA extracted from tumor and normal control tissue with multiplex PCR and sequenced with the ABI 3700 instrument in the Molecular Diagnostics Laboratory by the protocol-assigned technologist, as detailed in our previous

publication (43). Peak sizes are quantitated and the chromatogram tracings and quantitative data are reviewed with Drs. Hamilton and/or Rashid.

Mutation of the p53 gene in exons 5 through 8 will be evaluated by PCR amplification from tumor DNA and automated sequencing on the ABI 3700 instrument in the Molecular Diagnostics Laboratory by the protocol-assigned technologist, as in our previous publications (124, 125). The chromatogram tracings will be reviewed with Drs. Hamilton and/or Rashid.

Evaluation of TS, DPD, TP, ERCC1, ERCC2 and XPF expression will be carried out in the laboratory of Dr. Robert Diasio. Drs. Diasio and Soong have laboratory space of 2000 square feet on the sixth floor of the Wallace Tumor Institute located on the School of Medicine Campus at the University of Alabama at Birmingham. The labs are modern, wet laboratories set up for biochemical and molecular studies with space dedicated for cell culture, PCR and biochemical assays. In these laboratories are two kinetic PCR (Roche LightCycler and ABI7700 Sequence Detector) Instruments, an ABI310 Genetic Analyzer for DNA sequencing, a PALM Robot-Microbeam Laser Capture Microdissector, a Pharmacia GeneQuant II Spectrophotometer and a WAVE Denaturing HPLC Instrument for the detection of sequence variants.

Dr. Soong will be supervising the entire process from the receipt of samples, the design, validation and performance of assays to the compilation of the results. He has extensive expertise in assay design and translational studies and has developed a number of kinetic RT-PCR systems, application kits and quantification concepts used commercially and patented by Roche Diagnostics, including those to be used in this study. Dr. Soong has also published some of the largest series on the clinical relevance of p53 alterations, microsatellite instability and cytokeratin 20 in various cancer types, including colorectal cancer.

RNA Extraction from Paraffin-Embedded Tissue (PET) Microdissected PET from 10µm sections will be sent to the University of Alabama at Birmingham. RNA will be isolated from this tissue using the standardized protocols in the High Pure RNA Paraffin Kit (Roche Cat#3270289, Indianapolis, Indiana). Briefly, tissues are homogenized and digested overnight in a buffer containing Proteinase K. The digest is then loaded onto a spin column containing glass fibers that bind nucleic acids. Through successive washing steps, contaminants are removed and eventually nucleic acids are eluted from the column into a 50µl solution. This process also involves incubation with DNase I and a second Proteinase K digestion to maximize RNA purity. Using a prototype of this kit, an ability to amplify RNA from macrodissected paraffin-embedded tissue and a correlation between RNA levels obtained from these tissues and immunohistochemical results has been shown previously (126).

Kinetic RT-PCR Quantification of RNA levels of markers of 5-fluorouracil and oxaliplatin response. Quantification of DPD, TP and TS RNA levels will be performed by kinetic (or "real-time") RT-PCR on the LightCycler Instrument (Roche, Indianapolis, Indiana) according to the assay systems described in the LightCycler - DPD mRNA Quantification Kit^{PLUS} (Roche Catalog#3302938), LightCycler - TP mRNA Quantification Kit^{PLUS} (Cat#3302946) and LightCycler - TS mRNA Quantification Kit^{PLUS} (Cat#3302954) kits respectively. In these kits, 10µl of RNA eluate is converted to cDNA in a 30µl reaction including 1x reverse transcriptase reaction mix, deoxynucleotide triphosphates, RNase inhibitor, a gene specific primer and AMV reverse transcriptase; incubated at 25°C for 10 minutes, 42°C for 60 minutes and 94°C for 5 minutes. Four µl cDNA is then submitted to kinetic PCR in a 20µl reaction containing 1 x PCR reaction mix, a "hotstart" Taq polymerase and gene-specific oligonucleotide primers and fluorescent probes. The incubation times are 95°C for 5 minutes, 40 cycles of 95°C for 10 seconds, 62°C for 10 seconds and 72°C for 10 seconds before cooling at 40°C for 30 seconds.

In kinetic PCR, the addition of fluorescent probes allow monitoring of amplification kinetics and hence, determination of a crossing point (CP or "cycle threshold") at a partial cycle number at which fluorescence becomes detectable above background levels. CP values are

linearly correlated to gene concentration (127) hence, gene quantities are determined using CP values and an algorithm included in the LightCycler Relative Quantification software (Roche). The algorithm calculates equivalent quantities to standard curve methods (120). To standardize kits and normalize for sample loading and inter-run variation, final quantities are expressed as ratios of target to a reference (or “housekeeping”) gene in the test sample, relative to the ratios of target to reference gene in a calibrator sample included in each run. Calibrator samples are included in each kit and production lot-standardized.

The kits for DPD, TP and TS RNA quantification use the same kinetic RT-PCR system that has been validated previously (128). This system had a dynamic range of at least 1000000 and was able to detect down to a single gene copy for different gene targets. From 27 individual determinations, involving 3 different sample concentrations, 3 separate RT reactions and 9 individual PCR runs, the co-efficient of variation for the crossing point (CP) values of detection was 0.4-1.2% and the sample quantity was 12% for this system.

Detection mixes containing oligonucleotide primers and fluorescent probes for DPD, TP, TS and the reference gene, glucose-6-phosphate dehydrogenase (G6PDH), are included in each kit. For the quantification of ERCC1, ERCC2 and XPF RNA levels, detection mixes will be designed and validated for analysis in the same kinetic-RTPCR system as the other kits. To facilitate amplification from PET, small PCR amplicon sizes will be designed.

Immunohistochemical (IHC) analysis of DPD, TP and TS protein levels. Five µm sections containing areas of normal and tumor tissue and continuous to those used for the analysis of other molecular markers will be sent to the University of Alabama at Birmingham for IHC analysis. IHC detection of DPD, TP and TS protein expression will be performed according to the protocols in the Anti-DPD Antibody, Formalin-Grade (Roche, Cat #3183645), Anti-TP Antibody, Formalin-Grade (Cat#3183653) and Anti-TS Antiserum, Formalin-Grade (Cat#3186008) kits respectively. Briefly, after deparaffinization and rehydration, sections undergo antigen retrieval by steaming for 5 minutes. They are then blocked with 20% normal goat serum for 20 minutes before overnight incubation at 4°C with either DPD, TP or TS antibody/antiserum diluted 1:100. Secondary Envision+ peroxidase antibody (Dako Inc., Glostrup, Denmark), specifically anti-rabbit for DPD, TS and anti-mouse for TP, are added to the sections for 30 minutes before color development with liquid DAB (Dako) for 20 minutes and counterstaining with Mayer’s haematoxylin. For DPD, sections are incubated with rabbit anti-rat immunoglobulins (Dako) diluted 1:100 for 30 minutes prior to the addition of the secondary antibody. Between each incubation step, sections are washed twice with 1xPBS for 5 minutes. A negative control section without the addition of DPD, TP or TS-specific antibodies/antisera will be included for each IHC run. A positive control section from a tissue with known immunostaining patterns for DPD, TP and TS will also be included with each run and will be examined for consistency of staining.

Protein expression from the IHC stains will be evaluated using a semi-quantitative scoring strategy described previously that takes into account both the intensity and extent of staining (129). Immunostains are assessed on their intensity on a scale of 0 (no staining) to 4+ (strongest intensity). The proportion of cells of each intensity to a total of 100% is determined and the final score obtained by multiplying each intensity with the proportion of cells allotted to it, thus allowing a maximum score of 400 (100% at 4+ intensity). For each section, 8 individual IHC scores will be determined based on the localization of stains in combinations of normal mucosa or tumor, epithelium or stroma and nucleus or cytoplasm. To reduce bias, scores will be determined by two independent investigators and averaged.

It is recognized that there are additional predictive markers that may be of interest during the accrual period of this study. The banking of tissue blocks and/or slides (Section 11.4) will provide the necessary flexibility to add additional tumor markers. The study team and the Gastrointestinal Intergroup will consider the addition of future markers for analysis.

11.1.1 Tumor Marker Reporting

11.1.1.1 Chromosome 18q allelic loss: Loss of an 18q allele will be determined by a >50% reduction in the area under the peak for 1 allele in tumor DNA as compared to non-neoplastic tissue for at least 1 of 2 polymorphic markers. The results for each marker will be recorded along with the summary interpretation. (see Section 11.1.1.3 below)

11.1.1.2 Microsatellite Instability (MSI)

Microsatellite instability (MSI) status will be interpreted on the basis of shifts in allele size with the criterion of >50% increase in tumor DNA as compared to the corresponding peak in mucosal DNA on the chromatogram. The 8 dinucleotide and 3 mononucleotide markers will be assessed. Tumors are then classified using criteria from the National Cancer Institute-sponsored workshop on MSI in colorectal cancer (93). Results for each marker are recorded in the project database.

Classification of the tumor is based on the following criteria: microsatellite-stable cancers have shift in none of a minimum of eight evaluable markers; cancers with low levels of microsatellite instability (MSI-L) have shift in less than 30% of evaluable markers among a minimum of eight; and cancers with high levels of microsatellite instability (MSI-H) have shifts in >30% of evaluable markers among a minimum of eight. In microsatellite-stable cancers, loss of an 18q allele will be determined by a >50% reduction in the area under the peak in tumor of at least 1 of the 2 polymorphic markers, as compared to non-neoplastic tissue.

11.1.1.3 Molecular Classification

Each tumor is classified on the molecular pathway alterations and results of previous correlative studies. A standardized report form is prepared including the list of each marker results and the interpretation of the case as:

Microsatellite-stable with 18q allelic loss
Microsatellite-stable without 18q allelic loss
Low level of microsatellite instability (MSI-L) with 18q allelic loss
Low level of microsatellite instability (MSI-L) without 18q allelic loss
High level of microsatellite instability (MSI- with TGFβ1RII mutation
High level of microsatellite instability (MSI-H) without TGFβ1RII mutation
High level of microsatellite instability (MSI-H) with TGFβ1RII mutation

11.1.1.4 p53

p53 mutation analysis will be reported as:

No mutation

Mutation (nucleotide change, codon, exon and amina acid change.)

The report will be prepared by the technologist and the chromatogram reviewed and reports signed by Drs. Hamilton or Rashid.

11.1.1.5 Thymidylate Synthase (TS), Dipyrimidine Dehydrogenase (DPD), and Thymidine Phosphorylase (TP) Expression

TS, DPD and TP expression will be reported independently as gene quantity for RT-PCR and as score of 0-400 for immunohistochemistry.

11.1.1.6 ERCC1, ERCC2, and XPF Expression

ERCC1, ERCC2, and XPF expression will be reported independently as gene quantity for RT-PCR.

11.2 Specimen Processing for Molecular Analysis

Upon receipt in Dr. Hamilton's office, the case is logged into the project database and the stained slide is examined histologically by Dr. Hamilton or Dr. Asif Rashid of the GI Pathology Research Laboratory for the presence of tumor and mucosa and for tissue quality for quality assurance/quality control purposes. The review results are recorded in the database. Tumor and mucosa tissue areas for DNA extraction are marked on the H&E slide to serve as the microdissection guidance slide. The unstained slides and marked H&E slide are delivered to the Molecular Diagnostics Laboratory (CLIA-88 approved) at M.D. Anderson Cancer Center and logged into the project database. The demarcated areas are scraped by scalpel (the vast majority of colorectal cancers can be microdissected satisfactorily by scalpel scraping rather than the more time-consuming method of laser capture microdissection) into separate tubes by the project-assigned technologist. For unusual cases with difficult scalpel microdissection, Drs. Hamilton or Rashid will carry out laser capture microdissection in the Department of Pathology shared facility and the tubes will then be transported to the Molecular Diagnostics Laboratory for DNA extraction. The microdissected slides and histologic guidance slide are filed in the GI Pathology Research Laboratory (Stan Hamilton, MD, Principal Investigator) for possible future review.

11.2.1 DNA Extraction and Purification

The tube of tumor and the tube of mucosa are processed to DNA separately by the project-assigned technologist using standard methods in the Molecular Diagnostic Laboratory (MDL). An aliquot of DNA for marker analysis, an aliquot for collaborator analysis, and an aliquot for backup storage are prepared.

11.3 Banking

11.3.1 Tissue blocks and slides

The residuals tissue blocks and/or slides collected for the correlative studies described in Section 10.0 will be retained at the ECOG Central Tissue Repository for possible use in GI Intergroup approved future studies. Any residual blocks will be available for purposes of individual patient management upon specific written request. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

11.3.2 Residual DNA Specimen

The remaining DNA after analysis is stored in a -80°C freezer in the Molecular Diagnostics Laboratory in the event of additional need for additional analysis.

11.3.3 Collaborators' DNA Specimen

The aliquot of DNA for each case is stored in a -80°C freezer in the Molecular Diagnostics Laboratory for batch shipping to the ECOG PCO for later shipping to approved collaborators' laboratories when needed. The ECOG PCO is notified of the storage specimens for logging in the Pathology Coordinating Office database.

11.3.4 Backup DNA Aliquot

The backup DNA aliquot is stored in a -80°C freezer in the Gastrointestinal Pathology Research Laboratory at M.D. Anderson Cancer Center.

11.4 Sample Inventory Submission Guidelines

Inventories of all samples collected and the respective aliquots made and used on the above mentioned laboratory correlative studies will be submitted to the ECOG Coordinating Center

on a monthly basis. Inventories will be submitted electronically or by diskette by any laboratory holding and/or using any specimens associated with this study. Electronic submissions should be submitted to ecog.labdata@jimmy.harvard.edu. All other correspondence should be addressed to the attention of the Correlative Science Team.

11.5 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory correlative studies will be submitted to the ECOG Coordinating Center by the central laboratory on a quarterly basis. The quarterly cut-off dates are March 31, June 30, September 30 and December 31. Lab data are due at the ECOG Coordinating Center one week after these cut-off dates. Electronic submissions should be submitted to ecog.labdata@jimmy.harvard.edu. All other correspondence should be addressed to the attention of the Correlative Science Team.

11.6 CTSU Sample Submissions

Submit samples to ECOG Pathology Coordinating Office and follow instructions in Section 10.

12. Records to Be Kept

Please refer to the E3201 Forms Packet for the forms submission schedule and copies of all forms. The E3201 Forms Packet may be downloaded by accessing the ECOG world wide web home page (<http://www.ecog.org>). Forms must be submitted to the ECOG Coordinating Center, FSTRF, 900 Commonwealth Avenue, Boston, MA 02215 (ATTN: DATA).

12.1 This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly (due dates January 31, April 30, July 31, October 31) from the ECOG Coordinating Center to CTEP electronically.

12.2 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be used in support of a US marketing application (New Drug Application), all records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

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12.3 ECOG Radiation Oncology Quality Assurance Materials

All radiotherapy quality assurance materials should be submitted to QARC:*

Quality Assurance Review Center
ATTN: ECOG Materials
272 West Exchange Street, Suite 101
Providence, RI 02903-1025
Tel:(401) 454-4301
FAX: (401) 454-4683

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Radiation Oncology Materials	QARC Due Date
<p>Copy of Appendix IV: Checklist For Submission of Radiation Oncology Quality Assurance Materials</p> <p>ECOG Rectal Cancer On-Study Form</p> <p>E3201 Baseline Data Form</p> <p>Prescription Sheet for Entire Treatment</p> <p>Preoperative Imaging studies: CT with contrast and barium enema (if available)</p> <p>Treatment Planning CT/diagnostic imaging and reports</p> <p>Beam Verification (portal) Films of ALL Fields</p> <p>Simulation Films and/or DRR's of ALL Fields (indicating any planned field reductions)</p> <p>Picture of patient in treatment position</p> <p>Color Copies of Isodose Distributions along with the corresponding beam data printouts from the planning system (see Section 5.104)</p> <p>Monitor Unit Calculations</p> <p>Completed Daily Treatment Record</p> <p><u>3D-Conformal Planning: Submit the following in addition to the above materials</u></p> <p>Description of each treatment field</p> <p>Orthogonal anterior/posterior and lateral films if not part of portals</p> <p>BEV's of each treatment field</p> <p>REV or overview diagram</p> <p>Dose Volume Histograms</p>	<p>Within 1 week of the completion of radiation</p>

All materials must be labeled with the ECOG assigned Protocol and Sequence numbers

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Please contact QARC ECOG CRA TEL: 401-454-4301 or FAX: 401-454-4683 for clarification as necessary

13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

14. References

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Intergroup Randomized Phase III Study of Postoperative Irinotecan, 5-Fluorouracil and Leucovorin vs Oxaliplatin, 5-Fluorouracil and Leucovorin vs 5-Fluorouracil and Leucovorin for Patients with Stage II or III Rectal Cancer Receiving Either Preoperative Radiation and 5-Fluorouracil or Postoperative Radiation and 5-Fluorouracil

Version Date: June 26, 2008

Appendix I

Suggested Patient Consent Form

You are being asked to take part in this study because you have rectal cancer and you may benefit from additional treatment. This is a type of clinical trial (research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision and discuss it with your friends and family.

WHY IS THIS STUDY BEING DONE?

This study involves treatment with chemotherapy, radiation therapy and surgery. This research is being done to compare the effects (good and bad) of a combination of chemotherapy medications. To date, there have been very few studies of different combinations of chemotherapies for patients with rectal cancer, who have already had surgery and radiation. This study will compare the investigational treatment combinations of irinotecan/leucovorin/5-fluorouracil or oxaliplatin/leucovorin/5-fluorouracil with the standard therapy leucovorin/5-fluorouracil.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 3000 people in the United States and Canada will take part in this study.

WHAT IS INVOLVED IN THIS STUDY?

This is a randomized study which means that the three chemotherapy treatment combinations are compared with each other to find out if one is better and also to see if the order in which therapies are given will affect outcome. If you agree to enter this trial, you will be randomly assigned to receive one of the three chemotherapy combinations. You have an equal chance of an assignment to any one. This helps to make the results of the research more scientifically sound. Neither you nor your doctor will have a say as to which schedule you are assigned to, but both you and your doctor will be informed as to which treatment you will receive.

The majority of patients with newly-diagnosed rectal cancer are treated with a combined program of chemotherapy, radiation and surgery; however, the order or sequence in which these treatments are given may vary, as may the chemotherapy which is administered during radiation. Patients and their physicians get to choose which of two treatment groups they will be in.

There are two treatment groups in this trial. One group receives radiation therapy combined with 5-fluorouracil chemotherapy before surgery. The second group receives surgery first, followed by one of the combination chemotherapies, followed by radiation therapy with 5-FU, followed by more combination chemotherapy. The radiation will be given Monday through Friday for about six weeks. You and your doctor will have a choice as to how the 5-fluorouracil will be administered. During the chemotherapy, the 5-fluorouracil may be administered by vein over several minutes with the leucovorin for four consecutive days of the first and fifth week of radiation OR the 5-fluorouracil may be administered continuously through a catheter in a large vein during the entire course of the combined radiation and chemotherapy (six weeks). If you are participating in a clinical trial (R-04) conducted by the National Surgical Adjuvant Project for Breast and Bowel Cancers (NSABP), you are potentially eligible to participate in this study. If you enter this study (E3201), you may receive a pill form of 5-fluorouracil (capecitabine), which you will take twice a day during the course of the radiation. The use of capecitabine with radiation is ONLY allowed for patients if they are receiving it by participating in R-04. In effect, you will be participating in both studies.

Whether you receive radiation with 5-FU before or after surgery, there is a rest period of at least three weeks (usually four to eight weeks) until you have recovered adequately from your operation. Group one patients (pre-operative radiation with 5-FU) will have surgery within three to six weeks after completing radiation. All patients will be treated according to one of the treatment schedules described below after their surgery.

[Please note: If you have received chemotherapy and radiation followed by surgery as described in the treatment plan, you may be able to participate in this trial. Your doctor will determine if you can join. You, also, will receive treatment according to one of the schedules described below.]

Schedule A - this is a two day treatment given every 2 weeks for a total of eight 2-week cycles. Medications are given before chemotherapy to prevent nausea and vomiting. All of the chemotherapy drugs will be given intravenously (through a vein). Irinotecan is given over 90 minutes; leucovorin is given over 2 hours, followed by 5-FU (5-fluorouracil) given as a quick infusion, followed by 5-FU given as a constant infusion through a portable pump over the next 46 hours.

Schedule B - this is a two day treatment given every 2 weeks for a total of eight 2-week cycles. Medications are given before chemotherapy to prevent nausea and vomiting. All of the chemotherapy drugs will be given intravenously (through a vein). Oxaliplatin is given over 2 hours; leucovorin is given over 2 hours, followed by 5-FU (5-fluorouracil) given as a quick infusion, followed by 5-FU given as a constant infusion through a portable pump over the next 46 hours.

Schedule C - this treatment is given weekly for six weeks followed by a two-week break and is given for a total of three 8-week cycles. All of the chemotherapy drugs will be given intravenously (through a vein). Leucovorin is given over 2 hours; 5-FU (5-fluorouracil) is given as a quick infusion after the start of the leucovorin.

Schedule D - this is a two day treatment given every two weeks for four 2-week cycles, followed by combined radiation therapy and chemotherapy. After completion of radiation therapy, four more 2-week cycles of the chemotherapy will be given. Medications are given before chemotherapy to prevent nausea and vomiting. All of the chemotherapy drugs will be given intravenously (through a vein). Irinotecan is given over 90 minutes; leucovorin is given over 2 hours, followed by 5-FU (5-fluorouracil) given as a quick infusion, followed by 5-FU given as a constant infusion through a portable pump over the next 46 hours.

Schedule E - this is a two day treatment given every two weeks for four 2-week cycles, followed by combined radiation therapy with chemotherapy. After completion of radiation therapy, four more 2-week cycles of chemotherapy will be given. Medications are given before chemotherapy to prevent nausea and vomiting. All of the chemotherapy drugs will be given intravenously (through a vein). Oxaliplatin is given over 2 hours; leucovorin is given over 2 hours, followed by 5-FU (5-fluorouracil) given as a quick infusion, followed by 5-FU given as a constant infusion through a portable pump over the next 46 hours.

Schedule F - this treatment is given weekly for six weeks followed by a two-week break. One 8-week cycle will be given followed by combined radiation therapy and chemotherapy. After completion of radiation therapy, two more 8-week cycles of chemotherapy will be given.

All of the chemotherapy drugs will be given intravenously (through a vein). Leucovorin is given over 2 hours; 5-FU (5-fluorouracil) is given as a quick infusion one hour after the start of the leucovorin

If you take part in the study, you will have the following tests and procedures. Some of the tests required for this study would be done even if you did not participate in the study.

- Female patients will have a pregnancy test.
- You will receive a complete physical exam and be seen by a physician at the beginning of each cycle of treatment and weekly during the course of radiation.
- Samples of your blood will be obtained, along with chest x-rays, CT scans or MRI to evaluate your health status.

In addition, you will be asked to fill out brief forms with questions about your bowel function. This will take about 10 to 15 minutes.

If you are in the group receiving radiation therapy with 5-FU before surgery, you will complete the questionnaire four (4) times:

1. Prior to radiation therapy
2. During the last week of radiation therapy
3. Immediately prior to surgery
4. Between 16 and 20 months following completion of radiation therapy

If you joined the study after your surgery, but received radiation therapy with 5-FU prior to surgery, you will complete the questionnaire two (2) times:

1. At registration
2. Between 16 and 20 months following completion of radiation therapy

If you are in the group receiving radiation therapy with 5-FU after surgery (and between cycles of chemotherapy), you will complete the questionnaire five (5) times:

1. Prior to surgery (if possible)
2. Prior to beginning adjuvant postoperative chemotherapy
3. Immediately prior to starting radiation therapy (RT)
4. During the last week of RT
5. Between 16 and 20 months following completion of RT

While you are on study, samples of your tissue, blood or bone marrow may be sent to a central laboratory to be examined by a central reviewer. This review is to confirm the results of the local laboratory review.

HOW LONG WILL I BE IN THE STUDY?

The actual treatment period on the study is approximately 8 months. We would like to keep track of your medical condition for a period of 10 years after entering the study, to look at the long-term effects of the treatment. You may stop participating at any time; however, we encourage you to talk to your doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for the following side effects. The chemotherapy and the radiation may cause some, all or none of the side effects listed. You should discuss these with your doctor. There may also be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and less uncomfortable. Many side effects go away shortly after the chemotherapy drugs are stopped, but in some cases side effects can be serious, long-lasting, permanent or life threatening. Death is rare, but possible.

Your physician will check you closely to see if any of these side effects are occurring and routine blood tests will be done to monitor the effects of treatment.

Treatment Schedules A and D (irinotecan, 5-fluorouracil and leucovorin)

Likely

- Diarrhea (loose stools, increased number of bowel movements)*
- Mouth sores which may make swallowing difficult
- Nausea (feeling sick to your stomach) and vomiting (throwing up)
- Sweats
- Low white blood cells (may make you more likely to get infection)
- Low red blood cells (may make you feel tired or weak)
- Low platelets (may make you more likely to have bruising or bleeding)
- Peeling skin on hands and feet
- Sensitivity to sunlight
- Stomach cramps/pain
- Loss of appetite
- Fatigue, weakness or lack of body strength

- Hair loss
- Watery eyes
- Taste changes

*Diarrhea can occur with most chemotherapy drugs, but it is more common with irinotecan. The diarrhea associated with irinotecan can happen at 2 different times. First, diarrhea can happen the day that you receive it (by vein), which can be treated with a single injection (shot) of a drug called atropine. The diarrhea can occur again, several days after the completion of the chemotherapy, and may last for several days. The best way to deal with this second occurrence is to notify your doctor immediately. Instructions will be given to you on how to treat the diarrhea.

Less Likely

- Skin rash
- Blurred vision
- Loss of nails
- Unsteadiness when walking
- Allergic reaction
- Headache
- Confusion
- Tingling of the fingers and toes
- Damage to the kidneys and liver
- Swelling of the colon, which could cause a life-threatening infection

Rare But Serious

- Stroke
- Spasms of the blood vessels that supply the heart, possibly leading to heart attacks
- Lung damage resulting in shortness of breath (may be permanent)
- Blood clots in legs and/or lungs
- Secondary cancers such as acute leukemia

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

Treatment Schedules B and E (oxaliplatin, 5-fluorouracil and leucovorin)

Likely

- Lowered white blood cells (may make you more likely to get infections)
- Lowered platelets (may make you more likely to bruise or bleed)
- Lowered red blood cells (may make you feel tired or weak)
- Nausea (feeling sick to your stomach) and vomiting (throwing up)
- Diarrhea (frequent bowel movements)
- Numbness or 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 breath or swallow
- Soreness, pain, skin irritation or redness where the drug is injected

Rev. 4/05
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- Temporary hair loss
- Swelling or infection of the bowel
- Mouth sores or sore throat which may make swallowing difficult
- Sunlight sensitivity
- Nail changes
- Constipation (having fewer bowel movements and harder stools)
- Dehydration (decreased fluid in the body because of diarrhea or inability to drink fluids)
- Appetite loss
- Skin darkening, hives, itchy or dry skin
- Rash
- Fever
- Shortness of breath
- Damage to the liver or kidneys
- Pain that could be in the belly, chest, bones, muscles or joints, along the spine and legs
- Fatigue (feeling tired all the time), weakness or lack of body strength
- Headache
- Trouble sleeping
- Hearing loss

Less Likely

- Flu-like symptoms such as fevers, chills and muscle aches
- Watery eyes, runny nose
- Pain and the risk of infection where the drug is injected
- High blood pressure
- Changes in heart beat (rapid and/or jumpy heart beat)
- Allergic reaction (symptoms vary but difficulty breathing, nausea, vomiting, diarrhea, skin rash and/or itching are common with allergic reactions)
- Swelling, soreness or infection of the bowel
- Vision changes (blurring), usually brief
- Temporary blockage or paralysis of the bowels resulting in abdominal pain and cramping which may prevent normal bowel movements
- Changes in the salts in the bloodstream such as phosphorous, calcium, magnesium, sodium and/or potassium
- Swelling of the lungs
- Swelling in the arms and legs
- Blistering on the palms of the hands and soles of the feet
- Changes in taste
- Upset stomach, heartburn, gas
- Dry mouth
- Hot flashes or flushing (redness of face and neck)
- Cough
- Hiccups
- Fluid collecting in the abdomen
- Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)
- Neuropathy: motor (muscle weakness due to nerve damage)
- Adult respiratory distress syndrome (ARDS) (respiratory failure)
- Hypoxia (a lower-than normal concentration of oxygen in the blood)
- Thrombosis/thrombus/embolism (vascular access-related) (blood clot)

Rare:

- Rev. 4/05 • Confusion, memory loss, depression, anxiety or other mental changes
- Rev. 4/05 • Lack of balance (feeling as if you might fall down), dizziness
- Chest pain or heart attack
- Rev. 4/05 • Blood clot(s) in the brain
- Slurred speech
- Rev. 4/05, 11/05 •
- Rev. 4/05 • Infection
- Rev. 4/05 • Abnormal eye muscle movement
- Rev. 4/05 • Muscle spasms or loss of normal muscular contractions
- Rev. 4/05 • Abnormal liver function
- Rev. 4/05 • Blood in the urine
- Rev. 4/05 • Pain while peeing, inability to pee, frequent need to pee
- Rev. 4/05 • Change in nerve function, lack of coordination, sleep disturbance, eyesight
- Rev. 4/05 • Seizures, passing out
- Rev. 4/05 • Hoarseness, laryngitis, loss or alteration in voice

Rare But Serious:

- Rev. 4/05 • Hemolytic Uremic Syndrome – a breakdown of red blood cells, low platelets and kidney failure together.
- Pulmonary Fibrosis - lung problems such as cough, shortness of breath, trouble breathing, build-up of scar tissue in lungs; thickening and stiffening of lung tissue. Can be life threatening - tell your doctor right away if you experience any of these problems.
- Disruption of blood proteins where bleeding and blood clots can occur at the same time, which could be life-threatening.
- Bleeding from any source including stomach (throwing up blood or black stools), lung (coughing up blood), bowels (blood in the stool) or brain; which could be life-threatening.
- Veno-occlusive disease – liver injury which leads to an enlarged liver, enlarged spleen, swelling in the abdomen and jaundice (yellowing of the skin); could be life-threatening.
- Although very rare, it is possible that treatment-related side effects could result in death.
- Rev. 11/05 • Tumor Lysis Syndrome – complication can occur when cancer cells are destroyed by treatment. Cell destruction may damage kidneys and change calcium levels, which may lead to kidney dialysis, usually on a short-term basis.
- Rev. 9/08 • Cholecystitis (inflammation of the gallbladder)
- Rev. 9/08 • Gastrointestinal – other (pneumonitis intestinalis) (air in the bowel)

Treatment Schedules C and F (5-fluorouracil and leucovorin)

Likely

- Diarrhea (loose stools, increased number of bowel movements)
- Mouth sores, which may make swallowing difficult
- Nausea (feeling sick to your stomach) and vomiting (throwing up)
- Temporary decrease in numbers of white blood cells (with possible risk of infection)
- Peeling skin on hands and feet
- Sensitivity to sunlight
- Loss of appetite
- Fatigue, weakness or lack of body strength
- Hair loss

- Watery eyes
- Nail changes
- Low platelet counts, causing you to bruise easily, develop spots on your skin that look like pinpricks or a rash, or bleed longer if you are hurt.
- Low red blood cell counts, which could result in increasing tiredness, pale skin, loss of ability to do physical tasks or exercises and shortness of breath.

Less Likely

- Skin rash
- Blurred vision
- Headache
- Allergic reaction
- Confusion
- Tingling of the fingers and toes
- Unsteadiness when walking
- Damage to the liver

Rare But Serious

- Spasms of blood vessels that supply the heart, possibly leading to heart attacks.
- Although very rare, it is possible that treatment-related side effects could result in death.

Radiation Therapy

Likely:

- General feeling of tiredness
- Loss of appetite
- Nausea
- Decrease in blood cell counts that can cause infection or bleeding problems
- Diarrhea
- Abdominal pain or cramping
- Bladder irritation with frequent urination
- Redness (or darkening) of the skin in the treatment area
- Rash, itching or peeling of the skin
- Hair loss in the treatment area, which may be permanent

Less Likely But Serious:

- Injury to the bladder, bowel, or other tissues in the pelvis or abdomen.
- Intestinal or urinary obstruction

Radiation will cause sterility (inability to bear a child) and lead to early menopause in women who have not yet gone through menopause.

Reproductive Risks

If you are pregnant or breast feeding, you cannot take part in this study. If you are a woman who has not gone through menopause, you will take a blood test to see if you are pregnant before you start treatment. If you are sexually active, your doctor strongly recommends that you take precautions to avoid the possibility of becoming pregnant because this therapy could kill or seriously damage an unborn child. Sexually active males are also strongly advised to use an accepted and effective method of contraception. For more information about risks and side effects, ask the researcher or contact

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you are taking part in this study, there may or may not be direct medical benefits to you. If you receive study treatment and do not show any benefit, your doctor will discuss alternative treatments with you. You have been told that, should your disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in your best interest or should your doctor feel that this treatment is no longer in your best interest, the treatment will be stopped. Further treatment will be discussed.

We hope the information learned in this study will benefit other patients with rectal cancer in the future.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options:

- Standard chemotherapy alone
- Radiation therapy alone
- Standard chemotherapy with radiation
- No therapy, with care to help you feel more comfortable. Treatments will reduce symptoms, relieve pain, and maximize comfort, dignity and control. Treatment is not directed at curing, slowing, or reversing the disease.

Your doctor can provide information about your disease and will be available to answer any questions about the research study.

WHAT ABOUT CONFIDENTIALITY?

This study is conducted by the Eastern Cooperative Oncology Group (ECOG). ECOG is a cancer group that conducts studies for the National Cancer Institute. Your doctor is a member of ECOG or another group that is participating in this study. To help protect your privacy, ECOG has obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS).

With this Certificate, ECOG cannot be forced (for example, by court subpoena) to disclose information that may identify you in any federal, state or local civil, criminal, administrative, legislative or other proceedings. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about you or your involvement in this research. Note, however, that if an insurer or employer learns about your participation and obtains your consent to receive research information, then ECOG may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your privacy.

Your identifiable health information is also protected by the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, which was issued by the Department of Health and Human Services. Except as required by law, ECOG will not be able to disclose identifiable health information, expected to be collected in this study to anyone other than you without your authorization, by a separate document you have signed or will be asked to sign.

Finally, you should understand that your doctor and ECOG are not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others and the Certificate does not prevent the review of your research records under some circumstances by certain organizations for an internal program audit or evaluation. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:

- Eastern Cooperative Oncology Group
- National Cancer Institute (NCI)
- Cancer Trials Support Unit (CTSU) – an NCI-sponsored organization designed to increase accrual by providing greater access to phase III trials.
- Food and Drug Administration
- Other regulatory agencies and/or their designated representatives
- Drug manufacturers, and/or their representatives
- NCI Central Institutional Review Board (CIRB)
- Central laboratories, reviewers, banks

WHAT ARE THE COSTS?

If you are put in the study arm that gets oxaliplatin, the Division of Cancer Treatment and Diagnosis, NCI will provide you with oxaliplatin free of charge for this study. Every effort will be made to ensure adequate supplies of oxaliplatin will be available for all participants. If the drug becomes commercially available for this indication, there is a remote possibility that you will be asked to purchase subsequent supplies. Your physician will discuss this with you, should this situation arise.

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 issues. Medicare should be considered a health insurance provider. You may find the National Cancer Institute's guide "Clinical Trials and Insurance Coverage - A Resource Guide" helpful. Ask your doctor for a copy. It is also available on the world wide web at <http://www.nci.nih.gov/ClinicalTrials/Insurance>. Click on the printable version.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. Although no funds have been set aside to compensate you in the event of injury or illness related to the study treatment or procedures, you do not give up any of your legal rights for compensation by signing this form.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

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 may leave the study at any time. Leaving the study, or choosing not to take part, will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, an independent group of experts, will 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?

For questions about the study or a research-related injury, contact your cancer doctor

_____ at _____.
NAME(S) TELEPHONE NUMBER

For questions about your rights as a research participant, contact the

NAME OF CENTER
Institutional Review Board (which is a group of people who review the research to protect your rights) at _____.
TELEPHONE NUMBER

WHERE CAN I GET MORE INFORMATION?

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

SIGNATURE

I agree to take part in this study. _____

Participant _____ Date _____

SCIENTIFIC STUDIES

This study includes laboratory tests that will analyze small samples of your tissue. The samples will be taken from the biopsy materials and/or the surgery tissue which has already been collected as a routine part of your diagnostic evaluation and surgical treatment. If you participate in the laboratory studies associated with this protocol, some of the leftover tissue will be sent to a research laboratory for analysis. Researchers will be performing these tests in order to better understand the biology of rectal cancer. They hope these studies will help them better understand this type of cancer. The results of these tests will not be sent to you or your doctor and will not be used in planning your care. These tests are only for research purposes and have no effect on your medical care. The researchers have no access to your identity. You and/or your insurance company will not be charged for these tests.

Making Your Choice

Please read the sentence below and think about your choice. After reading the sentence, circle "Yes" or "No." No matter what you decide to do, it will not affect your care. You can participate in the treatment part of the study without participating in the laboratory studies. If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

I agree to participate in the scientific laboratory tests that are being done as a part of this study.

Yes

No

Please print and sign your name here after you circle your answer.

Your Name: _____

Your Signature: _____ Date: _____

WILL ANY OF THE SAMPLES (E.G. TISSUE) TAKEN FROM ME BE USED FOR OTHER RESEARCH STUDIES?

About Using Tissue for Research

If you participate in the laboratory studies associated with this protocol, some of the tissue biopsy material obtained for the clinical study will be sent to a central laboratory for analysis. Slides of your bone marrow and blood may be submitted for central review to confirm local laboratory reviews.

We would like to keep some of the bone marrow and tissue that is left over for future research. If you agree, this bone marrow and tissue will be kept and may be used in research to learn more about cancer and other diseases. This bone marrow and tissue will

only be given to researchers approved by the Eastern Cooperative Oncology Group. Any research done on the bone marrow and tissue must also be approved by the researcher's Institutional Review Board.

Your bone marrow and tissue may be helpful for research whether you do or do not have cancer. The research that may be done with your bone marrow and tissue will probably not help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your bone marrow and tissue 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 bone marrow and tissue for future research is up to you. No matter what you decide to do, it will not affect your care and you may still take part in the Eastern Cooperative Oncology Group study.

If you decide now that your bone marrow and tissue can be kept for research, you can change your mind at any time. Just contact your study doctor and let him or her know that you do not want us to use your bone marrow and tissue. Then the bone marrow and tissue will no longer be used for research. It may be retained for diagnostic reviews related to the study. Tissue samples will be returned to the institutions upon written request.

In the future, people who do research may need to know more about your health. When the Eastern Cooperative Oncology Group gives them reports about your health, it will not give them your name.

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

Your bone marrow and tissue will be used only for research and will not be sold. You will not be paid for allowing your leftover bone marrow and tissue to be used in research even though the research done with your bone marrow and tissue may help to develop new products in the future. Similarly there will be no cost to you for any bone marrow and tissue collected and stored by the Eastern Cooperative Oncology Group.

It is possible that, at some time in the future, as part of deciding on what therapy to give you, a new test might be available that could be performed on some of the bone marrow and tissue now thought of as leftover. This situation is unusual, but it could happen. In order to see that not all the leftover bone marrow and tissue are used up, the Eastern Cooperative Oncology Group will take care to see that some of your bone marrow and tissue are stored for 10 years so that it is available should it be needed by you or your doctors. This will depend upon the amount of left over bone marrow and tissue that is submitted for this study; however, there may not be any left over bone marrow and tissue to store.

Benefits

The benefits of research using bone marrow and tissue include learning more about what causes cancer and other diseases, how to prevent them, how to treat them, and how to cure them.

Risks

There are very few risks to you from using your bone marrow and tissue for research. One is the release of information from your health records. The Eastern Cooperative Oncology Group will protect your records so that your name will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

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. You can participate in the treatment part of the study without participating in all or part of the bone marrow and tissue research studies. If you have any questions, please talk to your doctor or nurse, or call our research review board at _____.

IRB's phone number

-
- 1 My bone marrow and tissue may be kept for use in research to learn about, prevent, treat, or cure cancer.

Yes

No

- 2 My bone marrow and tissue may be kept for research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease).

Yes

No

- 3 My doctor (or someone from the Eastern Cooperative Oncology Group) may contact me in the future to ask me to take part in more research.

Yes

No

Please print and sign your name here after you circle your answers.

Your Name: _____

Your Signature: _____

Date: _____

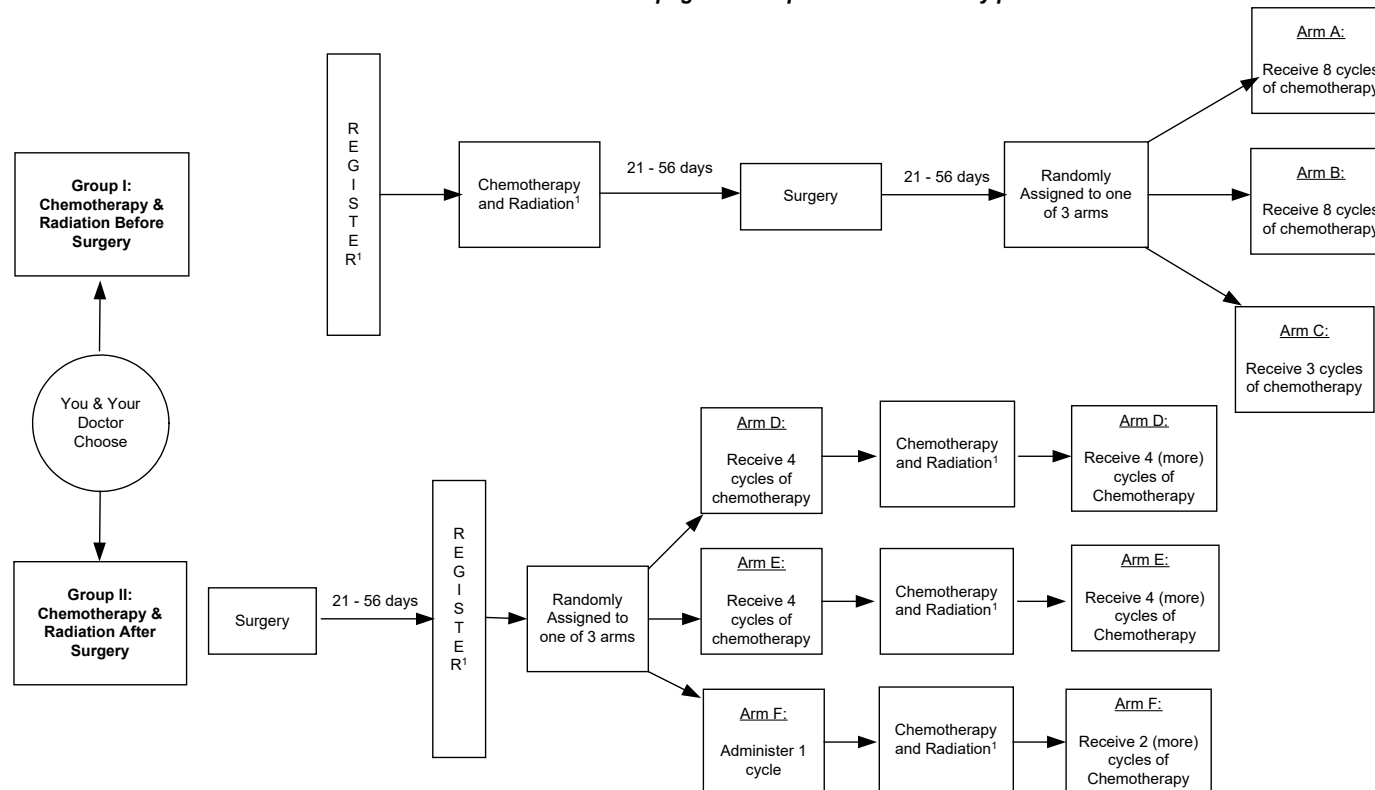
Study Plan

Page 1

Group I: If you and your doctor chose this group, you will be registered on-study & receive pre-operative radiation and chemotherapy. Then you will have surgery. About 3-8 weeks after surgery, you will receive 1 of 3 possible chemotherapy regimens.

Group II: If you and your doctor chose the 'sandwich' approach, you will have (had) surgery first and then, about 3-8 weeks after surgery, you will be registered on-study. You will receive radiation with chemotherapy 'sandwiched' between 1 of 3 possible (repeating) chemotherapy regimens.

See the boxes below and on page 2 for a 'picture' of the study plan



See Page 2 for Details on Chemotherapy Doses for Arms A, B, C, D, E, F

1. You will receive one of three allowed chemotherapy regimens with radiation.

- 5-FU over 24 hours 7 days a week during radiation
- 5-FU and leucovorin for 4 days during 1st and 5th week of radiation
- Capecitabine by mouth 2x each day during radiation

This regimen is available only to patients enrolled in NSABP R-04

Page Two of Study Plan

Arm A/Arm D

Irinotecan **IV** over 90 minutes.

Leucovorin **IV** over 2 hours.

5-FU **IV bolus injection**,
immediately following leucovorin dose.

Continuous infusion 5-FU over 46 hours by
ambulatory infusion pump beginning
immediately following **bolus** 5-FU.

Cycle = 2 treatment days every 2 weeks.

Arm B/Arm E

Oxaliplatin **IV** over 2 hours.

Leucovorin **IV** over 2 hours.

5-FU **IV bolus injection**,
immediately following leucovorin dose.

Continuous infusion 5-FU over 46 hours by
ambulatory infusion pump beginning
immediately following **bolus** 5-FU.

Cycle = 2 treatment days every 2 weeks.

Arm C/Arm F

Leucovorin **IV** over 2 hours once a week for
6 weeks followed by 2 weeks **rest**.

5-FU **bolus injection** 1 hour after the start of
the leucovorin infusion, once a week for
6 weeks followed by 2 weeks **rest**.

Cycle = 8 weeks.

IV = intravenous = in vein

Bolus = higher amount of drug all at once

Continuous infusion = fluid put into a vein over time

Ambulatory infusion pump = portable pump that gives you the drug

Rest = no chemotherapy drugs

**Intergroup Randomized Phase III Study of Postoperative Irinotecan, 5-Fluorouracil and Leucovorin vs
Oxaliplatin, 5-Fluorouracil and Leucovorin vs 5-Fluorouracil and Leucovorin
for Patients with Stage II or III Rectal Cancer Receiving Either Preoperative Radiation and 5-Fluorouracil
or Postoperative Radiation and 5-Fluorouracil**

**Appendix II
Pathology Submission Guidelines**

The following items are included in Appendix II:

1. Guidelines for Submission of Pathology Materials
(instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. List of Required Materials for E3201
4. ECOG Pathology Submission Form (#638)

Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG Pathology Coordinating Office:

Institutional Surgical Pathology Report
Pathology materials (see attached List of Required Material)
ECOG Pathology Material Submission Form (# 638)

Instructions:

1. Place the Patient ID label provided by the ECOG Coordinating Center in Part A of the ECOG Pathology Material Submission Form.

If a label is not available, **TYPE or PRINT** the following information in **Part A** of the form:

Patient's name (last, first)

Protocol number

Protocol case number (the patient's ECOG sequence number; for intergroup studies, include both the ECOG and other group's sequence numbers)

Patient's hospital number

Institution

Affiliate (if appropriate)

2. Complete blank areas of the pathologist's instructional memo, and forward it, along with the List of Required Material and the ECOG Pathology Material Submission Form, to the appropriate pathologist.
3. The pathologist should return to you the required pathologic samples and surgical pathology reports, along with the completed ECOG Pathology Material Submission Form (# 638) (Part B completed). If any other reports are required, they should be obtained from the appropriate department at this time.
4. Keep a copy of the ECOG Pathology Material Submission Form (# 638) for your records (the original should be sent to the PCO).
5. Double check that **ALL** required forms, reports, and pathology samples are included in the package to send to the Pathology Coordinating Office (see appropriate List of Required Material).

Pathology specimens submitted for a patient WILL NOT be processed by the Pathology Coordinating Office until all necessary items are received.

6. Mail pathology materials to:

ECOG Pathology Coordinating Office
Robert H. Lurie Comprehensive Cancer Center
of Northwestern University Medical School
Olson Pavilion - Room 8501
710 North Fairbanks Court
Chicago, IL 60611

If you have any questions concerning the above instructions, or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG Pathology Coordinating Office at Tel: (312) 503-3384 or Fax: (312) 503-3385.

LIST OF REQUIRED MATERIAL

E3201	<i>Intergroup Randomized Phase III Study of Postoperative Irinotecan, 5-Fluorouracil and Leucovorin vs Oxaliplatin, 5-Fluorouracil and Leucovorin vs 5-Fluorouracil and Leucovorin for Patients with Stage II or III Rectal Cancer Receiving Either Preoperative Radiation and 5-Fluorouracil or Postoperative Radiation and 5-Fluorouracil</i>
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Original Biopsy (Group I):

1. ECOG Pathology Material Submission Form (# 638) – Parts A & B completed.
2. Institutional pathology report (***must be included with EVERY pathology submission***).
3. A formalin-fixed, paraffin-embedded block from pre-treatment biopsy including cancer.

NOTE: If tissue blocks cannot be submitted, contact the PCO regarding the appropriate alternative sample submission.

Surgical Resection (All patients):

1. ECOG Pathology Material Submission Form (# 638) – Parts A and B completed.
2. Institutional pathology report (***must be included with EVERY pathology submission***).
3. The following blocks are requested:

- One block containing tumor tissue
- One block containing mucosa

NOTE: If tissue blocks cannot be submitted, contact the PCO regarding the appropriate alternative sample submission.

NOTE: Since blocks are being used for correlative studies, in some cases material may be depleted, and therefore, the block may not be returned.

NOTE: The Pathology Coordinating Office will forward a copy of the submission form to the ECOG Coordinating Center as well

NOTE: Paraffin blocks and/or slides submitted for this study will be retained at the ECOG Central Tissue Repository for possible use in future ECOG approved studies. Blocks will be available upon specific request for purposes of patient care.

NOTE: If pathology materials cannot be submitted, please indicate the reason for on the ECOG Pathology Material Submission Form (#638) and include a letter of explanation.

Upon Development of AML or MDS:

Rev. 3/07 **NOTE:** ECOG's diagnostic review project for secondary AML/MDS ended December 1, 2005. Submission of diagnostic slides upon diagnosis of secondary AML/MDS for central diagnostic review and classification is no longer required.



Eastern Cooperative Oncology Group

Coordinating Center

Frontier Science
900 Commonwealth Avenue • Boston, MA 02215
(617) 632-3610 • Fax: (617) 632-2990
Randomization: (617) 632-2022

Director: Sheilah Hurley, M.A.

Group Chair: Robert L. Comis, M.D.
Group Statistician: Robert Gray, Ph.D.

MEMORANDUM

TO: _____

(Submitting Pathologist)

FROM: Stanley Hamilton, M.D.
Chair
ECOG Pathology Committee

DATE: _____

SUBJECT: *Submission of Pathology Materials for E3201: Intergroup Randomized Phase III Study of Postoperative Irinotecan, 5-Fluorouracil and Leucovorin vs Oxaliplatin, 5-Fluorouracil and Leucovorin vs 5-Fluorouracil and Leucovorin for Patients with Stage II or III Rectal Cancer Receiving Either Preoperative Radiation and 5-Fluorouracil or Postoperative Radiation and 5-Fluorouracil*

The patient named on the attached ECOG Pathology Material Submission Form (# 638) has been entered onto an ECOG protocol by _____ (ECOG Investigator). This protocol requires the submission of pathology materials for laboratory studies.

Please complete **PART B** of the Submission Form. Keep a copy for your own records, and return the completed Submission Form, the surgical pathology report(s), the slides and/or blocks, and any other required material (see attached List of Required Material) to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the ECOG Pathology Coordinating Office.

Please note: Since blocks are being used for laboratory studies, in some cases the material may be depleted, and, therefore, the block may not be returned.

NOTE: Paraffin blocks and/or slides submitted for this study will be retained at the ECOG Central Tissue Repository for possible use in future ECOG approved studies. Blocks will be available upon specific request for purposes of patient care.

NOTE: If pathology materials cannot be submitted, please indicate the reason for on the ECOG Pathology Material Submission Form (#638) and include a letter of explanation.

If you have any questions regarding this request, please feel free to contact the Pathology Coordinating Office at Tel: (312) 503-3384 OR FAX: (312) 503-3385.

The ECOG CRA at your institution is:

Name: _____

Address: _____

Phone: _____

Thank you.

INSTRUCTIONS: Please complete and submit this form along with all pathology material and corresponding pathology reports requested by the protocol.
See list of required materials specific to EACH protocol.

PART A: TO BE COMPLETED BY DATA MANAGER

Date Sample Sent to ECOG ____ / ____ / ____ (M,D,Y)

Data Manager _____

Telephone No. () _____

FAX No. () _____

ECOG Parent Prot. No. _____ Seq. No. _____

PLACE ID LABEL HERE

Patient's Name _____
ECOG Prot. No. _____ ECOG Patient Seq. No. _____
Participating _____ Participating _____
Group Prot. No. _____ Group Patient ID No. _____
Group _____ Institution _____
Step No. _____ Affiliate _____

PART B: TO BE COMPLETED BY THE SUBMITTING PATHOLOGIST

	STATUS * (See Below)	DATE SPECIMEN COLLECTED (M,D,Y)	DISEASE SITE	NUMBER OF SLIDES	TYPE OF STAIN	SPECIMEN ID NUMBERS
COMPLETE FOR SLIDES		/ /				
		/ /				
		/ /				
COMPLETE FOR BLOCKS	STATUS * (See Below)	DATE SPECIMEN COLLECTED (M,D,Y)	DISEASE SITE	NUMBER OF BLOCKS	TYPE OF FIXATIVE	SPECIMEN ID NUMBERS
		/ /				
		/ /				

* **STATUS:** Please **identify** the clinical status of the sample.
List **ALL** that apply.

1. Original Diagnostic Material
2. Pre-Protocol Treatment Biopsy
3. Post-Protocol Treatment Biopsy
4. Post-Surgery Biopsy
5. Relapse/Recurrence
6. Remission/Response
7. Other, Specify _____

Submitting Pathologist _____

Telephone No. () _____

Address _____

INSTITUTION COMMENTS _____

Can this sample be retained by the ECOG Central Tissue Repository? ____ Yes ____ No

NOTE: Samples submitted for protocols requiring submission for tissue banking will not be returned except for purposes of individual patient management. For this reason, the submitting pathologist should retain at least one paraffin block at their institution.

[A block has been retained at the submitting institution: ____ Yes ____ No]

Please **CIRCLE THE REASON** for non-submission and **INCLUDE** a formal letter of explanation:
State Regulations, Institutional Policy, Insufficient Tissue, Patient Refusal, Other

specify other _____ Pathologist or Investigator's Signature _____

PART C: ECOG COORDINATING CENTER USE ONLYDate Sample Received by ECOG ____ / ____ / ____
M D YDate Sent to Central Lab ____ / ____ / ____
M D YDate Sample Sent to Reviewer ____ / ____ / ____
M D Y

Items Received (if different from above) _____

Name of Reviewer _____

NOTES: _____

INVESTIGATOR: Keep a copy for your files and submit original form to destination specified in protocol. 2/96

**Intergroup Randomized Phase III Study of Postoperative Irinotecan, 5-Fluorouracil and Leucovorin vs
Oxaliplatin, 5-Fluorouracil and Leucovorin vs 5-Fluorouracil and Leucovorin
for Patients with Stage II or III Rectal Cancer Receiving Either Preoperative Radiation and 5-Fluorouracil
or Postoperative Radiation and 5-Fluorouracil**

Appendix III

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at <http://www.ecog.org>. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME]

[DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important clinical program. Many questions remain unanswered in cancer. With the help of people like you who participate in these programs, we will achieve our goal of effectively treating and ultimately curing cancer

We believe this program will provide you with high quality, thorough care. Your physician and research staff will maintain very close contact with you. This is important to allow your physician to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of **[INSTITUTION]** and the Eastern Cooperative Oncology Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

**Intergroup Randomized Phase III Study of Postoperative Irinotecan, 5-Fluorouracil and Leucovorin vs
Oxaliplatin, 5-Fluorouracil and Leucovorin vs 5-Fluorouracil and Leucovorin
for Patients with Stage II or III Rectal Cancer Receiving Either Preoperative Radiation and 5-Fluorouracil
or Postoperative Radiation and 5-Fluorouracil**

Appendix IV

ECOG Checklist for Submission of Radiation Oncology Quality Assurance Materials

Patient: _____ Protocol: **E3201** Sequence # _____

Send Material c/o

Quality Assurance Review Center

Attention: ECOG Materials

272 West Exchange Street, Suite 101

Providence, RI 02903-1025

For the Radiation Oncologist:

Name: _____

Address: _____

Phone: _____

Fax: _____

Email: _____

Date Radiation Began: _____

Final Review materials must be submitted withing 1 week of completion of radiation:

DATE SUBMITTED: _____

Copy of Appendix IV: Checklist For Submission of Radiation Oncology QA Materials

ECOG Rectal Cancer On-Study Form (copy)

E3201 Baseline Data Form

Prescription Sheet for **Entire** Treatment

Preoperative imaging studies: CT with contrast and barium enema (if available)

Treatment Planninf CT/diagnostic imaging and report

Beam Verification (portal) Films of **All** Fields

Simulation Films and/or DRRs of **All** Fields

Picture of patient in treatment position

Color Copies of Isodose Distributions along with the corresponding bean data

Printouts from the planning system (see Section 5.1.0.4)

Monitor Daily Treatment Record

Partial Daily Treatment Record

3D-Conformal Planning: Submit the following in addition to the above materials

Description of each treatment field

Orthogonal anterior/posterior and lateral films if not part of portals

BEV's of portals

REV of overview diagram

Dose Volume Histogram

All materials must be labeled with the ECOG assigned Protocol and Sequence numbers

Please contact QARC ECOG CRA – TEL: 401-454-4301 FAX: 401-454-4683 for clarification as necessary.

**Intergroup Randomized Phase III Study of Postoperative Irinotecan, 5-Fluorouracil and Leucovorin vs Oxaliplatin,
5-Fluorouracil and Leucovorin vs 5-Fluorouracil and Leucovorin
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or Postoperative Radiation and 5-Fluorouracil**

Appendix V

Staging Criteria- Rectum

Primary Tumor (T)

- T1 Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades through the muscularis propria into the subserosa, or into nonperitonealized perirectal tissues
T4 Tumor perforates the visceral peritoneum or directly invades or is adherent to other organs or structures*

***NOTE:** Direct invasion of other organs or structures includes adherence to or invasion of other organs or structures including other segments of colorectum by way of extension beyond the serosa (e.g., invasion of the sigmoid colon by a carcinoma of the proximal (rectum).

Regional Lymph Node(s) (N)

- N0 No regional lymph node metastasis
N1 Metastasis in 1 to 3 pericolic or perirectal lymph nodes
N2 Metastasis in 4 or more pericolic or preirectal lymph nodes
N3 Metastasis in any lymph node along the course of a named vascular trunk

Distant Metastasis (M)

- M0 No distant metastasis

Modified Astler-Coller Stage Grouping

Stage	A	T1	N0	M0
	B1	T2	N0	M0
Stage	B2	T3, T4a	N0	M0
	B3	T4b	N0	M0
Stage	C1	T1-2	N1 – 3	M0
	C2	T3-4a	N1 – 3	M0
	C3	T4b	N1 – 3	M0

Note: Modified Astler-Coller B is a composite of better (T3, N0, M0) and worse (T4, N0, M0) prognostic groups as is Modified Astler-Coller C (Any T, N1, M0 and any T, N2-N3, M0).

Intergroup Randomized Phase III Study of Postoperative Irinotecan, 5-Fluorouracil and Leucovorin vs Oxaliplatin, 5-Fluorouracil and Leucovorin vs 5-Fluorouracil and Leucovorin for Patients with Stage II or III Rectal Cancer Receiving Either Preoperative Radiation and 5-Fluorouracil or Postoperative Radiation and 5-Fluorouracil

Appendix VI

Comparison of Symptoms and Treatment Pharyngo-Laryngodesthesias and Platinum Hypersensitivity Reactions

Clinical Symptoms	Pharyngo-Laryngeal Dysesthesias	Platinum Hypersensitivity
Dyspnea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
O2 saturation	Normal	Decreased
Difficulty swallowing	Present (loss of sensation)	Absent
Pruritis	Absent	Present
Urticaria/rash	Absent	Present
Cold-induced Sx	Yes	No
BP	Normal or increased	Normal or decreased
Treatment	Anxiolytics, observation in a controlled clinical setting until symptoms abate or at the physician's discretion	Oxygen, steroids, epinephrine, antihistamines, bronchodilators; fluids and vasopressors, if appropriate.

Intergroup Randomized Phase III Study of Postoperative Irinotecan, 5-Fluorouracil and Leucovorin vs Oxaliplatin, 5-Fluorouracil and Leucovorin vs 5-Fluorouracil and Leucovorin for Patients with Stage II or III Rectal Cancer Receiving Either Preoperative Radiation and 5-Fluorouracil or Postoperative Radiation and 5-Fluorouracil

Appendix VII

Cancert Trials Support Unit (CTSU) Participation Procedures

REGISTRATION/RANDOMIZATION

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member web site or by calling the PMB at 301-496-5725 Monday through Friday between 8.30 am and 4.30 pm Eastern time. Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit all IRB/regulatory documents to the CTSU before they can enroll patients. All forms and documents associated with this study can be downloaded from the E3201 Web page on the CTSU registered member Web site (<http://members.ctsu.org>). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and all pertinent forms and documents are approved and on file with the CTSU.

Requirements for E3201 site registration:

- CTSU IRB Certification
- IRB/Regulatory Approval Transmittal Form
- IRB-approved consent form
- Radiation Therapy Facility Inventory Form

Requirements for patient enrollment on E3201

- Patient must meet all inclusion criteria and no exclusion criteria should apply.
- Patient signed and dated consent.
- All baseline laboratory tests and prestudy evaluations performed.
- Pathology materials submitted per Section 10.0 (provided patient has given consent)
- Patient completed baseline QOL forms.

CTSU PROCEDURES FOR PATIENT ENROLLMENT

The choice of pre-operative chemo/XRT (GROUP I) versus post-operative chemo/XRT (GROUP II) is at the discretion of the treating physician and must be declared at the time of registration. The physician must also identify the surgical procedure to be performed. (See Section 5.0 for details.) Please refer to Section 3 for explanation of Group I PS.

GROUP I patients are registered but not randomized until 21-56 days from date of total resection.

GROUP I PS (patients who have received chemotherapy/RT and surgery per protocol) are registered and randomized at the same time.

GROUP II patients are registered and randomized at the same time. Treatment should start within five (5) working days after registration/randomization.

Registration instructions for Group I (including Group I PS) and II patients and Randomization instructions for Group I PS and II patients:

Contact the CTSU Patient Registration Office by calling 1-888-462-3009 to alert the CTSU Patient Registrar that an enrollment is forthcoming. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- E3201 Eligibility Check (Step 1 - Registration)
- E3201 Eligibility Check (Step 2 - Randomization) Group II patients only

Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 am and 4:30 p.m., Mon-Fri, Eastern time. The CTSU registrar will check the investigator and site information provided to ensure that all regulatory requirements have been met. The registrar will also check the forms for completeness and follow-up with the site to resolve any discrepancies. Once investigator and patient eligibility are confirmed, the CTSU registrar will contact the Eastern Cooperative Oncology Group to obtain the patient ID assignment (to be used on all future forms and correspondence), and if this is a Group II patient, the CTSU registrar will also obtain a randomization assignment at this time. The CTSU registrar will convey this information to the enrolling site by phone followed by a confirmation e-mail or fax.

Randomization instructions for Group I patients:

Group I patients may not be randomized until 21-56 days from date of total resection.
Complete the following forms:

- CTSU Data Transmittal Form
- E3201 Eligibility Check (Step 2 - Randomization)

Fax this form to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 am and 4:30 p.m., Mon-Fri, Eastern time. The CTSU registrar will contact the Eastern Cooperative Oncology Group to obtain a randomization assignment. The CTSU registrar will convey this information to the enrolling site by phone followed by a confirmation e-mail or fax.

Rev. 3/07

DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) and transmittals associated with this study must be downloaded from the E3201 Web page located on the CTSU registered member Web site (<https://members.ctsu.org>). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.
2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals directly to the ECOG [refer to contacts table] unless an alternate location is specified in the protocol. Do not send study data to the CTSU. A completed CTSU-ECOG coversheet should accompany all data submissions.
3. The ECOG Coordinating Center will mail query notices and delinquency reports directly to the site for reconciliation. Please send query responses and delinquent data to the ECOG Coordinating Center and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and **must keep their CTEP AMS account contact information current**. This will ensure timely communication between the clinical site and the ECOG Coordinating Center.

SPECIAL MATERIALS OR SUBSTUDIES

Radiation materials submission

The Quality Assurance Review Center (QARC) will perform a Final Review of radiation oncology materials for E3201: at the completion of radiation oncology therapy. Final Review materials are to be submitted within 1 week of completion of radiation.

CTSU investigators should follow the instructions in section 5.0 and Appendix IV of the protocol and submit all requested RT materials and documentation directly to the QARC office (Note: CTSU investigators should **not** send RT dosimetry materials to the CTSU). Please send a copy of the ECOG Checklist for Submission of Radiation Oncology Quality Assurance Materials (Appendix IV of protocol) to the CTSU accompanied by a CTSU Data Transmittal Form.

Rev. 3/07

Pathology Review and Correlative Studies

- Participation in the correlative studies is optional and requires patient consent.
- Do not send specimens, supporting clinical reports, or transmittals to the CTSU.

Quality of Life

The FACT Diarrhea Subscale Questionnaire, Bowel Function Questionnaire, and Uniscale will be used to assess rectal function in study participants. Administration instructions and schedule are outlined in Section 5.6 of the protocol.

Rev. 3/07

SERIOUS ADVERSE EVENT (AE) REPORTING

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.
2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Expedited Report System (AdEERS) from either the Adverse Events tab of the CTSU member homepage (<https://members.ctsu.org>) or by selecting Adverse Event Reporting Forms from the document center drop down list on the E3201 Web page.
3. Do not send adverse event reports to the CTSU.
4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via the NCI/CTEP AML-MDS Report Form in lieu of AdEERS. Submit the completed form and supporting documentation as outlined in the protocol.

DRUG PROCUREMENT

CTSU investigators should refer to section 8.2 for detailed instructions on drug ordering, preparation, administration and accountability. Completed Clinical Drug Requests (NIH-986) for investigational IND agents should be faxed (301-480-4612) or mailed directly to the Pharmaceutical Management Branch (PMB).

Investigational IND agents: Oxaliplatin (Note that the PMB will ship drug only to the shipping address specified by the CTSU investigator on their FDA form 1572.)

Commercial Agents: Irinotecan, Leucovorin, 5-Fluorouracil, Capecitabine.

REGULATORY COMPLIANCE AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. (e.g., NSABP members may only request credit for protocols pertaining to breast or colorectal cancers). Registrations to protocols for other disease sites may still take place through CTSU without receiving credit for your NSABP activities. Per capita reimbursement will be issued directly from CTSU.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data Update System (CDUS) Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.

Intergroup Randomized Phase III Study of Postoperative Irinotecan, 5-Fluorouracil and Leucovorin vs Oxaliplatin, 5-Fluorouracil and Leucovorin vs 5-Fluorouracil and Leucovorin for Patients with Stage II or III Rectal Cancer Receiving Either Preoperative Radiation and 5-Fluorouracil or Postoperative Radiation and 5-Fluorouracil

Rev. 11/05

Appendix VIII

Cooperative Research and Development Agreement (CRADA)

Rev.
11/05

The agent, Oxaliplatin, used in this protocol is provided to the NCI under a Cooperative Research and Development Agreement (CRADA) between Sanofi-Aventis (hereinafter referred to as "Collaborator") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" terms of award modifications, apply to the use of Oxaliplatin in this study:

1. Oxaliplatin may not be used for any purpose outside the scope of this protocol, nor can Oxaliplatin be transferred or licensed to any party not participating in the clinical study. Collaborator data for Oxaliplatin are confidential and proprietary to Collaborator and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational agents are also confidential and should not be shared or distributed without the permission of the NCI.
2. Clinical Trial Data and Results and Raw Data developed under a CRADA will be made available exclusively to Collaborator, the NCI and the FDA, as appropriate.
3. When a Collaborator(s) wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for cooperative group studies, or PI for other studies) of Collaborator's wish to contact them.
4. Any data provided to Collaborator for Phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
5. Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator for advisory review and comment prior to submission for publication. Collaborator will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator's intellectual property rights, are protected. Copies of abstracts should be provided to CTEP for forwarding to Collaborator for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript press release and/or abstract should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
6130 Executive Boulevard Suite 7111
Rockville, MD 20852
FAX (301) 402-1584

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

Intergroup Randomized Phase III Study of Postoperative Irinotecan, 5-Fluorouracil and Leucovorin vs Oxaliplatin, 5-Fluorouracil and Leucovorin vs 5-Fluorouracil and Leucovorin for Patients with Stage II or III Rectal Cancer Receiving Either Preoperative Radiation and 5-Fluorouracil or Postoperative Radiation and 5-Fluorouracil

Rev. 11/05

Appendix IX

Diarrhea Management Instructions

How to Manage Diarrhea

While you are receiving the chemotherapy drugs and radiation therapy, you may experience diarrhea. In some individuals, diarrhea has been severe. Therefore, it is important that you follow the instructions noted below if you experience diarrhea while being treated.

What Is Diarrhea?

Diarrhea is when your bowel movements are loose or watery and more frequent than is usual for you. In order to help manage the diarrhea that your treatment may cause, you will need to keep track of your bowel movements. Keeping a diary may be the easiest way to do this. The diary should record how many bowel movements you have during the day, when they occur and the consistency of the stool (formed, loose or watery). Having diarrhea for a long period of time can result in problems such as dehydration. It is best to treat it early when it first begins. You should contact your doctor or nurse if you begin experiencing this side effect.

What Do I Take To Stop the Diarrhea?

The medication used to treat the diarrhea is called loperamide. The most common brand of loperamide is Imodium. Loperamide comes in the form of a 2 milligram (mg) caplet and is available without a prescription at most pharmacies and grocery stores in the health and beauty aids section.

The loperamide may cause some side effects. These side effects are drowsiness, tiredness and dizziness. It is important to avoid driving motorized vehicles or operating machinery if you experience any of these side effects.

When Should I Start Taking the Loperamide and For How Long?

At the first sign of diarrhea you will need to begin taking loperamide (Imodium) according to the directions below. (These will differ from the usual instructions found on the label.) If you do not start taking loperamide right away, severe diarrhea can occur that could require hospitalization. It is also important to stop taking any laxatives (medications to treat constipation such as milk of magnesia, Colace, Dulcolax, or Senakot).

Please follow these instructions carefully:

- Take two caplets (4 mg) at the first sign of any change in your normal bowel movement as described above.
- Continue taking one caplet (2 mg) every 2 hours until you have returned to your normal pattern of bowel movements for at least 12 hours. It is important to continue taking the loperamide even during the night. However, during the night you can take two caplets (4mg) every four hours instead of one caplet (2 mg) every two hours.
- Be sure to drink plenty of fluids each day (several glasses of water, fruit juice, soda, soup, etc). It is important to try to replace fluid that is being lost because of the diarrhea. This will help prevent

dehydration and will not cause more diarrhea. You should avoid caffeinated beverages (coffee, tea, cola), alcoholic beverages and dairy products.

- Avoid high roughage foods like high-fiber cereals containing bran or whole grain, broccoli, cabbage, beans, fresh vegetables or fruit, fried food, chocolate or doughnuts.

Please call your doctor or nurse if you have any questions about taking loperamide, if your diarrhea does not improve, or if you experience new symptoms.