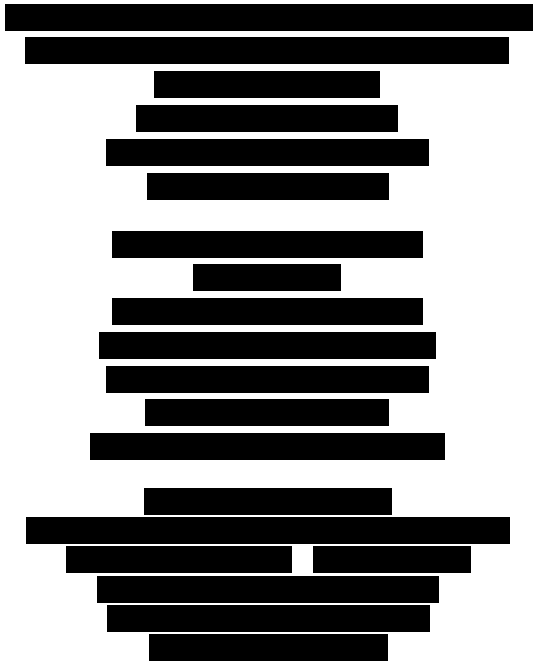
Alliance for Clinical Trials in Oncology ('Alliance')

N1048 (PROSPECT**): A Phase II/III Trial of Neoadjuvant FOLFOX with Selective Use of Combined Modality Chemoradiation versus Preoperative Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision

** Pre-operative Radiation Or Selective Preoperative radiation and Evaluation before Chemotherapy and TME

ClinicalTrials.gov Identifier: NCT01515787

For any communications regarding this protocol, please contact the Protocol Coordinator on page 5



***Investigator having NCI responsibility for this protocol**

Drug Availability
Commercial Agents: Oxaliplatin, Leucovorin, Capecitabine, 5-Fluorouracil

Participating Organizations
Alliance / Alliance for Clinical Trials in Oncology,
ECOG-ACRIN / ECOG-ACRIN Medical Research Foundation, Inc.,
NRG / NRG Oncology foundation, Inc., SWOG / SWOG,
CCTG / Canadian Cancer Trials Group

NCTN Group Champions:

ECOG-ACRIN

[redacted]

SWOG

[redacted]

NRG

[redacted]

CCTG

[redacted]

Study Statisticians:

Clinical and Correlative Studies

[redacted]

QOL and PRO-CTCAE Studies

[redacted]

Alliance Statistics and Data Center

[redacted]

Study Co-Chairs:

Medical Oncology

[redacted]

Patient Reported Outcomes

[redacted]

Correlative Sciences

[redacted]

Quality of Life

[redacted]

Surgery

[redacted]

Pathology

[redacted]

Radiology

[redacted]

Radiation Oncology

[redacted]

Alliance GI Committee Leadership:

[redacted]

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. [redacted] Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at [redacted] Contact the CTSU Help Desk with any OPEN related questions by phone or email : [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website ([redacted]). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (i.e. patient eligibility or treatment-related) see Protocol Contacts, pages 2, 3, & 5.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – [redacted] All calls and correspondence will be triaged to the appropriate CTSU representative.		

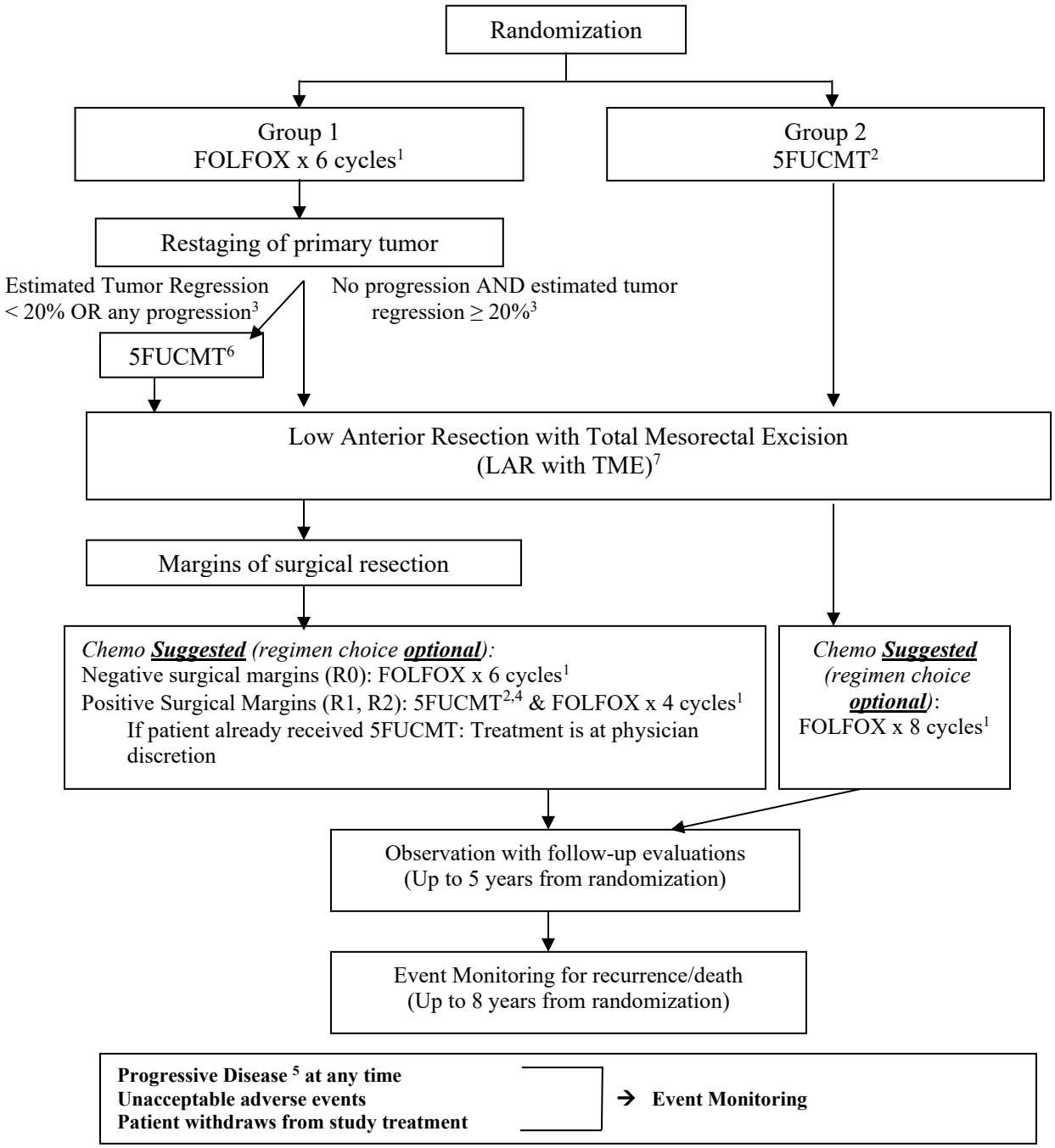
Protocol Resources

Questions:	Contact Name:
Test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted]
Drug administration, infusion pumps, nursing guidelines	[redacted]
Protocol document, consent form, regulatory issues	[redacted]
Radiation quality control	[redacted]
Radiology quality control	[redacted]
Surgical Quality Assurance	[redacted] **Send Surgical Quality Assurance materials to**: [redacted]
Paraffin-embedded tissue and non-paraffin biospecimens	[redacted]
Biospecimen Management System (BioMS)	[redacted]
Adverse Events (CTEP-AERS, MedWatch, Non-AER, AML/MDS)	[redacted]

Note: There will be no waivers of eligibility per NCI.

Table of Contents

Schema



[1]Cycle length = 14 days; [2] 5FUCMT duration = 5.5 weeks; 5FUCMT = 5-fluorouracil OR capecitabine + radiation therapy.; [3] This is a clinical estimation as to whether there has been at least a 20% decrease in the tumor in response to neoadjuvant FOLFOX treatment made on the basis of both tumor imaging and clinical tumor response based on proctoscopy (see Section 11); [4] No patient will receive 5FUCMT more than once;.[5] If there is progressive disease at the restaging of primary tumor after 6 cycles of FOLFOX, Group 1 patients proceed to 5FUCMT instead of event monitoring. If the patient refuses to receive 5FUCMT but will still undergo TME, the patient should be followed per protocol; [6]May be initiated any time after restaging scan; [7] All operative and pathology reports must be submitted (see Section 11.3).

Generic name: Oxaliplatin Brand name(s): Eloxatin® Abbreviation: OXAL Availability: Commercial	Generic name: Leucovorin Brand name(s): Abbreviation: CF Availability: Commercial	Generic name: Capecitabine Brand name(s): Xeloda® Abbreviation: CAPCIT Availability: Commercial	Generic name: Fluorouracil Brand name(s): Adrucil® Abbreviation: 5-FU Availability: Commercial

1.0 BACKGROUND

1.1 Potential Role for Neoadjuvant FOLFOX

Potential Role for Neoadjuvant FOLFOX for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision

The American Cancer Society estimates that about 40,000 new cases of rectal cancer are diagnosed in the US each year, and these are expected to cause about 22,000 deaths (American Cancer Society, 2009). Currently the standard of care for all Stage II (T3/T4N0) and Stage III (TanyN1/N2) rectal cancer is tri-modality therapy including chemotherapy, radiation, and surgery (NIH consensus conference, 1990). Numerous studies have revealed that pelvic radiation reduces local recurrence while systemic chemotherapy improves overall survival (Gastrointestinal Tumor Study Group, 1985; Fisher et al., 1988; Krook et al., 1991; Tepper et al., 1997; Wolmark et al., 1993). The purpose of radiotherapy is to decrease local recurrence rates and secondarily, to increase the potential for rectal sphincter preservation. Local recurrence is a major cause of morbidity and has a severe adverse impact on patients' quality of life. For that reason, utilization of radiotherapy for rectal cancer treatment was an important advance when it was introduced in the 1980s. However, radiation also has the potential for adverse effects on patient-centered outcomes such as sphincter and bowel function, loss of fertility in young patients, as well as diminished bone marrow reserve which is disadvantageous in the event of distant metastatic disease.

In a landmark German study, Sauer et al. compared preoperative with postoperative chemoradiation (50.4 Gy plus continuous infusion of fluorouracil) in 823 patients with resectable rectal cancer (Sauer et al., 2004). The local recurrence rate after five years was lower in the preoperative treatment group (6% *v* 13%; p = 0.006) while the frequency of distant metastases and survival showed no significant difference. The estimated 2 year disease free survival (DFS) from this trial was 82%. Preoperative treatment was associated with an impressive decrease in toxicity (grade 3 or 4 toxic effects 27% *v* 40% postoperative). Validation for the role of neoadjuvant 5-FU based chemoradiation therapy vs. postoperative chemoradiation reported by Sauer et al was recently confirmed by the National Surgical Breast and Bowel Project (NSABP R-03). After a median follow up of 8.4 years, in a population at somewhat higher risk than will be enrolled onto our proposed study, the 2-yr incidence LRR rate was 8% and the 2-year DFS rate was 78% (Roh et al., 2009). For these reasons, pre-operative pelvic chemoradiation is now considered the standard of care for locally advanced rectal cancer. The contemporary US treatment paradigm consists of neoadjuvant 5FUCMT, followed by surgery and additional 8-10 cycles of adjuvant 5-FU based chemotherapy.

The proposed study does not use new agents, but rather sequences existing well established strategies in a different way to capitalize upon the progress achieved in each treatment modality since 1990 when the current treatment paradigm was established. It is therefore essential that we do not compromise the currently favorable outcomes that are typically achieved using tri-modality therapy for all patients. The rationale for this concept stems from a confluence of factors related to contemporary management of locally advanced rectal cancer:

Neoadjuvant radiation results in overtreatment of some patients.

Although preoperative chemoradiation reduces toxicity compared to the previous standard of post-operative treatment, chemoradiation remains associated with significant short-term and long-term side-effects. This has resulted in considerable debate whether all Stage II and III rectal cancer patients require such an intensive treatment approach (Carne and Nelson, 2004). This dispute has been fueled by reports indicating significantly reduced local recurrence rates when the surgical technique is performed by mesorectal excision (Carlsen et al, 1998; Enker et al,

1999; MacFarlane et al., 1993). Some centers have therefore recommended that radiation can be eliminated in patients with disease limited to the perirectal tissue (i.e., T3N0/T3N1 patients) and without extensive nodal or contiguous organ involvement (Carne et al., 2004; Enker et al., 1999; Merchant et al., 1999). However, radiation remains the standard of care and is recommended by most clinical practice guidelines. Moreover, a randomized trial led by the Dutch demonstrated that even when TME is performed, pelvic radiation decreases the rate of local recurrence.

Pelvic radiation is associated with both short and long-term morbidity.

Combined modality therapy is associated with considerable short term toxicity, which is seen in up to 50% of patients (Matzel et al., 2003). Treatment is time intensive for patients in that it requires 28 daily visits to receive treatment as well as additional visits to receive either oral or intravenous 5-fluorouracil. Most importantly, the long-term effects of pelvic radiation can be substantial, including fibrosis and autonomic nerve injury which may be manifested by increased fecal incontinence, urgency and frequency, and higher rates of bladder and sexual dysfunction when compared to outcomes for patients that do not receive pelvic radiation (Sauer et al., 2004.; Paty et al., 1994; Shibata et al., 2004; Glimelius et al., 2003.; Minsky et al., 1995; Temple et al., 2003). Following pelvic radiation for rectal cancer, the uterus is not competent to sustain pregnancy. In addition, because the pelvis is an active site of hematopoiesis, patients who undergo pelvic radiation may have diminished ability to withstand subsequent myelosuppressive therapy, a consideration that is more relevant in an era where a greater number of chemotherapeutic options are available for metastatic disease. Pelvic fracture after modest trauma such as an uncomplicated fall also occurs more commonly among patients whose pelvis has been irradiated.

Patients with rectal cancer succumb to metastatic disease and neoadjuvant radiation delays initiation of systemic therapy.

Current rectal cancer treatment paradigms do not deliver systemic chemotherapy for 14-18 weeks from initiation of neoadjuvant chemoradiotherapy and this delay is potentially disadvantageous because it allows a window for metastatic dissemination of disease. The standard treatment timeline is as follows: 5.5 weeks of combined modality treatment; 4-6 week recovery; surgical resection; 4-6 week postoperative recovery; and then initiation of adjuvant therapy. As a result, no systemic therapy is delivered to treat micrometastases for over 3 months from treatment onset. This delay may allow a window of opportunity for growth of small volume disease outside the pelvis. On this basis, there is rationale for moving systemic treatment more proximally into the treatment regimen.

Both systemic therapy and surgical technique have substantially improved in the last decade.

Pelvic radiation treats residual disease left behind when either the mesorectal excision was incomplete or tumor was invading the mesorectal envelope. Local control is critically important because of the immense morbidity associated with pelvic recurrence. Traditional surgery, now outmoded, involved blunt digital dissection of the mesorectum which often resulted in tearing the mesorectal fascia and resulting in incomplete resection of the nodal basin around the rectum and a positive radial margin. In this setting, postoperative chemoradiation reduced local recurrence by sterilizing tumor deposits left in the pelvis from inadequate surgery. The introduction and acceptance of total mesorectal excision (TME) and the subsequent standardization of sharp dissection of the lymph node bearing tissue, resulted in low radial positive margin rates and therefore very low recurrence rates. This has spurred a debate about whether radiotherapy remains necessary in the patient who has undergone an appropriate and successful TME.

This question was addressed in the TME trial set up by the Dutch Colorectal Cancer Group that randomized between standardized and quality-controlled TME surgery alone and TME surgery preceded by short-term pre-operative radiotherapy. This study was reported in the New England Journal in 2001-- the Dutch TME trial (Kapiteijn et al., 2001). This study helped to clarify the contribution of neoadjuvant radiation to rectal cancer therapy and underscored the importance of surgical technique. This study demonstrated that neoadjuvant radiation does not influence long-term survival. Second, it confirmed that neoadjuvant radiation improves local control even when TME is performed. A third important message emerged indirectly from the Dutch study. The rate of local recurrence for patients treated in the control group without radiotherapy was substantially lower than the 25% local recurrence noted in the historical rectal cancer trials. The Dutch study thus provides us with indirect evidence that improved surgical technique (TME) itself has contributed to decreased local recurrence while noting that pelvic radiation still contributes to further decrease in pelvic recurrence. There have also been significant advances in systemic chemotherapy for patients with colorectal cancer that have emerged since 2002 (Goldberg et al., 2004; Grothey et al., 2004; Saltz et al., 2000). Response rates for patients with primary and metastatic colorectal cancer treated with modern chemotherapy regimens such as 5-FU, leucovorin, oxaliplatin (FOLFOX) have routinely exceeded 50% and are frequently as high as 60-70% (Goldberg et al.,2004; Grothey et al., 2004). In the context of improved surgical technique, improved chemotherapy and better radiologic staging, many have questioned whether rectal cancer treatment can be streamlined and/or simplified. Preliminary Work Supports the Selective Strategy

This protocol builds on pilot work conducted by study leaders at Memorial Sloan-Kettering Cancer Center. In a single institution trial (MSKCC07-021) that started in March 2007, 32 patients, of whom 22 had clinical node-positive disease, were treated according to the proposed schema with the exception that the regimen also included bevacizumab for the first 4 cycles of therapy. Two patients did not complete neoadjuvant FOLFOX secondary to cardiac complications likely attributable to and/or bevacizumab. Of 30 who did complete neoadjuvant treatment, all had R0 TME rectal resections. Eight of 30 have had pathologic CRs. There was 1 post-operative death and there have been 3 patients with recurrence. All 3 recurrent patients have had pulmonary metastases without local recurrence. The results of this pilot trial were published in the Journal of Clinical Oncology in January 2014 (Schrag et al., 2014). We now seek to extend the strategy of selective use of combined modality therapy with 5FU (5FUCMT) and tailoring treatment based on tolerance of and response to induction FOLFOX and to establish its efficacy in the multi-center setting. In the pilot trial, bevacizumab was included for the first 4 cycles of therapy. However, based on more recent data from other studies indicating that bevacizumab does not increase response rate, and does not improve survival in the adjuvant setting (C-08 trial), it is not included in the proposed neoadjuvant regimen.

1.2 Proposed Study Overview

The study investigators hypothesize that neoadjuvant FOLFOX can safely and efficaciously be delivered as an alternative 5FUCMT without compromising either the ability to perform a pelvic R0 resection, the local control rate or overall disease free survival for appropriately selected locally advanced rectal cancer patients who are treated with contemporary surgical technique including TME and contemporary FOLFOX chemotherapy. We further hypothesize that early administration of FOLFOX will provide optimal systemic therapy for any clinically occult micrometastases which may be present, and that pre-operative elimination of radiation to select patients will allow more complete delivery of post-operative FOLFOX. We anticipate that this strategy will minimize toxicity and optimize outcomes for appropriately selected locally advanced rectal cancer patients.

Specifically, this phase II/III trial seeks to determine whether 6 cycles of neoadjuvant FOLFOX followed by comprehensive restaging with *selective* use of 5FUCMT followed by total mesorectal excision (TME) achieves favorable outcomes for patients with locally advanced (clinical T3N0, T3N1, T2N1) rectal cancer. The current standard of care for locally advanced rectal cancer involves use of 5FUCMT for *all* patients. In the intervention group, 5FUCMT is used *selectively* and is administered to the subset of patients randomized to the intervention group who are either:1) unable to complete 6 cycles of FOLFOX; 2) have evidence of progression after 6 cycles of FOLFOX; 3) fail to undergo an pelvic R0 resection or 4) withdraw consent from the study.

Eligible study subjects include adults who are candidates for curative intent sphincter-sparing surgery and lack high risk features such as tumor encroaching upon the mesorectal fascia or distal tumors.

This study has the potential to dramatically influence our approach to rectal cancer treatment. Recognizing the small number of patients who participated in the pilot phase II study and their location at a single specialty center, a phase II component is regarded as essential to minimize risks associated with the intervention group that might only become manifest in the multi-center context. Moreover, the phase II component is randomized, which will permit meaningful comparisons and minimize the potential for selection bias. The design is highly efficient in that it proceeds from phase II directly to phase III. If the intervention compromises favorable outcomes, it will not proceed to phase III evaluation. The study strikes a balanced position between competing viewpoints and priorities in order to move the field forward and represents cooperation by a large number of investigators.

1.3 Clinical Correlative Studies (QOL and PRO-CTCAE)

Clinical Correlative Studies (QOL and PRO-CTCAE) – for background, aims, and methodology see Appendices VII and VI; see Section 4.0 for test schedule and Section 17.0 for data submission.

1.4 Biological Correlative Studies

Biological Correlative Studies (Genomic characterizations, Immunologic studies, and Pharmacogenomics) – See Appendices XII-XIV for background, aims, and methodology and see Section 14.0 for specimen logistics.

2.0 GOALS

2.1 Treatment

2.1.1 Primary Objectives

2.1.1.1 Phase II component: To assure that neoadjuvant FOLFOX followed by selective use of 5FUCMT group (Group 1) maintains the current high rate of pelvic R0 resection and is consistent with non-inferiority for time to local recurrence (TLR).

2.1.1.2 Phase III component: To compare neoadjuvant FOLFOX followed by selective use of 5FUCMT (Group 1) to standard 5FUCMT (Group 2) with respect to the primary endpoint of Disease-free Survival (DFS).

2.1.2 Secondary Objectives

2.1.2.1 To compare time to local recurrence between the two treatment groups.

2.1.2.2 To compare the proportion of patients who achieve a pathologic complete response (pCR) at the time of surgical resection between the two treatment groups.

2.1.2.3 To compare overall survival between the two treatment groups.

2.1.2.4 To evaluate and compare the adverse event profile and surgery complications between the two treatment groups.

2.1.2.5 To estimate the proportion of patients in the selective group (Group 1) who receive: 1) pre-operative 5FUCMT; 2) post-operative 5FUCMT; 3) either pre- or post-operative 5FUCMT.

2.1.2.6 To compare the neoadjuvant response scores (NAR) between the two treatment groups.

2.2 Clinical Correlative Studies

2.2.1 Quality of Life (QOL)

2.2.1.1 Primary: To compare bowel function in patients randomized to the neoadjuvant FOLFOX followed by selective use of 5FUCMT vs. standard 5FUCMT at approximately 1 and 2 years post-operatively.

2.2.1.2 Secondary:

2.2.1.2.1 To compare sexual function separately within men and within women between groups at approximately 1 and 2 years post-operatively.

2.2.1.2.2 To compare bladder function between groups at approximately 1 and 2 years post-operatively.

2.2.1.2.3 To compare health-related quality of life between groups at 1 and 2 years post-operatively.

2.2.1.3 Exploratory: To assess the correlation between bladder, bowel, and sexual function and quality of life; to investigate factors associated with bladder, bowel, and sexual dysfunction; to compare bladder and bowel function over time between genders; and to perform subgroup analyses based on other sociodemographic factors.

2.2.2 Patient-Reported Outcomes Version of the Common Terminology Criteria (PRO-CTCAE)

2.2.2.1 Primary:

2.2.2.1.1 To evaluate the feasibility of implementing the PRO-CTCAE in an NCI-sponsored treatment trial.

2.2.2.1.2 To evaluate the feasibility of implementing the PRO-CTCAE at Alliance sites.

2.2.2.1.3 To evaluate the feasibility of patients self-reporting symptoms during treatment by using the PRO-CTCAE.

2.2.2.2 Secondary:

2.2.2.2.1 To evaluate and compare patients' self-reported symptom burden during treatment between groups using the PRO-CTCAE system

2.2.2.3 Exploratory:

2.2.2.3.1 To evaluate whether exposure to patient-reported symptoms influences CTCAE symptom reporting by research staff

2.3 Biological Correlative Studies

2.3.1 Genomic Characterization of Rectal Tumors using Molecular Inversion Probe (MIP) Arrays and MALDI-TOF Mass Spectrometry.

2.3.1.1 Primary: To prospectively use MIP array technology and mass spectrometry-based genotyping to identify copy number aberrations and somatic mutations that mediate tumor formation using formalin-fixed, paraffin-embedded (FFPE) tumor tissue from patients participating in the current study.

2.3.1.2 Secondary: To correlate the MIP array copy number and mutational data from patients with locally advanced rectal cancer with clinical outcome in each treatment cohort. The clinical outcomes include pathologic complete response, time to recurrence, time to pelvic recurrence, and overall survival.

2.3.2 Immunologic Studies – Indicators of Immunologic Activation in Locally Advanced Rectal Cancer.

2.3.2.1 To identify immune markers for response to neoadjuvant chemotherapy or chemoradiation using very well established, validated immunologic assays.

2.3.2.2 To investigate the ability of neoadjuvant FOLFOX or chemoradiation to augment anti-tumor immunity against rectal cancer.

2.3.2.3 To identify novel immune targets in rectal cancer.

2.3.3 Pharmacogenomics: Assessment of Germline Variation as a Predictor of Response and Toxicity to Platinum-based Chemotherapy and to Radiation Therapy in Patients with Rectal Cancer.

2.3.3.1 Primary:

2.3.3.1.1 To determine whether germline genetic variants in candidate genes of interest are associated with response and/or toxicity to platinum and 5FU-based chemotherapy.

2.3.3.2 Secondary:

2.3.3.2.1 To determine whether germline genetic variants in candidate genes of interest are associated with response and/or toxicity to radiation therapy.

2.3.3.2.2 To assess whether genetic risk variants identified in genome-wide association studies of colorectal cancer susceptibility are associated with rectal cancer clinical outcome and response to therapy.

3.0 PATIENT ELIGIBILITY

For SAKK sites, please refer to the Swiss Specific Appendix for instructions regarding patient screening, enrollment and identification.

3.1 Registration – Inclusion Criteria

3.1.1 Age ≥ 18 years at diagnosis.

3.1.2 Diagnosis of rectal adenocarcinoma.

3.1.3 Radiologically measurable or clinically evaluable disease as defined in Section 11.0.

3.1.4 ECOG Performance Status (PS): 0, 1 or 2.

3.1.5 For this patient, the standard treatment recommendation in the absence of a clinical trial would be combined modality neoadjuvant chemoradiation followed by curative intent surgical resection.

3.1.6 Candidate for sphincter-sparing surgical resection prior to initiation of neoadjuvant therapy according to the primary surgeon.

3.1.7 Clinical Stage: T2N1, T3N0, T3N1.

- N2 disease is to be estimated as four or more lymph nodes that are ≥10 mm.
- Clinical staging should be estimated based on the combination of the following assessments: physical exam by the primary surgeon, CT or PET/CT scan of the chest/abdomen/pelvis and either a pelvic MRI or an ultrasound (ERUS). If a pelvic MRI is performed, it is acceptable to perform CT of the chest/abdomen, omitting CT imaging of the pelvis.

3.1.8a The following laboratory values obtained ≤ 28 days prior to registration.

- Absolute neutrophil count (ANC) ≥ 1500/mm^3
- Platelet count ≥ 100,000/mm^3
- Hemoglobin > 8.0 g/dL
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
- SGOT (AST) ≤ 3 x ULN
- SGPT (ALT) ≤ 3 x ULN
- Creatinine ≤1.5 x ULN

3.1.8b Negative pregnancy test done ≤ 7 days prior to registration, for women of childbearing potential only.

3.1.8c Patient of child-bearing potential is willing to employ adequate contraception. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives, or double barrier method (diaphragm plus condom).

3.1.8d Provide informed written consent.

3.1.8e Willing to return to enrolling medical site for all study assessments.

3.2 Registration – Exclusion Criteria

3.2.1 Clinical T4 tumors.

3.2.2 Primary surgeon indicates need for abdominoperineal (APR) at baseline.

3.2.3 Evidence that the tumor is adherent to or invading the mesorectal fascia on imaging studies such that the surgeon would not be able to perform an R0 resection (one with negative margins). Please reference the end of Section 7.4.2 for details.

3.2.4 Tumor is causing symptomatic bowel obstruction (patients who have had a temporary diverting ostomy are eligible).

3.2.5 Chemotherapy within 5 years prior to registration. (Hormonal therapy is allowable if the disease free interval is ≥ 5 years.)

3.2.6 Any prior pelvic radiation.

3.2.7 Other invasive malignancy ≤ 5 years prior to registration. Exceptions are colonic polyps, non-melanoma skin cancer, ductal carcinoma in situ, bladder carcinoma in situ, or carcinoma-in-situ of the cervix.

3.2.8 Any of the following because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects.

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.2.9 Co-morbid illnesses or other concurrent disease which, in the judgment of the clinician obtaining informed consent, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

4.0 SCHEDULE OF TESTS

4.1 Pre-operative Testing Schedule: Group 1 (FOLFOX and Selective 5FUCMT)

	Active Monitoring Phase						
Tests and procedures	≤ 28 days prior to registration	≤ 60 days prior to registration OR after registration but before start of treatment	At baseline (before start of treatment)	Prior to each new cycle of FOLFOX (± 3 days)	Restaging ≤ 28 days after completion of FOLFOX (in other words, ≤ 28 days after cycle 6 day 14 of FOLFOX	Weekly (W) or biweekly (every 2 weeks; B) during 5FUCMT	Surgery[12]
History and physical exam	X			X	X	X (B)	
Pulse, blood pressure and temperature	X			X	X	X (W)	
ECOG performance status (PS)	X			X	X	X (B)	
Weight			X	X	X	X (B)	
Height			X				
Adverse event assessment[1]			X	X	X	X (B[13])	
Hematology[2]	X			X		X (W)	
Chemistry[3]	X						
Carcinoembryonic antigen (CEA)		X			X		
Research blood sample (see Section 14.0)[4 R]			X				X
Pregnancy test [5]	X						
Rectal exam and proctoscopy		X[6]			X		
Rectal tumor tissue biopsy (see Section 14.0) [R]		X[7]					X
Pathologic confirmation of rectal adenocarcinoma		X					X
MRI or ERUS of the pelvis (MRI preferred)	X[8]				X[8]		
CT of the Chest (contrast optional)	X[9]						
CT of abdomen with contrast	X[9]						
CT of this pelvis with contrast (Optional if pelvic MRI performed)	X[9]				X[9]		
Completion of PRO-CTCAE by patient[10] (see Appendix V)			X	X		X (W)	
QOL Assessment[11] (see Appendix VI)			X[14]		X[14]		
Photographs evaluating TME specimen for Surgical QA (see Appendix VII)							X

Shaded columns indicate Group 1 patients who were assigned to 5FUCMT based on restaging of primary tumor or inability to tolerate FOLFOX.

NOTE: Time points specified in the footnotes below override time points listed above for the specific test or procedure.

Table 4.1 Footnotes

1. Patients must have assessment at the time of progressive disease, study withdrawal, or removal.
2. Hematology includes hemoglobin, platelets and absolute neutrophil count (ANC).
3. Chemistry includes SGOT (AST), SGPT (ALT), total bilirubin, creatinine. Additional chemistries (e.g., Mag, Phos, LDH) are not required and should be performed in accordance with clinical necessity. Blood work does not have to be performed at the trial site; it can be performed at other locations.
4. Mandatory research blood draws will be collected at baseline (≤ 28 days of start of FOLFOX) and ≤ 28 days prior to surgery.
5. Pregnancy test required for females of childbearing potential ≤ 7 days of registration.
6. Rectal exam and proctoscopy are ideally to be performed by the primary surgeon. Proctoscopy should be performed ≤ 60 days prior to registration or after registration but before the start of treatment. Ideally, the surgeon should perform pre and post induction treatment proctoscopies. A gastroenterologist may perform proctoscopy in lieu of the surgeon, but then must also perform the follow-up exam. Proctoscopy may be accomplished using rigid proctoscopy or as part of a flexible sigmoidoscopy or colonoscopy.
7. If a rectal tumor tissue biopsy was performed at an outside facility and can be obtained for confirmation of the diagnosis and for submission of the research specimen, it is adequate, and a repeat biopsy is not necessary. If a biopsy is performed at the accruing site, the following procedure is suggested: Obtain four large pinch biopsies in a viable section of the tumor (leading edge) and fix in formalin and embed in paraffin as per standard pathology practice. These specimens can be processed as routine clinical specimens by pathology. Samples from this biopsy must later be sent to the pathology core (at Ohio State) for correlative science. Rectal tumor biopsy may be performed within 60 days before registration OR between registration and the start of treatment. See Section 14.0 for submission instructions.
8. Scan is to be performed within 60 days prior to registration. Use same imaging modality throughout the study. Radiology scans do not have to be performed at the trial site; they can be performed at other locations as long as images are available for review. (See Appendix VIII for suggested MRI Technical and Quality Requirements.)
9. A PET/CT scan may be performed in lieu of a CT scan with contrast, but a CT scan is preferred. Scans do not have to be performed at the trial site; they can be performed at other locations as long as images are available for review. Scan is to be performed within 60 days prior to registration. Contrast is preferred but not required for the CT of the chest. Contrast is REQUIRED for the CT of the abdomen. If pelvic MRI is performed, omission of the CT scan of the pelvis is acceptable. If pelvic MRI is not performed, restaging pelvic CT scan is required.
10. The PRO-CTCAE is required for patients enrolled at US and Canadian sites who are fluent in reading and speaking English or Spanish; patients will be asked by PRO-CTACE staff to use the website or Interactive Voice Response System by telephone to report once at baseline and, once every week during pre-op active treatment. Following surgery, patients will report once every six months for three years. See Appendix V.
11. The QOL is required for patients who are fluent in reading and speaking English accrued at US and English-speaking Canadian sites; sites must administer pre-printed booklets to patients (photocopies not acceptable). Sites may order these booklets by filling out and submitting the "CTSU Supply Request Form" available at [redacted] (Please be sure to order both male and female QOL booklets from CTSU). Booklet should be administered by the site research staff in clinic at the following time points: baseline, 1-2 weeks prior to surgery and 12 months +/- 6 weeks and 24 months +/- 6 weeks after rectal resection. In the event that a patient is not seen in clinic at 12 and 24 months +/- 6 weeks after rectal resection, the site research staff will follow-up with the patient via telephone and/or mail. See Section 4.5 and Appendix VI
12. Recommendation: Surgery should be performed within 3-6 weeks of the 6th dose of neoadjuvant FOLFOX therapy or within 5-8 weeks of the last dose of RT if 5FUCMT is required. Actual timing of surgery is at the discretion of the treating clinician. Tissue block submission from surgical resection is mandatory (see Section 14.0 for submission instructions).
13. Adverse Events form to be completed at the start of week 1 of 5FUCMT, at the start of week 3 of 5FUCMT and at the start of week 5 of 5FUCMT.
14. For patients enrolled after 02/01/2016, QOL is no longer needed as the accrual goal has been reached.

R. Research funded (see Section 18.0).

For SAKK sites, please refer to the Swiss Specific Appendix for instructions regarding Precaution.

4.2 Pre-operative Testing Schedule: Group 2 (5FUCMT)

Tests and procedures	Active Monitoring Phase					
	≤ 28 days prior to registration	≤ 60 days prior to registration OR after registration but before start of treatment	At baseline (before start of treatment)	Weekly (W) or biweekly (every 2 weeks; B) during 5FUCMT	≤ 28 days after completion of 5FUCMT	Surgery[12]
History and physical exam	X			X (B)	X	
Pulse, blood pressure and temperature	X			X (W)	X	
ECOG performance status (PS)	X			X (B)	X	
Weight			X	X (B)	X	
Height			X			
Adverse event assessment[1]			X	X (B[13])	X	
Hematology[2]	X			X (W)		
Chemistry[3]	X					
Carcinoembryonic antigen (CEA)		X			X	
Research blood sample (see Section 14.0)[4 R]			X			X
Pregnancy test [5]	X					
Rectal exam and proctoscopy		X[6]				
Rectal tumor tissue biopsy (see Section 14.0) [7 R]		X				X
Pathologic confirmation of rectal adenocarcinoma		X[7]				X
MRI or ERUS of the pelvis (MRI preferred)	X[8]					
CT of the Chest (contrast optional)	X[9]					
CT of the abdomen with contrast	X[9]					
CT of the pelvis with contrast (optional if pelvic MRI performed)	X[9]					
Completion of PRO-CTCAE by patient[10] (see Appendix V)			X	X (W)		
QOL Assessment[11] (see Appendix VI)			X[14]		X[14]	
Photographs evaluating TME specimen for surgical QA (see Appendix VII)						X

Note: Post-operative test schedule appears in Section 4.3

NOTE: Time points specified in the footnotes below override time points listed above for the specific test or procedure.

Table 4.2 Footnotes

1. Patients must have assessment at the time of progressive disease, study withdrawal, or removal.
2. Hematology includes hemoglobin, platelets and absolute neutrophil count (ANC).
3. Chemistry includes SGOT (AST), SGPT (ALT), total bilirubin, creatinine. Additional chemistries (e.g., Mag, Phos, LDH) are not required and should be performed in accordance with clinical necessity. Blood work does not have to be performed at the trial site; it can be performed at other locations.
4. Mandatory research blood draws will be collected at baseline (≤ 28 days of start of 5FUCMT) and ≤ 28 days prior to surgery.
5. Pregnancy test required for females of childbearing potential ≤ 7 days of registration.
6. Rectal exam and proctoscopy should be performed by the primary surgeon. Proctoscopy should be performed ≤ 60 days prior to registration or after registration but before the start of treatment. A gastroenterologist may perform proctoscopy in lieu of the surgeon. Proctoscopy may be accomplished using rigid proctoscopy or as part of a flexible sigmoidoscopy or colonoscopy.
7. If a rectal tumor tissue biopsy was performed at an outside facility and can be obtained for confirmation of the diagnosis and for submission of the research specimen, it is adequate, and a repeat biopsy is not necessary. If a biopsy is performed at the accruing site, the following procedure is suggested: Obtain four large pinch biopsies in a viable section of the tumor (leading edge) and fix in formalin and embed in paraffin as per standard pathology practice. These specimens can be processed as routine clinical specimens by pathology. Samples from this biopsy must later be sent to the pathology core (At Ohio State) for correlative science. Rectal tumor biopsy may be performed within 60 days before registration OR between registration and the start of treatment. See Section 14.0 for submission instructions.
8. Scan is to be performed within 60 days prior to registration. Use same imaging modality throughout the study. Radiology scans do not have to be performed at the trial site; they can be performed at other locations as long as images are available for review. (See Appendix VIII for suggested MRI Technical and Quality Requirements.)
9. A PET/CT scan may be performed in lieu of a CT scan with contrast, but a CT scan is preferred. Scans do not have to be performed at the trial site; they can be performed at other locations as long as images are available for review. Scan is to be performed within 60 days prior to registration. Contrast is preferred but not required for the CT of the chest. Contrast is REQUIRED for the CT of the abdomen. Contrast CT of the pelvis is required for patients who have ERUS. If pelvic MRI is performed CT scan of the pelvis is optional.
10. The PRO-CTCAE is required for patients enrolled at US and Canadian sites who are fluent in reading and speaking English or Spanish; patients will be asked by PRO-CTCAE staff to use the website or Interactive Voice Response System by telephone to report once at baseline and, once every week during pre-op active treatment. Following surgery, patients will report once every six months for three years. See Appendix V.
11. The QOL is required for patients who are fluent in reading and speaking English accrued at US and English-speaking Canadian sites; sites must administer pre-printed booklets to patients (photocopies not acceptable). Sites may order these booklets by filling out and submitting the "CTSU Supply Request Form" available at [redacted] (Please be sure to order both male and female QOL booklets from CTSU). Booklet should be administered by the site research staff in clinic at the following time points: baseline, 1-2 weeks prior to surgery and 12 months +/- 6 weeks and 24 months +/- 6 weeks after rectal resection. In the event that a patient is not seen in clinic at 12 and 24 months +/- 6 weeks after rectal resection, the site research staff will follow-up with the patient via telephone and/or mail. See Section 4.5 and Appendix VI.
12. Recommendation: Surgery should be performed within 5-8 weeks of the last dose of RT. Actual timing of surgery is at the discretion of the treating clinician. Tissue block submission from surgical resection is mandatory (see Section 14.0 for submission instructions).
13. Adverse Events form to be completed at the start of week 1 of 5FUCMT, at the start of week 3 of 5FUCMT and at the start of week 5 of 5FUCMT.
14. For patients enrolled after 02/01/2016, QOL is no longer needed as the accrual goal has been reached.

R. Research funded (see Section 18.0).

For SAKK sites, please refer to the Swiss Specific Appendix for instructions regarding Precaution.

4.3 Post-operative Testing Schedule: Groups 1 and 2

Tests and procedures	At completion of post operative treatment	9 months from randomization ± 1 month	Annually starting at 15 months from randomization until 5 years after randomization ± 1 month	Every 6 months starting at 15 months until 5 years after randomization ± 1 month	At PD, withdrawal or removal[8]
History and physical exam		X		X	X
Pulse, blood pressure and temperature		X		X	X
ECOG performance status (PS)		X		X	X
Weight		X		X	
Adverse event assessment [1]	X	X		X	X
Carcinoembryonic antigen (CEA) [2]		X		X q3 months for 1st year of surveillance, then q6 months. Deviations are not violations	
Colonoscopy [3]			X at months 15 and 51 after randomization		
Proctoscopy [4]			X		
Surveillance CT scan with contrast (chest/abdomen/pelvis) [5]			X		X
Completion of PRO-CTCAE by patient [6] (see Appendix V)				X After surgery, complete once every 6 months for 3 years	
QOL Assessment [7] (see Appendix VI)			X Until 2 years after randomization only		

Laboratory testing during post-operative treatment is at discretion of treating physician
NOTE: Time points specified in the footnotes below override time points listed above for the specific test or procedure.

Table 4.3 Footnotes

1. Patients must have assessment at the time of progressive disease, study withdrawal, or removal.
2. Blood work does not have to be performed at the trial site, it can be performed at other locations. 1st year of surveillance = 1st post-treatment year.
3. A full surveillance colonoscopy should be performed at approximately 15 and 51 months after randomization. More frequent evaluation may be indicated based on findings such as adenomatous polyps or genetic predisposition. Surveillance colonoscopy does not need to be performed every 6 months. For the assessments when colonoscopy is performed, because it includes visualization of the rectum, proctoscopy does not also need to be performed. Deviations in the timing of colonoscopy will not constitute a study violation.
4. Rectal exam and proctoscopy should be performed annually starting 15 months from randomization.
5. A PET/CT scan may be performed in lieu of a CT scan with contrast, but a CT scan with contrast is preferred. Scans do not have to be performed at the trial site; they can be performed at other facilities as long as data are available for review by the site. Contrast is preferred but not required for the CT of the chest. Contrast is required for the CT of the abdomen and pelvis.
6. See Appendix V.
7. Postoperatively sites must administer pre-printed booklets with QOL survey at 12 months +/- 6 weeks (~15-18 months after randomization) and 24 months +/- 6 weeks (~27-30 months after randomization) after rectal resection. In the event that a patient is not seen in clinic at 12 and 24 months +/- 6 weeks after rectal resection, the site research staff will follow-up with the patient via telephone and/or mail. See Section 4.5 and Appendix VI. For patients enrolled after 02/01/2016, QOL is no longer needed as the accrual goal has been reached.
8. Upon identification and confirmation of PD per Section 11.1.4.2.3 or withdrawal from the Section 4.3 observation follow-up, patients should proceed to the annual Event Monitoring Phase (Section 4.3.1) until a total of 8 years post-randomization.

For SAKK sites, please refer to the Swiss Specific Appendix for instructions regarding Precaution.

4.3.1 Event Monitoring Folow-up Phase

Event Monitoring Phase[1]			
After completion of Section 4.3 Post-operative Observation Schedule *Every 12 Months*	After PD *Every 12 Months*	Withdrawal *Every 12 Months*	Death
X[2]	X[2]	X[2]	X[2]

Table 4.3.1 Footnotes:

1. Patients who stop treatment early, withdraw from observation follow-up, progress per Section 11.1.4.2.3, or complete the Section 4.3 Post-operative observation schedule will proceed to annual Event Monitoring (i.e. Survival Follow-up) until a total of 8 years post-randomization. If a patient is still alive 8 years after registration, then no further follow-up is required.
2. Clinical assessments (i.e. disease status evaluations) are not required in Event Monitoring per protocol. However, site research staff should review patient electronic health records and/or contact the treating institution if the patient moved, to obtain disease status evaluation data. Recurrent disease data is crucial to the primary endpoint of this protocol which is disease-free survival.

4.4 Patient-Reported Outcomes

Patient-Reported Outcomes Versions of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) Assessment (see Appendix V).

For SAKK sites, PRO-CTCAE assessments are not applicable as outlined in the Swiss Specific Appendix.

4.4.1 Study Site Staff PRO-CTCAE Credentialing

Note: At least one staff personnel from the site study team should credentialed to perform patient PRO-CTCAE training and registration prior to the first patient's baseline visit.

PRO-CTCAE Training and Registration

To obtain credentialing to perform PRO-CTCAE patient training, send an email request to the PRO-CTCAE Coordinator at [redacted] The coordinator will contact you to schedule a date and time for live interactive training using the telephone. Please note that the training does not require viewing of an instructional video; a PRO-CTCAE training video is not posted on the CTSU website. Training will require about 30 minutes and is required only once.

Training will include: 1) how to register a patient to PRO-CTCAE reporting by either telephone using the interactive voice response system (IVRS) or by computer using the PRO-CTCAE website; 2) how to explain and demonstrate the PRO-CTCAE telephone and computer systems to patients; 3) how to monitor your patients' PRO-CTCAE reporting.

The PRO-CTCAE Coordinator will email notice of the certification to the site, and the site must submit the confirmation of certification form to the CTSU Regulatory Office via the Regulatory Submission Portal (see Section 6.2). The CTSU will list the certification on the CTSU Regulatory Support System (RSS). Study teams may check the status of their certification by logging into the CTSU website, clicking the blue 'Regulatory' tab, then

clicking the beige 'Site Registration' tab, then entering their CTEP site number and protocol number N1048 in the text boxes and clicking 'Go.'

For any questions or concerns, please send email to [redacted]

4.4.2 Patient PRO-CTCAE Training

All patients enrolled at U.S. and Canadian sites who can read and speak English or Spanish will be required to participate in PRO-CTCAE reporting by either telephone using the interactive voice response system (IVRS) or by computer using the PRO-CTCAE website. Patients may choose their reporting mode. Site study staff will train the patient how to use the IVRS or website; this training will require about 10 to 20 minutes per patient.

Because patients will self-report PRO-CTCAE symptoms from home, patients will not require access to a telephone or a computer during regularly scheduled clinic visits. However, in order for site personnel to train patients who choose telephone reporting, access to a telephone will be required. If this is not possible, the site study staff may provide this training over the telephone by calling the patient after s/he leaves the clinic. Likewise, for patients who choose computer reporting, access to an Internet-enabled computer is necessary.

Patients choosing to report by telephone will call telephone number [redacted] **enter userID and PIN**, then answer the verbal questions concerning symptoms and health concerns. This will require about 5 minutes.

Patients choosing to report by computer will go to the PRO-CTCAE website at [redacted] enter username and password, and then answer the questions. This will require about 5 minutes.

Reference cards for both the telephone IVRS system and the computer website will be provided to the patient as shown below. These reference cards, available in English and Spanish, are available on the CTSU website for sites to print for patients. Both a help line and website are listed on the cards; should a patient have difficulties, s/he may call telephone number [redacted]

PROSPECT RECTAL CANCER STUDY (N1048)
Automated Telephone [IVRS] System Reference Card

1. To access your survey by phone, please call toll-free [redacted]
2. You will need your ID number and PIN to access your survey.
   _____
3. Please answer the questions about your symptoms; this will require less than 5 minutes

If you have any questions, please either: call your doctor's office at _____, send an email to [redacted]

Please remember that the information you report through PRO-CTCAE goes only to the research team. Always discuss your symptoms with your doctor or nurse during regular visits

Thank you for agreeing to participate in the PROSPECT study!

PROSPECT RECTAL CANCER STUDY (N1048)
Website Reference Card

1. To access your survey, please type this link into your browser: [redacted]
2. You will need your username and password
   _____
3. Please answer the questions about your symptoms; this will require less than 5 minutes

If you have any questions, please either: call your doctor's office at _____, send an email to [redacted]

Please remember that the information you report through PRO-CTCAE goes only to the research team. Always discuss your symptoms with your doctor or nurse during regular visits

Thank you for agreeing to participate in the PROSPECT study!

4.4.3 Patient PRO-CTCAE Reporting

Note: Site study staff must clearly convey to the patient that the information regarding symptoms collected by the PRO-CTCAE self-report are for research purposes only and are not monitored by a physician. Study staff must advise patients to directly contact their doctor for any concerning symptoms.

During the pre-operative period, patients will be required to use either the telephone IVRS system or the computer website to self-report symptoms once weekly on a day and time pre-arranged by the patient and the site study personnel. This reporting should require about 5 minutes and should occur approximately 3 days prior to the scheduled clinic visit.

Patients will be asked by site study personnel to provide a telephone number and an active email address if they have one for contact. Patients who do not self-report as scheduled will receive an automated reminder call or email. If there is no response to two successive reminders, an automatic email notification will be sent to the PRO-CTCAE Coordinator who will then call the patient to administer the PRO-CTCAE items verbally and enter the patient's verbal responses into the PRO-CTCAE web system.

Data reported by patients into the PRO-CTCAE electronic platform will be stored in a secure database on a server hosted at the National Cancer Institute. This NCI database will be available electronically to the cooperative group statistical center for remote access.

4.4.4 Study Site PRO-CTCAE Reporting

Sites will be randomly assigned at the time of training by the PRO-CTCAE Coordinator to report adverse events either by: (a) using the Solicited AE Form from the paper forms packet posted on the CTSU or Alliance website, or (b) using a Solicited AE Form generated from the PRO-CTCAE system which contains the patient's PRO-CTCAE scores. Details of the randomization can be found in Appendix V. For sites assigned to (a), the AE form should be printed by site study staff from the paper forms packet posted on the CTSU or Alliance website. For sites assigned to (b), the AE form should be printed from the PRO-CTCAE system (instructions will be provided during PRO-CTCAE training). Both forms are entered into RAVE.

Six months (+/- 1 month) after registering the first patient to the PRO-CTCAE web system, and optionally again at 12 months (+/- 1 month), site study personnel will be asked to complete a very brief questionnaire about the PRO-CTCAE system via email from the PRO-CTCAE Coordinator.

4.5 Quality of Life Assessments

For SAKK sites, QOL assessments are not applicable, as outlined in the Swiss Specific Appendix.

Note: The sample size for the QOL component was reached on 02/01/2016. Therefore, patients registered to this study after 02/01/2016 will not be required to participate in the Quality of Life Assessment component of the study and will not complete the paper Quality of Life (QOL) questionnaire booklets. Patients registered prior to 02/01/2016 should continue to complete the QOL questionnaire booklets per the schedule found below.

The QOL study is required for all eligible patients randomized in the phase II or phase III component of the study until the maximum number of 460 patients has been accrued. Patients must use pre-printed questionnaire booklets ordered from the CTSU website (Note: There are 2 versions of the QOL booklet. One for males and one for females. Be sure to order both male and female booklets from CTSU). Patients who can read and speak English are eligible to participate in the QOL portion of the study. QOL questionnaire booklets will be completed by the patients at regularly scheduled clinic visits occurring at:

1. Baseline (before start of treatment at time of randomization)
2. 1-2 weeks prior to surgery (after neoadjuvant treatment e.g. at time of surgical consent)
3. 12 months +/- 6 weeks (corresponds to ~15-18 months after randomization)
4. 24 months +/- 6 weeks (corresponds to ~27-30 months after randomization) after rectal resection

If the patient was not seen in clinic at 12 and 24 months ± 6 weeks after rectal resection and/or a QOL questionnaire booklet is not completed by the patient during a scheduled clinic visit at one of the specified time points, the site study staff should follow-up with the patient by telephone and/or mail in order to minimize missing data. The mode of QOL administration (paper vs. telephone) and the date of completion will be noted on the form. If a patient chooses to complete the survey via telephone, sexual function questions (IIEF for men and FSFI for women) will not be administered due to their sensitive nature.

To assess bowel function, the 19 item Bowel Function Index (Temple et al., 2005) will be used. To assess sexual function, gender specific questionnaires will be used, specifically the International Index of Erectile Function (Rosen et al., 1997) and the Female Sexual Functioning Index (Rosen et al., 2000). Bladder function will be assessed using two items from validated questionnaires. We will assess global HRQL using the EuroQOL5D-5L which evaluates domains of pain, anxiety, physical function, ambulation and activities of daily living as well as the linear analogue scale. These instruments have been embedded in many prior NCCTG and CALGB clinical trials and reproducibly assess health related quality of life in a succinct manner. The entire functional assessment can be completed in less than 30 minutes with an average of 10-20 minutes per patient. Refer to Appendix VI for more details.

5.0 STRATIFICATION AND GROUPING FACTORS

5.1 Stratification Factors (Used for Randomization to Group 1 or Group 2)

5.1.1 ECOG Performance Status: (0 or 1) vs. 2

6.0 REGISTRATION/RANDOMIZATION PROCEDURES

All Site Staff (Alliance and CTSU institutions). This study is supported by the NCI Cancer Trials Support Unit (CTSU).

For SAKK sites, please refer to the Swiss Specific Appendix for activation instructions, including copies of the physician agreements.

6.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);

- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at [redacted] For questions, please contact the [redacted]

6.2 Cancer Trials Support Unit Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

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

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at [redacted] to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling [redacted]

- Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:Local IRB documentation;
-
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.
- In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:Holds an active CTEP status;
- Active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and

- Compliance with all protocol-specific requirements (PSRs).

Downloading Site Registration Documents:

- Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms: Log in to the CTSU members' website ([redacted]) using your CTEP-IAM username and password;
- Click on Protocols in the upper left of the screen:
- Enter the protocol number in the search field at the top of the protocol tree; or
- Click on the By Lead Organization folder to expand, then select Alliance, and protocol number #N1048.
- Click on Documents, Protocol Related Documents, and use the Document Type filter and select Site Registration to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Requirements for N1048 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Protocol Specific Requirements that are required but not necessary for CTSU approval (site can open N1048 and register patients PRIOR to completing the 2 following items):

1. PRO-CTCAE Credentialing (should be completed before the first study participant's baseline visit; see Section 4.4.1)
2. IMRT and/or 3D Conformal Radiation Therapy Credentialing (should be completed before the first study participant starts radiation therapy; see Section 7.3.2)
    a. For applicable NCTN studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at [redacted] to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.
    b. IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC to begin the modality credentialing process.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: [redacted] or [redacted] in order to receive further instruction and support.**Checking Site's Registration Status:**

- Site registration status may be verified on the CTSU members' website. Click on Regulatory at the top of the screen;
- Click on Site Registration; and
- Enter the sites 5-character CTEP Institution Code and click on Go:
- Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

6.3 Patient Enrollment and Randomization

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

- Requirements for OPEN access: A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at [redacted] or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at [redacted] For any additional questions, contact the CTSU Help Desk at [redacted] To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

6.4 Treatment Assignment

Treatment assignment will be calculated using a dynamic allocation procedure that balances the marginal distributions of the stratification factors between the two treatment groups. ECOG performance status, defined in Section 5.0, together with the randomizing site, will be used as stratification factors.

6.5 Correlative Studies

For SAKK sites, please refer to the Swiss Specific Appendix for details regarding translational research.

6.5.1 Acquisition of Rectal Tumor Tissue

This is mandatory for pathologic confirmation of diagnosis and correlative research component that are part of this study and the patient will be automatically registered onto this component. Patients may have had a previous biopsy acquired prior to study registration. **This outside specimen may be used in lieu of a repeat tumor biopsy at the registering site**. However, in some cases, the outside tumor specimen will be suboptimal. In this context, the primary surgeon or gastroenterologist at the study site should perform a rectal tumor biopsy at the time of proctoscopy. In addition to submission for routine clinical processing and confirmation of the diagnosis of rectal adenocarcinoma, a portion of the tumor should be submitted to the Ohio State Pathology Lab for research purposes (see Section 14.0). If a tumor biopsy specimen is not obtained at the registering site, an adequate tumor specimen that confirms the diagnosis of rectal adenocarcinoma should be obtained from the outside pathology source. A sample of this tumor specimen should be submitted to the Ohio State Pathology lab. Specific instructions and mailing addresses are in Section 14.0.

Rectal tumor biopsy may be performed within 60 days of registration OR between registration and the start of treatment.

The suggested method for rectal tumor acquisition is to obtain four biopsies from the leading edge of the primary rectal tumor. The leading edge should be sampled so as to avoid the center of the tumor which is more often necrotic. The use of alligator forceps though a rigid proctoscope is recommended. Pinch biopsies via a flexible endoscope are an alternative but are often associated with lower yield of adequate tissue specimen. This tissue should be embedded into a formalin fixed paraffin embedded block and processed as routine clinical specimens by pathology. Samples from this biopsy should later be sent to the pathology core (at Ohio State) for correlative science. See Section 14.0 for instructions.

6.5.2 Acquisition of Blood Samples

The patient will be automatically registered onto the correlative research component (see Section 14.0). The correlative study will attempt to understand the molecular events related to tumor response to either FOLFOX or 5FUCMT.

6.5.3 Informed Consent for Correlative Studies

At the time of registration, the following will be recorded (found on the informed consent document):

1. Patient has given permission to the Alliance to store and use his/her **blood samples** for use in future research to learn about, prevent, or treat cancer.
2. Patient has given permission to the Alliance to store and use his/her **blood samples** for use in future research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
3. Patient has given permission to the Alliance to give his/her stored **blood samples** for use in future research to outside researchers.
4. Patient has given permission to the Alliance to store and use his/her **tissue samples** for use in future research to learn about, prevent, or treat cancer.
5. Patient has given permission to the Alliance to store and use his/her **tissue samples** for use in future research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
6. Patient has given permission for the Alliance to give his/her stored **tissue samples** for use in future research to outside researchers.

6.6 Treatment Prior to Registration

Treatment cannot begin prior to registration and must begin ≤ 21 days after registration.

6.7 Prior to Treatment

6.7a Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified in the test schedule.

6.7b All required baseline conditions (see Section 10.5.1) must be documented and graded.

6.7c Treatment on this protocol must commence at the accruing membership site under the supervision of an Alliance or CTSU member physician.

6.7d After informed consent is obtained from the patient and prior to starting the treatment, baseline PRO-CTCAE assessments and QOL questionnaires must be completed. Blood and tissue samples should be obtained prior to treatment.

7.0 PROTOCOL TREATMENT

For SAKK sites, please refer to the Swiss Specific Appendix for information on drug supply and handling, including drugs / radiotherapy / surgery in protocol.

NOTE: The primary physician must see the patient at the initial visit and assume responsibility for adherence to protocol treatment. Subsequent visits and participation in shared care models with RNPs/PAs/etc. is acceptable provided that all protocol procedures are followed and all reports are submitted.

7.1 Group 1 Pre-Operative Treatment Schedule (FOLFOX)

FOLFOX (5-fluorouracil + leucovorin + oxaliplatin)

Agent[1]	Dose[6]	Route	Day[2]	Retreatment[3,4]
Oxaliplatin	85 mg/m^2	IV over 2 hours	Day 1	Repeat every 14 days for a total of 6

				cycles
Leucovorin[5]	400 mg/m^2 bolus	IV over 2 hours	Day 1	Repeat every 14 days for a total of 6 cycles
5FU	400 mg/m^2 bolus over 5-15 minutes then 2400 mg/m^2 continual over 46-48h total dose	IV	Day 1 Days 1 to 2	Repeat every 14 days for a total of 6 cycles

1. Oxaliplatin is administered first, prior to leucovorin; alternatively leucovorin may be administered (via separate infusion containers) concurrently with oxaliplatin.
2. FOLFOX cycle = 14 day cycles for 6 cycles.
3. If necessary to accommodate holidays, patient schedule or other justified circumstance, the schedule may be modified by ± 7 days.
4. Patients who cannot tolerate six cycles of FOLFOX or those that require dose modification below dose level -2 will receive preoperative 5FUCMT. There are no restrictions on dose modifications for the 6th cycle of neoadjuvant FOLFOX. If for example, a patient has dose limiting neuropathy or a hypersensitivity reaction that precludes administration of the 6th dose of FOLFOX or any one of its component agents, the patient should proceed to undergo restaging as per the directives for Group 1.
5. Alternate folinic acids (i.e., levo-leucovorin) may be substituted for Leucovorin if Leucovorin is not available. Note: Levo-leucovorin is twice as potent as leucovorin; dosages should be adjusted accordingly. Dosages are at the discretion of the treating physician. **Dose modifications of leucovorin up to and including omission of leucovorin or its analogues imposed by drug shortages will not constitute protocol violations.**
6. The dose modification schema for FOLFOX (see Section 8.0) is suggested. **Oncologists may use clinical judgment in making dose modifications that deviate from the suggested schema. These will not constitute protocol violations.**

7.2 Group 2 Pre-operative Treatment Schedule (5FUCMT) and Group 1 Pre-Op Treatment Schedule if Patient Receives Pre-operative 5FUCMT

5FUCMT (5-fluorouracil OR capecitabine + radiation therapy)

Agent	Dose	Route	Day
5FU OR	225 mg/m^2 per day	Continuous IV infusion administered concurrently with RT	Continuous IV infusion either 5 or 7 days per week during RT
Capecitabine[1,2,3]	825 mg/m^2 BID	Orally administered concurrently with RT	5 days per week on days of planned RT
Radiation Therapy (RT)	see Section 7.3.3		5 days per week

1. Capecitabine is an acceptable alternative to 5-FU for chemosensitization during radiotherapy.
2. Patients must be counseled about the importance of compliance with capecitabine. A capecitabine diary is provided for convenience but does NOT need to be submitted. Compliance, with mention of missed doses, must be documented in the patient's medical record by site study personnel.
3. Patients should take their doses of capecitabine orally daily, one dose in the morning and one dose in the evening, about 12 hours apart for 5 days per week during radiation therapy. Patients should swallow capecitabine tablet(s) whole with a full glass of water, about 8 ounces of water, within 30 minutes after a meal. Patients should not try to make up a missed or vomited dose, never double up on a dose and tell their doctor if they miss a dose. Patients must return any remaining capecitabine tablets at the end of the 5.5 week long period to their doctor.

7.3 Radiation Therapy

7.3.1 Quality Assurance Monitoring Program

Radiation Therapy facilities participating in NCI sponsored protocols must be active in the IROC Houston (RPC) Quality Assurance monitoring program.

7.3.2 Radiation Therapy Credentialing

This protocol allows physician discretion as to the use of Intensity Modulated Radiation Therapy (IMRT) or 3D conformal planning techniques.

Sites using only IMRT need only complete item 1 below. Sites using only 3D Conformal need only complete item 2 below. Sites using both IMRT and 3D conformal need to complete both items 1 and 2 below. Items 1 and/or 2 only need to be completed ONCE for each radiation therapy planning technique that will be used for this study. Items 1 and/or 2 must be completed before the first study participant starts radiation therapy; sites may enroll patients prior to completing items 1 and/or 2.

1. Sites using Intensity Modulated Radiation Therapy (IMRT) planning techniques in this study must complete either the IMRT benchmark on the IROC Rhode Island (QARC) website ([redacted] under the tab labeled "Benchmarks"); or the IMRT head and neck phantom study on the IROC Houston (RPC) website ([redacted]). The IMRT facility questionnaire located on the IROC Houston website must also be completed.
2. Sites using 3D conformal radiation therapy in this study must complete the 3D conformal benchmark and questionnaire located on the IROC Rhode Island (QARC) website ([redacted] under the tab labeled "Benchmarks").

To determine if your site is already credentialed for use of 3D Conformal planning and/or IMRT, send an email to [redacted] or call [redacted] or visit the IROC Houston website at [redacted] and click 'credentialing' as it appears in red text on the top web banner, then click credentialing status inquiry.

In addition to items 1 and 2 above, radiation therapy quality assurance documentation must be submitted to IROC RI (QARC) for each study patient; detailed instructions can be found in Section 7.3.9.

7.3.3 Radiation Therapy Characteristics

Note: If protocol radiotherapy is delayed by more than 14 days or discontinued early, IROC RI (QARC) must be notified of the reason(s) and the date(s). Notification is not required for shorter delays due to toxicity, weather, linac maintenance problems, or similar logistical reasons. The notification must be submitted via email to [redacted] or fax [redacted]

Field	Dose (Gy)	Number of Fractions	Fraction Size	Rx Length	Rx Days
Initial	45	25	1.8 Gy	5 weeks	Monday through Friday
Boost	5.4	3		3 days	
Total	50.4	28			

Group 2: Radiation begins on Day 1 of neoadjuvant chemotherapy and continues for 28 consecutive weekdays. The trial administers 1.8 Gy per day without a break except for weekends and holidays.

Equipment

Modality: Linear accelerator-based photons with a minimum energy of 6 MV will be used. IMRT is allowed, for which inverse-planning capable software is required. IMRT may be delivered either at fixed gantry angles with a multileaf collimator or in rotational mode using a multileaf collimator or tomotherapy.

Geometry: Teletherapy units with a source-to-axis distance of 100cm. Calibration: Teletherapy units used in this study shall have their calibration verified by the Radiological Physics Center (RPC).

7.3.4 Target Volume Definitions for Conformal Therapy or IMRT

ICRU-50 and ICRU-62 prescription methods and nomenclature shall be utilized for this study. The volumes are to be defined by planning CT/MRI techniques as well as PET scans when clinically appropriate. While PET scans are not mandated as part of the protocol, for those patients who have PET scans available, the information may be used to aid in treatment planning. The inferior extent of palpable tumors should be determined by physical examination.

Gross Tumor Volume (GTV): This includes the primary tumor and any pelvic nodes felt involved grossly with metastatic disease. Assessment of the primary tumor and nodal disease may be made on the basis of endoscopy, CT, PET-CT, MRI, or transrectal ultrasonography. The entire rectal circumference at the level of the tumor should be included as GTV.

Clinical Target Volume (CTV): This includes the GTV and the following nodal groups: perirectal nodes; presacral nodes; internal iliac; and common iliac nodes below the L5-sacral junction.

Planning Target Volume 1 (PTV 1): This will provide a margin around the CTV to compensate for the inter- and intra-fraction uncertainty consequent to daily setup uncertainty and to potential internal organ motion. By definition, the PTV will consist of a symmetrical 7 mm expansion around the CTV. In the event that a PTV extends outside of the skin surface, the clinician should manually trim the PTV contours to be 3-5 mm inside the outer skin (unless there is direct skin involvement).

The following are guidelines for generating CTV and a unified PTV:

- Rectal GTV (+1.5 cm radially, +2.5 cm craniocaudally) = CTV
- Nodal GTV + 1.5cm symmetrical expansion = CTV
- Uninvolved iliac vessels + 1.0 cm = CTV
- Presacral lymphatic CTV is generated by contouring the entire sacral hollow from mid S1-S5 and 8 mm tissue anterior to the anterior border of the sacral bone
- The mesorectum and perirectal lymphatic CTV is generated by utilizing anatomic landmarks:
    - Posterior Border: anterior border of the sacrum and gluteus maximus
    - Lateral Border: ileum, piriformis and obturator muscles
    - Anterior Border: should include the interface with the bladder, vagina, uterus or prostate
    - Inferior Border: the levators

The PTV 1 is generated by expanding all of the above structures by 0.7 cm symmetrically and unifying them into one 3-dimensional volume for planning purposes.

Planning Target Volume 2 (PTV 2): The PTV for the cone down volume is an expansion of the GTV by 3 cm and the presacrum, provided the small bowel does not receive more than 5,000 cGy. This volume should not extend beyond PTV1.

Examples of contoured patients (anorectal atlas) are available for review on the ATC website ([redacted] or at the RTOG website ([redacted]). These examples are excellent resources for the contouring of normal structures as well as GTV, CTV and PTV design, and their use is strongly encouraged.

Suggested Field Borders for 3-D Conformal Treatment

For the first course, use of PA and opposed laterals is recommended. An AP field may be used at the discretion of the treating radiation oncologist if it results in improved dose homogeneity without increasing the small bowel dose unnecessarily.

Standard PA (and AP if used) Field:

Inferior	The minimum would be at least a 3 cm margin from the inferior extent of the cancer, or at the anal verge for cancers within 5 cm of the verge on digital rectal examination. The anal verge should be identified by a marker on simulation.
Lateral	2 cm lateral to the bony pelvis taken at its widest point.
Superior	L5-S1 junction.

Standard Opposed Lateral Portals:

Superior	To correspond to PA fields.
Inferior	To correspond to PA fields.
Anterior	This will cover the lower common and internal iliacs as defined on CT scans. Anatomically this will extend anteriorly to approximately the anterior one-third of the acetabulum.
Posterior	This must include 2 cm posterior to the presacrum.

The cone down field shall have a minimum 3 cm margin around the GTV but must include the whole of the sacral hollow. It is acceptable to use only opposed lateral fields, or to include a PA field, for the cone down treatment.

7.3.5 Localization, Simulation, and Immobilization

A custom immobilization device (such as Alpha Cradle for supine patients and an Alpha Cradle with bowel displacement device for prone patients) is suggested to minimize set-up variability. Simulation may be done with the patient in the supine "arms up" position for patients with very thin body habitus or the prone "arms up" position for patients of moderate or large body habitus, using a CT-simulator with a slice thickness ≤ 5 mm. Oral CT contrast is strongly suggested. An anal marker at the verge is required.

Weekly portal imaging is required; more frequent portal imaging is encouraged for patients being treated in the prone position on a bowel displacement device.

Portal imaging is the most common system used to verify patient position, in particular when the target volume is believed to possess a fixed spatial relationship with visualized bony anatomy. Orthogonal paired (AP and lateral) portal images (MV or kV) are required for IMRT and 3-D CRT to verify that the isocenter is in correct alignment relative to the patient position.

Volumetric imaging is allowed in this study. This includes in-room kV or MV cone beam or conventional CT imaging. If volumetric imaging is used (including tomotherapy), a screen capture of the fused CT images can be printed to demonstrate in room verification.

Treatment planning CT scans will be required to define gross target volume and clinical target volumes. The treatment planning CT scan should be acquired with the patient in the same position and using the same immobilization device as for treatment.

All tissues to be irradiated must be included in the CT scan. CT scan thickness should be 0.5 cm or smaller slices through the region that contains the primary target volumes. The regions above and below the target volume may be scanned also with slice thickness of 0.5 cm.

7.3.6 Organs at Risk (OARs)

Small Bowel: This is defined on planning CT study. Only the small bowel encompassed in the fields is to be included as part of the DVH. Bowel exclusion techniques are permitted. No portion of the small bowel shall receive a dose in excess of 5,000 cGy. It is recognized that there will be significant patient heterogeneity regarding the volume of the bladder and bowel that overlaps with the PTV. When a choice must be made between target coverage and sparing normal tissue, the priority should be given to target coverage. The constraints listed below are intended as guidelines; exceeding the recommended constraints will not be considered a protocol violation.

Constraints for Conformal or IMRT Planning:

Small bowel:	• No more than 150 cc above 3,500 cGy • No more than 70 cc above 4,000 cGy • No more than 35 cc above 4,500 cGy • None above 5,000 cGy
Femoral heads:	• No more than 50% above 3,000 cGy • No more than 40% above 4,000 Gy • No more than 5% above 4,500 cGy • No femoral head volume should receive 5000 cGy
Bladder:	• Mean dose < 4,000 cGy

7.3.7 Target Dose

Prescription Dose and Fractionation:

PTV1	The total dose to the PTV1 will be 4,500 cGy in 25 fractions (180 cGy to the PTV1 each day).
PTV2	A cone down dose of 540 cGy will be delivered to PTV2 in 3 fractions of 180 cGy per day (total dose 5,040 cGy).

Fractionation:

Treatment shall be given 5 days per week.

Prescription Isodose Surface:

Dose is to be prescribed to an isodose surface that encompasses the PTV and that satisfies the dose uniformity guidelines below. The minimum dose to PTV1 and PTV2 shall be no less than 95% of the protocol specified dose for that volume.

Dose Definition:

Dose is to be specified in cGy to muscle.

Tissue Heterogeneity:

Calculations shall take into account the effect of tissue heterogeneities.

Dose Uniformity:

PTV1 and PTV2 shall both be encompassed within the isodose surface corresponding to 95% of the prescription dose for that volume. The maximal dose should be no more than 110% of the prescription dose; the maximal volume to receive 110% of the prescription dose should be kept below 10% of the PTV, as evaluated by dose volume histogram.

IMRT Plan Verification:

If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the plan's fluence distributions can be recomputed for a phantom geometry.

7.3.8 Rests and Interruptions

Uninterrupted radiation treatment is intended. Treatment may be interrupted for the development of acute toxicity. The specific reason(s) for any treatment interruption must be recorded in the treatment chart. Treatment interruptions exceeding fourteen (14) days will be considered a major protocol deviation. See Section 7.3.10 for definitions of major and minor protocol deviations. Treatment interruption is mandated for severe diarrhea or other regional symptoms of severity > Grade 3 by Common Terminology Criteria. No modifications in dose will be made for interruptions in therapy.

NOTE: If protocol radiation therapy is delayed or interrupted for more than 14 days, IROC RI (QARC) must be notified of the reason(s) and date(s) that radiotherapy was held. It is not necessary to report single-day breaks that are required for logistical reasons such as weather or linac maintenance.

Patient Monitoring During Treatment:

During radiation therapy, all patients should be seen by a healthcare provider for radiation therapy management visits at least once weekly with standard supportive care measures.

Treatment Interruptions:

Treatment interruptions that are required because of treatment-related adverse events, patient noncompliance or refusal, major intervening illness, or major holidays will not result in protocol violation. See Section 8.1 for additional information concerning treatment interruptions and adverse events.

7.3.9 Quality Assurance Documentation

Digital Submission:

Submission of treatment plans in digital format as DICOM RT is required. Digital data must include CT scans, structures, plan, and dose files. Submission may be by either SFTP or CD. Instructions for data submission are on the IROC Rhode Island Web site at [redacted] Any items on the list below that are not part of the digital submission may be included with the transmission of the digital RT data via sFTP or submitted separately. Digital format is preferred.

Within **one week of the completion of radiotherapy**, the following data for all patients shall be submitted for review:

External Beam Treatment Planning System

1. Digitally reconstructed radiographs (DRR) for each treatment field, showing the collimator and beam aperture. Please include two sets, one with and one without overlays of the target volumes and organs at risk. When using IMRT, orthogonal setup DRR's are sufficient.
2. RT treatment plans including CT, structures, dose, and plan files. These items are included in the digital plan.
3. Dose volume histograms (DVH) for the composite treatment plan for all target volumes and required organs at risk. A DVH shall be submitted for all required organs at risk. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVHs are included in the digital plan.
4. Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

Supportive Data

1. A copy of the patient's radiotherapy record including prescription, and the daily and cumulative doses to all required areas
2. If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by IROC and the radiation oncology reviewers.

Forms

1. QARC RT-1 Dosimetry Summary Form
2. QARC RT-2 Form

These forms may be completed electronically in PDF format at [redacted]

Supportive Data and Forms may be included with the transmission of the digital RT data via sFTP or submitted separately via e-mail to DataSubmission@QARC.org or mailed to:

[redacted]

Questions regarding the completion of the RT-1/IMRT Dosimetry Summary Form and RT-2 data forms, dose calculations or documentation should be directed to:

[redacted]

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

[redacted]

7.3.10 Quality Assurance Reviews

The Radiation Study Co-Chair, Harvey Mamon, MD, PhD, will perform RT Quality Assurance Reviews of completed cases on a regular basis.

Definitions of Protocol Deviations

1. Prescription Dose

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

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

2. **Dose Uniformity**

   Minor Deviation: Less than 95% of the PTV (PTV1 or PTV2) receives at least 95% of its protocol specified dose, or more than 10% of PTV2 receives more than 110% of the protocol dose.

   Major Deviation: Less than 95% of the PTV (PTV1 or PTV2) receives at least 90% of its protocol specified dose, or more than 10% of PTV2 receives more than 120% of the protocol dose.

3. **Volume**

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

   Major Deviation: Transection of tumor or potentially tumor bearing area (CTV).

4. **Treatment Interruptions**

   No Deviation: Treatment interruptions less than 8 treatment days

   Minor Deviation: Treatment interruptions of 8 to 14 treatment days

   Major Deviation: Treatment interruptions exceeding 14 treatment days

7.4 Radiologic Imaging

7.4.1 Imaging Equipment and Technical Specifications

For further information regarding required imaging equipment and technical specifications, please refer to Appendix VIII.

7.4.2 Radiology Review at the Primary Treatment (Accrual) Site

All imaging studies are to be interpreted by radiology staff at the patient's primary treatment site. Imaging staff at the primary treatment site will interpret scan, make determinations about eligibility, clinical staging and treatment response and prepare reports as part of standard practice. **These assessments will be recorded and used to assess response as well as outcomes.**

When results of staging studies do not agree, the study that identifies the most advanced stage disease should be used to make determinations about staging and/or eligibility.

The primary interpretation of all imaging studies will occur at each site, and each site will make the initial determination for each patient as to:

1. Study eligibility
2. Initial MRI study adequacy
3. Baseline TNM status
4. Post-treatment MRI Response categorized as >=20% or <20% (Group 1 only)

Acceptable Images:

In cases where ERUS is the modality selected to evaluate the primary rectal tumor, an accompanying CT for complete pelvic disease staging should also be interpreted by the on site radiologist. The CT images obtained during a PET/CT scan are often suboptimal but will be accepted in lieu of a CT.

Review Images:

Radiologists at the sites will assess the following image attributes in conjunction with treating physicians and record the information on case report forms. The central review will complete a parallel process (not in real-time) but will also evaluate the image quality.

- Did the patient meet baseline eligibility criteria?
- Did the primary rectal tumor decrease in size by an estimated 20% or more after neoadjuvant FOLFOX? (GROUP 1 only)
- Did the patient's restaging studies show evidence of progression in either the primary rectal tumor or target lymph nodes? (GROUP 1 only)
- Did patient restaging studies show new evidence of advanced disease? (GROUP 1 only)

Estimated Radiographic T Stage (Using AJCC 7th Edition Definitions):

This should be estimated as T1, T2, or T3.

T4 tumors are ineligible.

Estimated Radiographic N Stage:

For purposes of achieving consistent interpretation in this protocol:

Node positivity determination: Entry criteria nodes will be measured in short-axis diameter and for the purposes of study entry will be considered positive if 5mm in short axis.

Radiographic N2 status is estimated as: 4 or more nodes that measure 10mm or more in short-axis.

Radiographic N1 status is estimated as: fewer than 4 lymph nodes that measure 10 mm or greater in short axis but 1 or more lymph nodes that measure 5 mm or greater

Presence of Distant Disease:

Nodal stations considered suspicious for metastatic disease (M1) for rectal cancer are: common iliac, external iliac and inguinal nodes.

Distance of the Tumor from the Mesorectal Fascia Reflection:

Patients with tumors with a distance of 1mm or less from the mesorectal fascia reflection have threatened radial margins. These patients are typically not amenable to curative intent sphincter-sparing TME resection and therefore are ineligible. As per exclusion criteria 3.2.3, patient eligibility is based on lack of evidence of tumor that is adherent to the mesorectal fascia and the ability to perform a curative intent sphincter-sparing TME resection at diagnosis. This determination is made by the primary surgeon.

7.4.3 Central Radiology Review (Quality Assurance)

Central Radiology Review is to ensure consistency of study implementation across sites given the complexities of radiologic staging of locally advanced rectal cancer. Central radiology review may share feedback about image interpretation with the primary site. **However, decisions about clinical management based on interpretation of baseline images and decisions about treatment and estimation of clinical response to neoadjuvant FOLFOX (Group 1) are to be made by the primary treating physician(s) at the accruing site.**

Central radiology review (quality assurance) in this trial has four essential purposes:

1. To confirm that registered patients met eligibility criteria;
2. To ensure consistency of baseline clinical staging;
3. To estimate as to whether Group 1 patients achieve a 20% reduction in primary tumor size in response to neoadjuvant FOLFOX;
4. To understand the location and nature of locally recurrent rectal cancer.

Baseline MRI (or CT if MRI is not available; MRI preferred) will be reviewed by the central radiologist in order to confirm that patients met eligibility criteria.

Restaging MRI (or CT if MRI is not available; MRI preferred) performed after induction FOLFOX will be reviewed for patients randomized to Group 1 to estimate response. The imaging review of the post-treatment imaging for Group 1 patients will indicate whether the estimated clinical response to FOLFOX was equal to or greater than a 20% reduction in tumor area (cm2) per MRI criteria.

The Central Radiology review team may communicate to the sites (by email) if evidence of major protocol violations (e.g., presence of metastatic disease) are identified. **Decisions about clinical management based on interpretation of images rest with the accruing site and primary clinical team based on the best clinical interests of the patient.** Final decisions and adjudication of discrepant interpretations rest with the sites and the primary physicians.

Difference between Site Review and Central Review:

The information recorded by central radiology reviewer includes all of the information recorded by the site plus some supplemental information about image quality. Information recorded by central imaging review is also more granular in order to advance the science of imaging.

Image Quality: Because assessment of the quality of images is of critical importance, the quality of each image will be assessed. Quality ratings will include ‘Suboptimal’ (some motion or lower than optimal signal or resolution) or ‘Optimal’ (optimal resolution and signal).

7.4.4 Submitting Images to the Imaging Core Lab for Central Review

Central Radiology Review is for quality assurance purposes and is not done in “real-time.” As such, sites should submit images to the Imaging Core Lab at Ohio State University as soon as feasible. (See Appendix IX for more detailed information.)

Banking of MRI and/or CT images, according to the patient consent permission, is for future research. As protocols are developed, they will be presented for IRB review and approval.

Schedule of Submission of Imaging Scans for Central Radiologic Review

	Submit electronically at [redacted] For help, email [redacted]	
Study Type	**Group 1: FOLFOX**	**Group 2: 5FUCMT**
If the patient receives an MRI and a CT at baseline, submit the **Baseline MRI** to Central Radiology for review	Submit as soon as feasible.	Submit as soon as feasible.
If the patient receives an ERUS and a CT at baseline, submit the **Baseline CT** to Central Radiology for review	Submit as soon as feasible.	Submit as soon as feasible.
If the patient receives an MRI at restaging*, submit the **Restaging MRI** to Central Radiology for review	Submit as soon as feasible.	Scan not required. If scan was performed, submit
If the patient receives an ERUS and a CT at restaging*, submit the **Restaging CT** to Central Radiology for review	Submit as soon as feasible.	Scan not required. If scan was performed, submit
Surveillance Imaging: MRI, CT, PET-CT to identify recurrent disease	Submit as soon as feasible.	Submit as soon as feasible.
*Note: At restaging, use the same imaging modality that was used at baseline for a given patient. ERUS studies do not need to be submitted. NOTE: Central Radiology Review is for quality assurance purposes and is not done in "real-time"; Decisions about clinical management based on interpretation of images rest with the accruing site and primary clinical team based on the best clinical interests of the patient.		

Images should be de-identified and transmitted electronically from each participating site to the Imaging Core Lab at The Ohio State University as soon as feasible. The website for uploading these images is [redacted] If your site does not yet have an account/log-in information, please email [redacted] to request an account/log-in information.

7.4.5 Postoperative Images for Event Monitoring

Pelvic imaging (MRI or CT) for all patients who are identified as having local recurrence should be submitted for central review. This information will facilitate ascertainment of the location of recurrent disease in relation to the radiation field.

7.4.6 Surveillance Images

Study outcomes of local and distal recurrence will often be ascertained based on routine surveillance imaging performed long after all chemotherapy, radiation and surgery have been completed. Studies that identify recurrences should also be submitted for central review. The central radiology reader will categorize whether there is evidence of local recurrence (cancer in the pelvis), distant recurrence, both or neither. The Central Radiology PI interpretation will stand as the final interpretation in cases of disagreement with the site radiologist regarding determination of local and/or distant recurrence.

7.5 Post-operative Therapy

Post-operative therapies outlined here are suggestions and may be modified at the discretion of the treating physician. There are no specific timing rules for initiating post-operative therapy. All post-operative treatments (whether they follow the suggestions outlined here or not) must be reported on the Post-Operative Treatment Form.

Suggested Post-Operative Treatment Regimens:

- If participant is in Group 1 and has margins of surgical resection of R0, the suggested post-op treatment regimen is to administer 6 cycles of FOLFOX chemotherapy.
- If participant is in Group 1 and has margins of surgical resection of R1 or R2, the suggested post-op treatment regimen is to administer 5.5 weeks of 5FUCMT chemoradiation and 4 cycles of FOLFOX chemotherapy (sequence is at the discretion of the treating physician).
- If a participant had received 5FUCMT prior to surgery, then the participant should not receive 5FUCMT after surgery.
- If participant is in Group 2, the suggested post-op treatment regimen is to administer 8 cycles of FOLFOX chemotherapy.

The above post-operative treatment regimens are suggested. If a physician administers a different or modified post-operative treatment regimen, it will not be a protocol violation.

Post-operative treatment is discretionary. Therefore post-operative care may be performed at an institution other than the registering institution (if it is delivered). However, the primary recruiting site remains responsible for completion of all study forms and reporting follow-up and patient outcomes. Participation in shared care models (ex: staggered follow-up at the primary recruiting site and a more convenient site) is acceptable provided that documentation is available. The primary recruiting site remains responsible for reporting of and adherence to all protocol requirements. **Please refer to the Alliance policy and procedures document posted on the Alliance website for the policy on engagement in research by non-registering institutions. If the NCTN Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.**

8.0 SUGGESTED DOSAGE MODIFICATION BASED ON ADVERSE EVENTS

8.1 Radiation Therapy

Treatment interruptions are discouraged; however, they may be necessitated by uncontrolled diarrhea or other acute complications. The reason for and length of any such interruption must be documented. If the sum total of such interruptions exceeds 7 normally scheduled treatment days for reasons other than toxicity, this would be a minor treatment violation. For further information about major and minor protocol deviations, please refer to Section 7.3.

A minimum of 4 daily radiation therapy treatments are required in any given week. Any missed radiation treatments will be made up at the end of the treatment schedule such that the total number of delivered 1.8 Gy fractions remains 28.

If chemotherapy is held, radiation therapy will continue. If radiation is held, chemotherapy is also held. Radiation therapy may be held for grade 4 cellulitis of the perineum or grade 4 neutropenia or other radiation-associated toxicity. Radiation should be restarted subsequent to recovery at the discretion of the radiation oncologist as per standard practice.

System/Organ/Class (SOC)	Adverse Event	Suggested Dosage Change
		Grade 2 – Continue at current dose

Blood and lymphatic system disorders	Thrombocytopenia	Grade 3 – Hold until recovery ≤ grade 1 then resume Grade 4 – Hold until recovery ≤ grade 1 (platelets ≥ 75 x 10^9/L) then resume
	Neutropenia	Grade 3 or 4 - Hold until recovery ≤ grade 1 then resume
	Febrile Neutropenia	Grade 3 or 4 - Hold until resolution of fever and neutropenia ≤ grade 1. Hold until the ANC ≥ 1200 /mm^3 and fever has resolved then resume
Gastrointestinal disorders	Diarrhea	Grades 1 or 2 – Continue at current dose Grade 3 – If grade 3 for > 4 days, hold until recovery ≤ grade 1 then resume Grade 4 - Hold until recovery ≤ grade 1 then resume

8.2 FOLFOX Chemotherapy and 5-FU Combined Modality

Guidelines for dose modifications are suggested recommendations based on standard practice and prior NCI protocols that use these regimens.

Variations in dose modifications strategies **will not be considered major protocol violations.** There are several exceptions to this flexibility for Group 1 neoadjuvant FOLFOX administration; these are described in the following paragraphs.

The dose modification guidelines listed in this section include:

Group 1

Neoadjuvant FOLFOX;

Neoadjuvant 5FUCMT (if it is administered);

Adjuvant 5FUCMT (if it is administered);

Adjuvant FOLFOX (if it is administered)

Group 2

Neoadjuvant 5FUCMT;

Adjuvant FOLFOX (if it is administered)

To facilitate a standardized approach across sites, tables with suggested dose modification criteria are provided. FOLFOX, 5-FU during radiation and capecitabine during radiation are all regimens that have been widely used in treatment of rectal cancer for many years. Investigators should refer to package inserts and local pharmacy practices for complete set of potential toxicities and adhere to best practices. Guidelines are repeated here to foster consistency across trial sites.

Group 1 patients (neoadjuvant and adjuvant FOLFOX) and Group 2 patients (adjuvant FOLFOX):

The following criteria are specific to Group 1 neoadjuvant FOLFOX: These criteria for dose reduction and dose delay for Group 1 neoadjuvant FOLFOX are mandatory and failure to adhere will constitute a protocol violation.

1. **Dose reduction:** If a Group 1 patient requires a dose reduction below level -2 (level -2 is allowed) during cycles 1-5 preoperative therapy, the patient will discontinue FOLFOX and be referred for preoperative 5FUCMT.
2. **Dose delay:** For Group 1 patients, if FOLFOX is held due to toxicity for more than 30 days from day one of the previous cycle, the patient will discontinue FOLFOX and be referred for preoperative 5FUCMT. This does not apply for cycle #6.

The following criteria are applicable to both Groups 1 and 2 and apply to both neoadjuvant and adjuvant therapy: the precise dose modification schema used and the symmetry of dose modification (e.g., reduce both 5FU and oxaliplatin symmetrically, or one preferentially) may be left to the discretion of the treating oncologist. **The modification schema in Table 8.1 is a guideline.**

Leucovorin dose may be decreased in concert with bolus 5-FU dose. If 5-FU is not administered, also do not administer leucovorin.

ALERT: ADR reporting may be required for some adverse events (see Section 10.0).

Table 8.1 Dose Levels of FOLFOX

Dose Level*	5-FU infusion	5-FU bolus	Oxaliplatin
0	1200 mg/m^2/day x 2 days (2400 mg/m^2 over 46-48 hours)	400 mg/m^2	85 mg/m^2
-1	960 mg/m^2/day x 2 days (1920 mg/m^2 over 46-48 hours)	320 mg/m^2	65 mg/m^2
-2	800 mg/m^2/day x 2 days (1600 mg/m^2 over 46-48 hours)	270 mg/m^2	50 mg/m^2
-3**	680 mg/m^2/day x 2 days (1360 mg/m^2 over 46-48 hours)	230 mg/m^2	40 mg/m^2

* Dose level 0 refers to the starting dose.

** If dose reduction below level -2 is required during cycles 1-5 of neoadjuvant therapy for a Group 1 patient, FOLFOX should be discontinued and the patient referred for 5FUCMT. Dose reduction to level -3 is only permitted during cycle 6.

All Group 2 patients and Select Group 1 patients (5FUCMT):

During pelvic radiation therapy, providers should administer either intravenous infusional 5-fluorouracil or alternatively oral capecitabine. If infusional 5-FU is selected, it should be started at a dose of 225 mg/m^2 per day to run continuously during radiation, either 5 or 7 days is acceptable. If capecitabine is selected, the starting dose should be 1650 mg/m^2 per day administered as two doses per day each at 825 mg/m^2. Rounding capcitabine doses that coincide with available tablet sizes is expected and encouraged. An optional capecitabine diary is included in Appendix III to facilitate medication compliance and reporting. Sites may use their own practice specific tracking systems.

Table 8.2 Dose Levels of 5FUCMT

Dose Level[1]	5-FU infusion[2]	Capecitabine[2,3,4]
0	225 mg/m^2/day	825 mg/m^2 bid
-1	175 mg/m^2/day	618.5 mg/m^2 bid
-2	135 mg/m^2/day	412.5 mg/m^2 bid
-3	100 mg/m^2/day	325 mg/m^2 bid

1 Dose level 0 refers to the starting dose.

2 **Note:** There are no dose level restrictions for either infusional 5-FU or capecitabine during 5FUCMT; in other words, the patients will remain active in the study and on schedule irrespective of any dose modifications to 5-FU and capecitabine made by the treating physician.

3 **Rounding to accommodate capecitabine tablet formulation is expected and acceptable**. Sites may use their institutional rounding guidelines if preferred. Tablets are not be split or crushed.

4 For additional information on modifying the dose of capecitabine during 5FUCMT according to BSA, please refer to Appendix IV.

8.3 Suggested FOLFOX Dose Modifications Based on Interval Adverse Events

Dose modifications during FOLFOX are at the discretion of the primary site. Modifications should be reported on study case report forms. Consistent with standard oncology practice, in the event of grade 3 toxicity, treatment should be delayed until recovery/resolution to <Grade 2 toxicity. Suggested dose modification guidelines are presented below for guidance. Adherence to institutional guidelines or standard algorithms included in electronic chemotherapy order entry systems is acceptable. These dose modification guidelines are applicable to Group 1 and Group 2 adjuvant and Group 1 neoadjuvant FOLFOX administration.

1. Patients should be assessed every 2 weeks for toxicity during FOLFOX.
2. Erythropoietin stimulating agents should not be administered at any point during this protocol.
3. Use of G-CSF (Neulasta or Neupogen) is at the discretion of clinicians but is not usually necessary. Pegylated GCSF (Neulasta) may be given on day of disconnection from 5FU infusion to FOLFOX patients who have previously experienced dose delays secondary to neutropenia as an alternative to dose reduction.

Table 8.3 Suggested FOLFOX Dose Modifications Based on Interval Adverse Events

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* is used unless otherwise specified			
SYSTEM/ORGAN/CLASS (SOC)	**ADVERSE EVENT**	**AGENT**	**DOSAGE CHANGE**
BASED ON INTERVAL ADVERSE EVENT (Occurring before Day 1 of Cycle)			
Blood and lymphatic Systemic disorders	Neutropenia ANC < 1200 **and/or** Thrombocytopenia Grade ≥ 2	5-FU Oxaliplatin	Hold up to 16 days until ANC ≥ 1200. If recovered in ≤ 16 days, resume at next lower dose level or resume at same dose level and administer pegylated GCSF 6 mg subcutaneously on day of 5FU disconnection. Hold up to 16 days until platelets ≥ 75,000. If recovered in ≤ 16 days, resume at next lower dose level.
Other Non-hematologic	Grade ≥ 2 (excluding alopecia)	5-FU Oxaliplatin	Hold treatment until ≤ grade 1 then resume at next lower dose level.

*Located at h[redacted]

The following describe actions in the Dosage Change column:

- Omit = Treatment is not given for this cycle
- Hold = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

8.4 Suggested 5FUCMT Dose Modifications (with either IV 5-FU or capecitabine)

Dose modifications during 5FUCMT are presented here for guidance and to foster consistency in protocol implementation across study sites. Several points are important to emphasize:

1. Patients should be assessed weekly for toxicity during 5FUCMT.
2. There is no limit on dose reductions; in other words, the patients will remain active in the study and on schedule irrespective of any dose modifications made by the treating physician.
3. Erythropoietin stimulating agents should not be administered at any point during 5FUCMT.
4. Use of G-CSF (Neulasta or Neupogen) is permitted at the discretion of the treating physician.
5. If toxicity has not improved to ≤ grade 1 within 16 days of last treatment with 5FU/capecitabine, radiation should be completed without 5FU/capecitabine chemosensitization.
6. For criteria for holding radiation therapy, please see Section 8.1.

Table 8.4 5FUCMT Dose Modifications Based on Interval Adverse Events

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* is used unless otherwise specified			
SYSTEM/ORGAN/ CLASS (SOC)	**ADVERSE EVENT**	**AGENT**	**DOSAGE CHANGE**
BASED ON INTERVAL ADVERSE EVENT (Occurring before Day 1 of Each Week of the 5.5 Weeks of Radiation Treatment)			
Blood and lymphatic Systemic disorders	Neutropenia grade ≥ 2 **and/or** Thrombocytopenia Grade ≥ 2	5-FU Capecitabine	Hold up to 16 days until ANC ≥ 1200. If recovered in ≤ 16 days, resume at next lower dose level. Note: there is no limit on dose reductions. If not recovered in 16 days (corresponding to 16 days from previous 5FU/capecitabine), complete radiation without 5FU/capecitabine sensitization. Hold up to 16 days until platelets ≥ 75,000. If recovered in ≤ 16 days, resume at next lower dose level. Note: there is no limit on dose reductions. If not recovered in 16 days (corresponding to 16 days from previous 5FU/capecitabine), discontinue 5FU/capecitabine and complete radiation without 5FU/capecitabine sensitization.
Other Non-hematologic	Grade ≥ 2 (excluding alopecia)	5-FU Capecitabine	Hold treatment until ≤ grade 1 then resume at next lower dose level. Note: there is no limit on dose reductions. If not recovered in 16 days (corresponding to 16 days from previous 5FU/capecitabine), discontinue 5FU/capecitabine and complete radiation without 5FU/capecitabine sensitization.

*Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

The following describe actions in the Dosage Change column:

- Omit = Treatment is not given for this cycle
- Hold = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

Table 8.5 FOLFOX Dose Modifications Based on Toxicities that Occur on Days 2-14 During Previous Cycle

Dose modifications during FOLFOX are presented here for guidance and to foster consistency in protocol implementation across study sites. Several points are important to emphasize:

1. Patients should be assessed every 2 weeks for toxicity during FOLFOX
2. Dose reductions are limited and must not be lower than dose level -2 during cycles 1-5.

a. Dose level-2 corresponds to an oxaliplatin dose <50mg/m^2 and an infusional 5FU dose<800 mg/m^2/day x 2 days (i.e., 1600 mg/m2 over 46-48 hours)

b. Dose reductions below level-2 including withholding either 5FU or oxaliplatin during cycle 6 are permissible.

c. If a patient requires a FOLFOX reduction that is lower than level -2 for cycles 1 through 5, then discontinue FOLFOX and refer the patient for 5FUCMT.

3. If a patient has not recovered within 28 days of treatment during cycles 1 through 5, reassign patient to 5FUCMT instead.
4. If a patient has not recovered within 28 days of treatment during cycle 6, refer for restaging.
5. Erythropoietin stimulating agents should not be administered.
6. Use of G-CSF (Neulasta or Neupogen) is discouraged.

Table 8.5 FOLFOX Dose Modifications Based on Toxicities that Occur on Days 2-14 During Previous Cycle

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* is used unless otherwise specified			
SYSTEM/ORGAN/CLASS (SOC)	**ADVERSE EVENT**	**AGENT**	**DOSAGE CHANGE**
AT TIME OF RETREATMENT (occurring at Days 1-14 during cycle)			
Gastrointestinal disorders	Nausea grade 2	Oxaliplatin	Intensify antiemetic therapy and proceed with FOLFOX at current dose level. Maximal antiemetic therapy includes a 5HT inhibitor (i.e., granisteron, odansetron, palonestron) as well as compazine, lorazepam, aprepitant, and decadron
	Nausea grade 3		If resolved to < grade 2 on day of treatment, may proceed with intensification of antiemetic therapy and current dose level of FOLFOX. If not resolved to < grade 2 on day of therapy, intensify antiemetic regimen and proceed with FOLFOX when resolved to < grade 2. May decrease oxaliplatin one dose level if not responsive to maximal antiemetic support.
	Nausea grade 4		If resolved to < grade 2 on day of treatment, may proceed with intensification of antiemetic therapy and current dose level of FOLFOX. If not resolved to < grade 2 on day of therapy, intensify antiemetic regimen and proceed with FOLFOX when resolved to < grade 2. Decrease oxaliplatin one dose level if not responsive to maximal antiemetic support.
		5-FU	

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 is used unless otherwise specified*			
SYSTEM/ORGAN/CLASS (SOC)	**ADVERSE EVENT**	**AGENT**	**DOSAGE CHANGE**
AT TIME OF RETREATMENT (occurring at Days 1-14 during cycle)			
	Vomiting grade 2	Oxaliplatin	Intensify antiemetic therapy and proceed with FOLFOX at current dose level. Maximal antiemetic therapy includes a 5HT inhibitor (i.e., granisteron, odansetron, palonestron) as well as compazine, lorazepam, aprepitant, and decadron.
	Vomiting grade 3	5-FU Oxaliplatin	If resolved to < grade 2 on day of treatment, may proceed with intensification of antiemetic therapy and current dose level of FOLFOX. If not resolved to < grade 2 on day of therapy, intensify antiemetic regime and proceed with FOLFOX when resolved to < grade 2. May decrease oxaliplatin one dose level if not responsive to maximal antiemetic support.
	Vomiting grade 4		If resolved to < grade 2 on day of treatment, may proceed with intensification of antiemetic therapy and current dose level of FOLFOX. If not resolved to < grade 2 on day of therapy, intensify antiemetic regimen and proceed with FOLFOX when resolved to < grade 2. Decrease oxaliplatin one dose level if not responsive to maximal antiemetic support.
	Diarrhea grade 2		If resolved to < grade 2, intensify antidiarrheal therapy and proceed with FOLFOX at current dose level. If not resolved to < grade 2, HOLD FOLFOX, intensify antidiarrheal therapy and proceed with FOLFOX when resolved to < grade 2.
	Diarrhea grade 3		If resolved to < grade 2, intensify antidiarrheal therapy and proceed with FOLFOX, decreasing 5FU and oxaliplatin one dose level. If not resolved to < grade 2, HOLD FOLFOX, intensify antidiarrheal therapy and proceed with FOLFOX decreasing 5FU and oxaliplatin one dose level when resolved to < grade 2
	Diarrhea grade 4		If resolved to < grade 2, intensify antidiarrheal therapy and proceed with FOLFOX, decreasing 5FU and oxaliplatin one dose level. If not resolved to < grade 2, HOLD FOLFOX, intensify antidiarrheal therapy and proceed with FOLFOX decreasing 5FU and oxaliplatin one dose level

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 is used unless otherwise specified*			
SYSTEM/ORGAN/CLASS (SOC)	**ADVERSE EVENT**	**AGENT**	**DOSAGE CHANGE**
AT TIME OF RETREATMENT (occurring at Days 1-14 during cycle)			
			when resolved to < grade 2 Hold FOLFOX until mucositis improves to < grade 2 then resume with one dose level reduction of 5-FU and the previous dose level of oxaliplatin
	Oral mucositis, Esophagitis, gastritis, pharyngeal mucositis, small intestinal mucositis, colitis, rectal and/or anal mucositis grade 3 Oral mucositis, Esophagitis, gastritis, pharyngeal mucositis, small intestinal mucositis, colitis, rectal and/or anal mucositis grade 4		Hold FOLFOX until mucositis improves to < grade 2 then resume with two dose level reduction of 5-FU and the previous dose level of oxaliplatin
Blood and lymphatic system disorders	Neutropenia ANC 1000-1199 Neutropenia ANC < 1000 Febrile neutropenia ANC <1000 and temp ≥ 38.5° C	5-FU Oxaliplatin	Hold FOLFOX until ANC ≥ 1200 then resume at previous dose levels. Hold FOLFOX until ANC ≥ 1200 then resume with one dose level reduction of both 5-FU and oxaliplatin for all subsequent cycles or at same dose level with pegylated GCSF given at a dose of 6 mg/kg on day of 5FU disconnection. Hold FOLFOX until fever has resolved and ANC ≥ 1200 then resume with one dose level reduction of both 5-FU and oxaliplatin for all subsequent cycles or at same dose level with pegylated GCSF given at a dose of 6 mg/kg on day of 5FU disconnection. Hold FOLFOX until platelets ≥ 75,000 then

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 is used unless otherwise specified*			
SYSTEM/ORGAN/CLASS (SOC)	**ADVERSE EVENT**	**AGENT**	**DOSAGE CHANGE**
AT TIME OF RETREATMENT (occurring at Days 1-14 during cycle)			
	Thrombocytopenia Platelets 50,000 – 74,999 Thrombocytopenia Platelets < 50,000		resume at previous dose levels. Hold FOLFOX until platelets ≥ 75,000 then resume FOLFOX with one dose level reduction of both 5-FU and oxaliplatin for all subsequent cycles.
ENT	Pharyngolaryngeal dysesthesia	Oxaliplatin	Increase the duration of oxaliplatin infusion to six hours for all subsequent cycles.
Pulmonary disorders	Cough, dyspnea, hypoxia, pneumonitis or pulmonary infiltrates, grade ≥ 3.	5-FU Oxaliplatin	Hold oxaliplatin until interstitial lung disease is ruled out. Continue 5-FU/leucovorin. Discontinue study if interstitial lung disease is confirmed.
Thrombotic microangiopathy	Hemolytic uremic syndrome (HUS) ≥ grade 3	5-FU Oxaliplatin	Discontinue oxaliplatin. Continue 5-FU/leucovorin.
Immune system disorders	Allergic reaction grade 1 Allergic reaction grade 2 Allergic reaction grade 3 or 4	Oxaliplatin Leucovorin	Decrease infusion rate by 50% until symptoms resolve, then resume at initial planned rate. Stop FOLFOX infusion. Administer H_1 and/or H_2 blockers and/or steroids according to local medical site policy. Restart infusion when symptoms resolve and pretreat before all subsequent doses. Treat according to local medical site policy. Stop the infusion. Discontinue FOLFOX. Treat according to local medical site policy.
Skin and subcutaneous tissue disorders	Extravasation	Oxaliplatin	Extravasation of oxaliplatin has been associated with necrosis. If extravasation is suspected, stop the FOLFOX infusion and restart at another site. Treat according to local medical site policy.

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 is used unless otherwise specified*			
SYSTEM/ORGAN/CLASS (SOC)	**ADVERSE EVENT**	**AGENT**	**DOSAGE CHANGE**
AT TIME OF RETREATMENT (occurring at Days 1-14 during cycle)			
Other Non-hematologic	Grade 3 or Grade 4	5-FU Oxaliplatin Leucovorin	Hold FOLFOX until toxicity ≤ grade 1 then resume with one dose level reduction of both 5-FU and oxaliplatin
Neurological	Neurotoxicity grade 2 persisting between treatment cycles Neurotoxicity grade 3 resolving to ≤ grade 2 between treatment cycles Neurotoxicity grade 3 persisting between treatment cycles Neurotoxicity grade 4	Oxaliplatin	Continue FOLFOX with previous dose level of 5-FU and one dose level reduction of oxaliplatin for all subsequent cycles. Continue FOLFOX with previous dose level of 5-FU and one dose level reduction of oxaliplatin for all subsequent cycles. Discontinue oxaliplatin. Continue 5-FU/leucovorin. Reassign to 5FUCMT if has not completed at least 5 cycles of FOLFOX. Discontinue oxaliplatin. Continue 5FU/leucovorin. Reassign to 5FUCMT if has not completed at least 5 cycles of FOLFOX.
Cardiovascular	Cardiac ischemia or infarction grade 3 or 4 Cerebrovascular ischemia grade 3 or 4		Discontinue all study therapy. Discontinue all study therapy.

*****Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

The following describe actions in the Dosage Change column:

- Omit = Treatment is not given for this cycle
- Hold = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

8.5 Oxaliplatin-induced Pharyngolaryngeal Dysesthesia

If a patient develops oxaliplatin-induced pharyngolaryngeal dysesthesia, evaluate the oxygen saturation with a pulse oximeter; if normal, an anxiolytic agent may be given and the patient observed in clinic until the episode has resolved. Increase the duration of infusion of oxaliplatin to six hours for all subsequent treatment cycles.

Pharyngolaryngeal dysesthesia may appear similar to a hypersensitivity reaction.

The table below compares the two.

Table 8.6 Comparison of the symptoms and treatment of pharyngolaryngeal dysesthesias and platinum hypersensitivity

Clinical Symptoms	Pharyngolaryngeal dysesthesias	Platinum hypersensitivity
Dyspnea	Present	present
Bronchospasm	Absent	present
Laryngospasm	Absent	present
Anxiety	Present	present
O_2 saturation	Normal	decreased
Difficulty swallowing	present (loss of sensation)	absent
Pruritis	Absent	present
Urticaria/rash	Absent	present
Cold-induced symptoms	Yes	no
Blood pressure	normal or increased	normal or decreased
Potential treatments	Anxiolytics, observation in a controlled clinical setting until symptoms abate or at the physician's discretion	Oxygen, steroids, epinephrine, bronchodilators; fluids and vasopressors, if appropriate

8.6 Dose Modifications Based on Body Weight

All dosing is to be determined solely by actual weight. 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.

The actual weight on the day of registration or the first day of treatment may be used for cycle 1 unless the change in the weight results in a change in calculated dose ≥10%, in which case the weight on the day of treatment should be used. Over the course of treatment it is not required to change the doses of 5-FU, leucovorin or oxaliplatin due to changes in weight unless the calculated dose changes by ≥10%.

Table 8.7 5FUCMT Dose Modifications Based on Retreatment

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* is used unless otherwise specified			
SYSTEM/ORGAN/CLASS (SOC)	**ADVERSE EVENT**	**AGENT**	**DOSAGE CHANGE**
AT TIME OF RETREATMENT (Occurring on Day 1-5 of Each Week of the 5.5 Weeks of Radiation Treatment)			
Gastrointestinal disorders	Nausea grade 3	5-FU Capecitabine	Hold 5-FU or capecitabine until nausea improves to ≤ grade 1 then resume 5-FU or capecitabine with one dose level reduction.
	Vomiting grade 3	5-FU Capecitabine	Hold 5-FU or capecitabine until vomiting improves to ≤ grade 1 then resume 5-FU or capecitabine at the previous dose level.
	Vomiting grade 4		Hold 5-FU or capecitabine until vomiting improves to ≤ grade 1 then resume 5-FU or capecitabine with one dose level reduction.
	Diarrhea grade 3	5-FU Capecitabine	Hold 5-FU or capecitabine until diarrhea improves to ≤ grade 2 then resume 5-FU or capecitabine with one dose level reduction.
	Diarrhea grade 4		Hold 5-FU or capecitabine until diarrhea improves to ≤ grade 1 then resume 5-FU or capecitabine with two dose level reductions.
	Oral mucositis grade 3	5-FU Capecitabine	Hold 5-FU or capecitabine until mucositis improves to ≤ grade 1. Omit 5-FU or capecitabine for remainder of cycle. Resume 5-FU or capecitabine with one dose level reduction for next cycle.
	Oral mucositis grade 4		Hold 5-FU or capecitabine until mucositis improves to ≤ grade 1. Omit 5-FU or capecitabine for remainder of cycle. Resume 5-FU or capecitabine with two dose level reductions for next cycle.
Gastrointestinal disorders	Esophagitis, gastritis, pharyngeal mucositis, small intestinal	5-FU Capecitabine	Hold 5-FU or capecitabine until mucositis improves to ≤ grade 1. Omit 5-FU or capecitabine for remainder of cycle. Resume 5-FU or capecitabine with one dose level reduction for next cycle.
	mucositis, colitis, rectal and/or anal		Hold 5-FU or capecitabine until mucositis improves to ≤ grade 1. Omit 5-FU or capecitabine for remainder of cycle. Resume 5-

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 is used unless otherwise specified*			
SYSTEM/ORGAN/CLASS (SOC)	**ADVERSE EVENT**	**AGENT**	**DOSAGE CHANGE**
AT TIME OF RETREATMENT (Occurring on Day 1-5 of Each Week of the 5.5 Weeks of Radiation Treatment)			
	mucositis grade 3 Esophagitis, gastritis, pharyngeal mucositis, small intestinal mucositis, colitis, rectal and/or anal mucositis grade 4		FU or capecitabine with two dose level reductions for next cycle.
Skin and subcutaneous tissue disorders	Palmer-plantar erythrodysesthesia syndrome grade 3	5-FU Capecitabine	Hold 5-FU or capecitabine for remainder of cycle. Decrease 5-FU or capecitabine by one dose level for the next cycle
Other non-hematologic	Grade 3 Grade 4	5-FU Capecitabine	Hold 5-FU or capecitabine until toxicity ≤ grade 1 then resume 5-FU or capecitabine with one dose level reduction. Discontinue 5-FU or capecitabine for remainder of cycle. Restart next cycle with one dose level reduction of 5-FU or capecitabine.

9.0 ANCILLARY TREATMENT/SUPPORTIVE CARE

9.1 Supportive Care

Patients should receive routine supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions.

9.2 Antiemetics

Antiemetics may be used at the discretion of the attending physician.

9.3 Blood Products

Blood products are permissible. The use of erythropoietin is strongly discouraged in the adjuvant setting and is not permitted in this trial.

9.4 Neulasta and Neupogen

Neulasta and Neupogen should not be started as part of initial therapy and are not usually necessary with neoadjuvant FOLFOX or chemoradiation, but may be used to support maintenance of dose delivery and schedule according to physician discretion. ASCO guidelines for the use of growth factors are described in "2006 Update of Recommendations for the Use of

White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guidelines" *J Clin Oncol* 24(19): 3187-3205, 2006.

9.5 Diarrhea

Diarrhea should be managed with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

Use of alternative agents such as Lomotil and tincture of opium is permissible.

10.0 ADVERSE EVENT (AE) REPORTING AND MONITORING

For SAKK sites, please refer to the Swiss Specific Appendix for information regarding safety reporting and SAEs.

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. However, CTCAE version 5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website: [redacted]

10.1.1 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the adverse event must be reported as an expedited report (see Section 10.4). Important: Expedited adverse event reporting requires submission of a CTEP Adverse Event Reporting System (CTEP-AERS) report(s) using CTCAE v5.0. Expedited reports are to be completed within the timeframes and via the mechanisms specified in Section 10.4 and 10.5. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Section 10.4 and Section 17.0).

10.1.2 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to **severity** for the purposes of regulatory reporting to NCI.

Note: A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected

The determination of whether an AE is expected is based on the agent-specific information provided in Section 15.0 of this protocol.

Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of this protocol.

Note: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.2.1 Comprehensive Adverse Events and Potential Risks (CAEPR) List

Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert (for those investigational agents that are available commercially) as well as company safety reports, AEs submitted through CTEP-AERS, and peer-reviewed publications that contain safety information not contained in the current IB or Package Insert. The safety profile for an investigational agent is reviewed at least annually in accordance with current Good Clinical Practice (cGCP) guidelines. It may be amended more frequently in response to an emerging safety profile for the agent/intervention, e.g., in conjunction with an Action Letter.

- Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR (see Section 15.1.7).

10.2.2 Studies Requiring the Inclusion of a CAEPR:

NCI requires the inclusion of a CAEPR in studies described below. Other studies can utilize the NCI CAEPR as well.

- For all studies conducted under a NCI IND.
- For all studies reviewed by CTEP/CIP that includes agents/interventions for which NCI has a CAEPR.

10.2.3 As the CAEPR is updated the SPEER is also revised and the revisions will be sent to all Principal Investigators registered to NCI-approved studies using the agent(s). A copy of the current CAEPR (containing the SPEER) may also be obtained via email from [redacted]

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event is *likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event is *doubtfully related* to the agent(s).
Unrelated - The adverse event is *clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.3.1 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormalities or birth defects, must be reported immediately if they occur at any time following treatment with an agent since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.3.2 Death

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention requires expedited reporting within 24-hours.

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.3.3 Secondary Malignancy

A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g. treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent be reported via CTEP-AERS. Three options are available to describe the event:

Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
Myelodysplastic syndrome (MDS)
Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.3.4 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS.

10.3.5 Pregnancy

Pregnancy occurring in a female patient should be reported via CTEP-AERS, using the even term and severity grade "pregnancy, puerperium and perinatal conditions – other, pregnancy (grade 3).

- Pregnancy should be followed until the outcome is known
- CTEP-AERS reports should be amended upon completion of the pregnancy to report pregnancy outcome (e.g., normal, spontaneous abortion, therapeutic abortion, fetal death, congenital abnormalities).

Pregnancy loss

- Pregnancy loss is defined in CTCAE as "Death in utero."
- Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.
- A Pregnancy loss should not be reported as a Grade 5 event under the Pregnancy, puerperium, and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.
- A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

10.4 Expedited Reporting Requirements

Expedited Reporting Requirements for Studies using Commercial Agent(s) ONLY:

Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour;
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

NOTE: Deaths clearly due to progressive disease should **NOT** be reported via CTEP-AERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).

Refer to Section 10.4.2 for NCI Contact Information or Technical Help regarding CTEP-AERS reporting.

In the rare event when internet connectivity is disrupted, a 24 hour notification must be made to NCI by telephone. An electronic report must be submitted immediately upon establishment of internet re-connection.

Please see Section 10.2 for more details regarding reporting of adverse events.

Please refer to Section 15.1.7 for the CAEPR and protocol specific exceptions to expedited reporting of serious adverse events.

10.4.1 Additional Instructions or Exclusions to CTEP-AERS Reporting

- All adverse events reported via AERS (i.e. serious adverse events) should also be forwarded to your local IRB, according to local IRB policies.
- Grade 1-3 nausea or vomiting and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 nausea or vomiting does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 diarrhea and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting
- Grade 3 diarrhea does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 mucositis and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting
- Grade 3 mucositis does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 hand foot syndrome and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting
- Grade 3 hand foot syndrome does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 dehydration and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting
- Grade 3 dehydration does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 fatigue and hospitalization resulting from such do not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 fatigue does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 hematosuppression (leukopenia, neutropenia, lymphopenia, anemia, and thrombocytopenia) with hospitalization resulting from such do not require AERs reporting, but should be reported via routine AE reporting

- Grade 3 hematosuppression (leukopenia, neutropenia, lymphopenia, anemia, and thrombocytopenia) does not require AERs reporting, but should be reported via routine AE reporting

10.4.2 Contact Information for NCI Safety Reporting

Website for submitting expedited reports	[redacted]
CTEP-AERS-MD Help Phone (for CTEP)*	[redacted] Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)
Cancer Imaging Program (CIP) Help Phone for SAE reporting*	[redacted] Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)
Fax for expedited report supporting Medical Documentation for CTEP trials	[redacted]
Fax for expedited report supporting Medical Documentation for CIP trials	[redacted]
CTEP-AERS-MD Help Email	[redacted]
CIP SAE Reporting Email	[redacted]
Technical (e.g., IT or computer issues ONLY) Help Phone*	[redacted]
CTEP-AERS Technical Help Email	[redacted]
CTCAE v4 Help/Questions Email	[redacted]
CTEP-AERS FAQs link	[redacted]
CTEP-AERS Computer Based Training link	[redacted]

*Office phone and fax are accessible 24 hrs per day 7 days a week. The CTEP-AERS -MD phone line is staffed from Monday through Friday, 7:00 AM to 7:00 PM ET. Any phone call after these hours will go to voicemail. Please leave contact information and the phone call will be returned the following business day.

10.5 Other Required Expedited Reporting

EVENT TYPE	REPORTING PROCEDURE
Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	Complete an electronic-CRF Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form (via RAVE) within 5 working days of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form. If a CTEP-AERS report has been submitted, this form does not need to be submitted.

10.5.1 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to evaluate at baseline per CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Gastrointestinal disorders	Dysphagia	x	x
	Diarrhea	x	x
	Constipation	x	x
	Nausea	x	x
	Vomiting	x	x
	Mucositis oral	x	x
Respiratory, thoracic and mediastinal disorders	Dyspnea	x	x
Nervous system disorders	Peripheral sensory neuropathy	x	x
General disorders and administration site conditions	Pain	x	x
	Fatigue	x	x
Metabolism and nutrition disorders	Anorexia	x	x
Psychiatric disorders	Anxiety	x	x
	Depression	x	x

10.5.2 Submit via electronic Case Report Forms the following AEs experienced by a patient and not specified in Section 10.5.1:

10.5.2.1 Grade 4 AEs regardless of attribution to the study treatment or procedure.

10.5.2.2 Grade 5 AEs (Deaths)

10.5.2.2.1 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5.2.2.2 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.5.3 Refer to the instructions in the Case Report Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 TREATMENT EVALUATION

Guidance for Evaluation after Neoadjuvant Treatment

Group 2 patients (5FUCMT) are not required to undergo repeat tumor imaging or proctoscopy after chemoradiation. Reevaluation prior to surgery is at the discretion of the primary treating clinicians.

Group 1 patients (FOLFOX)

- Are required to undergo repeat tumor imaging after 6 cycles of FOLFOX. Repeat imaging should include the same modality that was used at baseline.
    - If a baseline MRI was performed, a post-FOLFOXx6 MRI should be repeated.
    - If a baseline ERUS was performed, a post-FOLFOXx6 ERUS should be repeated.
- Are required to undergo repeat clinical assessment of the primary tumor by proctoscopy
- The decision as to whether Group 1 patients proceed directly to TME or alternatively, receive 5FUCMT and only then undergo TME, will be made on the basis of both tumor imaging and clinical tumor response based on proctoscopy. **This is a clinical estimation as to whether there has been at least a 20% decrease in the tumor in response to neoadjuvant FOLFOX treatment. In the event of clinical disagreement, the surgeon who will perform the TME decides if there has been an estimated 20% clinical response.**

  Group 1 patients who do receive 5FUCMT are not required to undergo repeat tumor imaging after chemoradiation.

  Note: Proctoscopic assessment of whether there has been a 20% response is based on the performing clinician's estimation. This information should be combined with careful radiologic review of the baseline and post neoadjuvant FOLFOX images in order to estimate whether there has been a 20% clinical response. These assessments are clinical estimations due to the challenges inherent in clinical rectal cancer staging.

11.1 Radiological Tumor Evaluation

11.1.1 Timing of Restaging Evaluations: Group 1 Patients

Patients should be reevaluated within 4 weeks after completion of six cycles of pre-operative FOLFOX.

11.1.2 Definitions of Measurable and Non-Measurable Disease

11.1.2.1 Measurable Disease (RECIST adaptation)

Metastatic disease focus is considered measurable if its longest diameter can be accurately measured as 2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT or MRI. This criteria will be used to identify distant recurrence.

11.1.2.2 A lymph node is considered measurable for purpose of estimating clinical nodal status if its short axis is ≥ 5.0 mm when assessed by CT scan or pelvic MRI. For this study, internal target iliac lymph nodes must measure ≥ 10 mm.

11.1.2.3 A malignant lymph node is considered measurable for purposes of ascertaining metastatic recurrence if its short axis is ≥ 1.5cm when assessed by CT scan or pelvic MRI

11.1.2.4 Non-Measurable Disease (Standard definition per RECIST)

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥ 1.0 to < 1.5 cm). This includes: Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis < 1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.1.3 Guidelines for Evaluation of Measurable Disease

11.1.3.1 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up.

11.1.3.2 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- Evaluation of the primary rectal tumor by pelvic MRI is preferred. However, for patients who are not able to undergo a pelvic MRI or for clinicians who prefer it, an ERUS is acceptable. If ERUS is performed as an alternative to pelvic MRI at baseline, then an ERUS must also be performed at the time of restaging.
- In cases where ERUS is the modality selected to evaluate the primary rectal tumor, an accompanying CT for complete pelvic disease staging will also be interpreted by the on-site radiologist. A standard CT of the chest, abdomen and pelvis is required. For CT scans of the chest, contrast is preferred but not required. For CT scans of the abdomen and pelvis, contrast is required. In the event that radiologic studies yield inconsistent interpretation of T stage or N stage the modality that assigns the highest T stage or the highest N stage should be used for purposes of protocol eligibility.

11.1.3.3 Measurement at Follow-up Evaluation:

- Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

11.1.4 Measurement of Effect – Imaging Tumor Response to Neoadjuvant FOLFOX (Group 1 only)

Note: "Adapted RECIST" (as defined in this protocol) is used and consists of the following:

11.1.4.1 Target Lesions & Target Lymph Nodes:

- The Rectal Primary tumor is the primary target lesion. In addition, associated pelvic lymph nodes should be recorded and measured at baseline.
- In order for the patient to proceed directly to TME, there should be NO evidence of progression and there should be evidence of clinical response that is estimated as ≥20%.
- The primary rectal lesion is measured and followed as a bi-dimensional product to avoid measurements that include the GI tract lumen whether collapsed or filled with air, feces or contrast material which does not represent tumor tissue. The Bi-Dimensional Product (BDP) is the product of the longest diameter for the rectal primary tumor and the thickest wall. The BDP will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- Post-Baseline Bi-Dimensional Product (PBDP): The product of the longest diameter of the rectal primary tumor multiplied by the thickest wall will be calculated and reported as the post-bi-dimensional product (PBDP). If the radiologist is able to provide an actual measure for the target even if it is below 0.5 cm. If the target is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the rectal primary has likely disappeared, the measurement should be recorded as 0 cm.
- Given increased error in measuring smaller structures, and given differing qualities of MRI and their resolution, diminutive nodes are those measuring 0-4mm. These will not be considered evaluable for change. Evaluable nodes are those 5mm or greater in the mesorectal and superior hemorrhoidal location.
- To be labeled as a target lymph node: up to 4 nodes in the mesorectal, superior hemorrhoidal and internal iliac regions may be considered "target" lymph nodes. Mesorectal and superior hemorrhoidal regions must measure 5 mm or greater in the short axis. Internal iliac lymph nodes must measure 10 mm or greater in short axis.
- To categorize the primary tumor as consistent with clinical stage N2 disease, ≥4 lymph nodes must measure >10mm in short axis.

11.1.4.2 Imaging Response Criteria:

11.1.4.2.1 For purpose of restaging, a target lymph node must measure 5 mm or more in short axis.

- Target lymph nodes, which at baseline measure between 5 and 10mm short axis inclusive, must increase 3mm in size to be considered PD. Nodes between 11 and 20 mm short axis inclusive must increase in size 4mm to be considered PD. Nodes 20mm and greater in short axis must increase in size by 25%, (e.g., 20mm to 25mm, or 25mm to 31mm) to be considered PD.
- An internal target iliac lymph node ("obturator," etc.), must be greater than or equal to 10 mm in short axis diameter to be considered evaluable and will

follow the same rules as above for absolute increase in size.

11.1.4.2.3 Evaluation of the Rectal Primary and Target Lymph Nodes

1. Complete Response (CR):	All of the following must be true: a. Disappearance of the rectal primary. b. Each target lymph node must have decreased short axis to <5mm. c. No new sites of disease.
2. Partial Response (PR):	At least a 20% decrease in PBDP (bi-dimensional product of primary rectal lesion) No new sites of disease. No PD of any target lymph nodes
3. Stable disease (SD):	Defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
4. Progression (PD):	At least one of the following must be true: a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.5 cm short axis) and increased to ≥ 1.5 cm short axis during follow-up. b. At least a 20% increase in PBDP (bi-dimensional product of rectal primary lesion) taking as reference the BDP.

11.1.4.3 Overall Radiologic Tumor Response Status after Neoadjuvant FOLFOX

The radiologic tumor response status after neoadjuvant FOLFOX for Group 1 patients is determined by combining the patient's status on primary rectal tumor, target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease:

Primary Rectal Tumor & Target Lymph Nodes	**New Sites of Disease**	**Overall Radiologic Tumor Response Status**
CR	No	CR
PR	No	PR
SD	No	SD
Not all Evaluated	No	Not Evaluated (NE)
PD	Yes or No	PD

11.2 Clinical Tumor Evaluation

11.2.1 Schedule and Record Information for Proctoscopy and Rectal Examination

Proctoscopy Assessment	Group 1	Group 2	Record Group 1 Information	Record Group 2 Information
Baseline-pretreatment	Prior to first dose of FOLFOX	Prior to first dose of pelvic radiation	On Study Form	On Study Form
Reevaluation after initial neoadjuvant treatment	≤ 28 days after completion of FOLFOX (in other words, ≤ 28 days after cycle 6 day 14 of FOLFOX)	Not required. Performed at clinician's discretion	Reevaluation After Pre-Operative FOLFOX (Group 1 Only) **Form for Group 1:** AFTER FOLFOX, BEFORE 5FUCMT-Surgery	N/A
15 months from randomization	+/- 1 month	+/- 1 month	Disease Status Follow-up Form	Disease Status Follow-up Form
Annually (Every 12 months +/- 1 month) starting with 15 month reassessment	Continue until whichever comes first: any recurrent disease or 5 years from randomization	Continue until whichever comes first: any recurrent disease or 5 years from randomization	Disease Status Follow-up Form	Disease Status Follow-up Form

Rectal Examination	Group 1	Group 2	Record Group 1 Information	Record Group 2 Information
Baseline-pretreatment	Prior to first dose of FOLFOX	Prior to first dose of pelvic radiation	On Study Form	On Study Form
Reevaluation after initial neoadjuvant treatment	≤ 28 days after completion of FOLFOX (in other words, ≤ 28 days after cycle 6 day 14 of FOLFOX)	Not required. Performed at clinician's discretion	Reevaluation After Pre-Operative FOLFOX (group 1 Only) **Form for Group 1:** AFTER FOLFOX, BEFORE 5FUCMT-Surgery	N/A

11.2.2 Guidelines for Evaluation of Clinically Evaluable Disease

11.2.2.1 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment must be used to characterize each identified and reported lesion at baseline and at the follow up evaluation.
- Proctoscopy with direct visualization is the accepted clinical evaluation.
- Virtual colonoscopic assessments are not acceptable.

11.2.3 Definition of Clinically Evaluable Disease

To be clinically evaluable, a tumor must be directly visualized at proctoscopy and estimated to have a Clinical Bidimensional Product (BDP) of ≥ 1 centimeter.

11.2.4 Clinical Tumor Response Based on Proctoscopy Can be Classified as the Following:

- *Complete response (100%)*
- *Major response (51% to 100% smaller)*
- *Moderate response (21% to 50% smaller)*
- *Minimal response (0% to 20% smaller)*
- *Progression (tumor has enlarged)*
- *Unable to determine*

11.2.5 Treatment Decision for Group 1 Patients after Re-evaluation Following 6 Cycles of Neoadjuvant FOLFOX

- If there is any evidence of progressive disease (PD) on either imaging or clinical assessment, the patient proceeds to 5FUCMT.
- If there is an estimated ≥ 20% response on imaging OR if there is an estimated response of ≥ 20% on proctoscopy, the patient proceeds directly to TME.
- Otherwise, the patient proceeds to 5FUCMT.
- The primary surgeon adjudicates decision making in the event of clinical inconsistency or disagreement among clinical team members.

11.3 Pathological Tumor Response

All operative and pathology reports for the TME resection must be submitted. Reports must contain information about microscopic involvement of surgical resection margins.

De-identified reports may be submitted via iMedidata RAVE using the Supporting Documentation Form.

If site is unable to electronically submit the reports, de-identified operative and pathology reports may be submitted to the **Alliance Statistics and Data Center, Attention N1048 Data Manager** via:

Fax: [redacted]
or
Postal Mail: [redacted]

11.3.1 Definition of Surgical Margin Status

11.3.1.1 Margin Type:

Proximal Margins	The proximal surgical margin refers to the most cephalad portion of the specimen (closest to patient's head).
Distal Margins	The distal margin refers to the most caudad portion (closest to anal canal).
Radial Margins	The radial margin, synonymously termed circumferential margin refers to the outer circumference of the rectal specimen.

11.3.1.2 Margin Positivity:

Positive	A surgical margin is POSITIVE if the pathologist notes tumor within ≤ 1mm of any edge of the primary tumor specimen.
Close	A surgical margin is CLOSE if the pathologist notes tumor > 1 but ≤ 3mm of any edge of the primary tumor specimen.
Negative	A surgical margin is NEGATIVE if the pathologist notes that there is NO tumor within 3mm of any edge of the primary tumor specimen.

11.3.2 Overall Completeness of TME Resection

The AJCC 7th edition criteria will be used to categorize the completeness of the TME resection. This categorization schema should focus on the pelvic resection of the TME specimen. If distant tumor is appreciated intraoperatively (for example, a liver metastasis), the pelvic resection may still be considered R0.

R0 resection	All gross disease has been removed, and microscopic examination reveals all surgical margins free of tumor. This must include the proximal, distal and radial margin. Tumor > 1mm from the tumor resection margins is considered R_0. In some cases, intraoperatively, a surgeon may biopsy a liver nodule or retroperitoneal node. Resection will still be considered curative if pathologic examination reveals positive lymph nodes as long as the nodes were completely resected, unless there is also evidence of positive margins.
R1 resection	There is evidence of tumor manifest at 1 or more surgical resection margins based on microscopic pathologic assessment of the tumor specimen but there is no macroscopic evidence of tumor at any resection margin nor is there macroscopic evidence of residual tumor based on the surgeon's operative report.
R2 resection	The surgical pathologist identifies any macroscopic evidence of tumor at any of the surgical resection margins or there is macroscopic evidence of residual tumor based on the surgeon's operative report.
No resection	Removal of the primary tumor was not performed.

Pathologic TNM Staging: After TME resection, patients will be staged according to the AJCC7th edition schema.

T describes how far the main (primary) tumor has grown into the wall of the intestine and whether it has grown into nearby areas. Because this information will be ascertained from the surgical pathology report it is denoted with a prefix "p". Because it is ascertained after neoadjuvant treatment, the prefix "y" is also added (e.g., ypT3).

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
	IMPORTANT: **T4 PATIENTS ARE NOT ELIGIBLE FOR THIS STUDY AT BASELINE. T4A VERSUS T4B DISEASE CANNOT BE RELIABLY DISTINGUISHED RADIOGRAPHICALLY.** This categorization is included below because it is obtained from the AJCC 7th Edition schema. In rare cases, a patient may progress despite neoadjuvant treatment; a reassessment could indicate T4 disease. In this case, the radiologist should record the best clinical estimate using the AJCC criteria listed below:
T4a	Tumor penetrates to the surface of the visceral peritoneum
T4b	Tumor directly invades or is adherent to other organs or structures

N describes the extent of spread to nearby (regional) lymph nodes based on the rectal resection specimen. The prefix "yp" is added as described for T status.

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes

To have clinical N1 disease, a patient must have fewer than 4 lymph nodes that measure 10 mm or greater in short axis but 1 or more lymph nodes that measure 5 mm or greater.

The following table illustrates hypothetical results of MRI staging studies and works through examples to guide patient eligibility. It is recognized and widely known that MRI based clinical rectal cancer staging is imperfect. These criteria are included to foster consistency across study sites.

Lymph Node Number/Size	Clinical Node + Disease	Eligibility
Five 7 mm lymph nodes	Estimated cN1	Eligible
Six lymph nodes Two 12 mm lymph nodes Two 8 mm lymph nodes	Estimated cN1	Eligible
Six lymph nodes Four 12 mm lymph nodes	Estimated cN2	Ineligible

M describes the extent of spread to distant sites outside of the pelvis.

M0	No distant metastasis outside the pelvis
M1 **M1a:** **M1b:**	Distant metastasis outside the pelvis Confined to one organ or site In more than one organ/site

Summary pathologic stage will be coded using the AJCC7th edition system. Each of the component TNM features based on information available from surgical pathology will be grouped according to this schema; the prefix "y" is used to connote that pathology must be interpreted in the context of neoadjuvant treatment and the "p" connotes pathologic stage. See Appendix XIII for the AJCC 7th Edition schema for colorectal cancer staging.

Pathologic AJCC7 Summary Staging:

Stage	ypT	ypN	M
0	Tis	N0	M0
I	T1 T2	N0 N0	M0 M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2 T1	N1 or N1c N2a	M0 M0
IIIB	T3-T4a T2-T3 T1-T2	N1 or N1c N2a N2b	M0 M0 M0
IIIC	T4a T3-T4a T4b	N2a N2b N1-N2	M0 M0 M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

11.3.3 Degree of Pathological Treatment Response

Pathological response will be made based on assessment of the surgical specimen at the primary treatment site. All pathology reports from the primary treatment site will be reviewed and evaluated for major and minor discordances in interpretation. A randomly selected sample of 15% of the pathologic TME specimens will be reviewed by the Alliance Central Pathologist. If ≥ 5% but < 20% of the TME specimens are interpreted as having a major difference in outcome upon central review, then 30% of the TME specimens will be reviewed by the Alliance Central Pathologist. The Alliance will provide funding for the central review of 30% of the pathologic TME specimens. Irrespective of whether the Central Pathologist reviews 15% or 30% of TME specimens, if ≥ 20% of the TME specimens reviewed by the Central Pathologist result in a major discordance in interpretation, additional resources will be requested from the Alliance and NCI to review additional TME specimens. If this occurs, a protocol amendment will be submitted to the NCI for review and approval specifying whether 100% of the TME specimens require central review or whether the Central Pathologist's review will target specific sites with high rates of discordant interpretations.

A major discordance in treatment response will consist of a change from:

- R0 to R1/R2
- R1/R2 to R0
- Path CR to non-CR
- Non-CR to path CR
- Identification of a histology that is inconsistent with rectal adenocarcinoma (e.g. squamous cell)

A minor discordance in treatment response will exist if there is a change in interpretation such as:

- Change in N status
- Change in the number of involved nodes in the TME specimen
- Change in T status
- All other changes in treatment response, not defined above as a major discordance

This assessment is made in addition to the AJCC 7th edition summary staging.

11.3.3.1 **Pathological Complete Response (pCR)**:

A pCR must include no gross or microscopic tumor identified anywhere within the surgical specimen. This must include:

- No evidence of malignant cells in the primary tumor specimen **AND**
- No lymph nodes that contain tumor.

11.3.3.2 **Pathological Response other than a Complete Response**:

The definition of a non-pCR will include any surgical specimen that has any evidence of residual tumor manifest in the primary or regional lymph nodes.

For patients who do not meet criteria for a pCR, the extent of response to pre-operative therapy will be graded using the Tumor Regression Grade (TRG) schema that is included in the AJCC 7th edition. This was also used by Rodel in the pre/postoperative rectal cancer study and was subsequently adopted by the AJCC [Rodel (JCO 2005; 23:8688-8696)]. This schema evaluates the degree to which the primary rectal tumor specimen has responded to neoadjuvant treatment.

Tumor Regression Coding Based on AJCC 7th Edition

Tumor Regression Grade (TRG)	Response Categorization	Description
TRG-0	Complete	No viable cancer cells
TRG-1	Moderate	Single cells or small groups of cancer cells
TRG-2	Minimal	Residual cancer outgrown by fibrosis
TRG-3	Poor	Minimal or no tumor kill; extensive residual cancer

Source: AJCC Cancer Staging Manual, 7th Edition (2010) published by Springer New York, Inc.

11.3.3.3 **Neoadjuvant Response Score**

The Neoadjuvant Response Score (NAR) in rectal cancer has been used as a predictor of outcomes in locally advanced rectal cancer (George et al., 2015). It

remains controversial whether this predictor is superior to T and N staging (Imam et al., 2021; van der Valk et al., 2019). The NAR will be calculated for all participants and between group differences will be compared. The NAR as formulated by George, Allegra, and Yothers in 2015 will be used (George et al., 2015). Should there be updated versions of the formula, these updates will be incorporated. The NAR formula is estimated as:

$$NAR = \frac{[5\,pN - 3(cT - pT) + 12]^2}{9.61}$$

11.4 Post-operative Bowel Surveillance

A full colonoscopy is suggested at 15 and 51 months after randomization. More frequent evaluation may be indicated based on findings such as adenomatous polyps or the presence of genetic predisposition. It is suggested that patients who did not undergo a complete colonoscopy to the cecum prior to initiation of preoperative treatment, undergo colonoscopy to evaluate for secondary colonic lesions prior to surgical resection.

For proctoscopy and rectal examination, follow the schedules outlined in Section 11.2.1. Note that colonoscopy includes proctoscopy so that a colonoscopic surveillance examination also "counts" as a proctoscopic assessment.

11.5 Treatment Evaluation

Treatment evaluation for Group 1 and 2 patients after completion of surgery and post-operative chemotherapy (and possible radiation)

11.5.1 Patients will be evaluated as per the schedule of tests noted in Section 4.0

11.5.2 At the time of reevaluation, patients will be classified in the following manner:

11.5.2.1 No evidence of disease (NED)

11.5.2.2 Recurrence of disease (REC)

The appearance of rectal carcinoma in the primary site, nodal basin or distant organ sites during follow-up will be classified as recurrence cancer. Recurrence will be classified as local or distant.

Local recurrence	Any tumor located in the pelvis or the perineal scar
Distant recurrence	Any tumor outside the pelvis and the perineal scar

Patients may have local recurrence, distant recurrence, both or neither. Imaging should be used to document the extent of local and distant disease recurrence. Pathological confirmation of suspected distant metastasis should be performed based on clinical judgment and is not mandated.

Although pathologic confirmation of recurrence is not mandated, local and distant recurrences will be categorized based on supporting evidence. Recurrences will be categorized based on whether they are evident from:

Pathology:	Use this category if there is any pathology or cytology demonstrating recurrent rectal cancer.
Serial Imaging:	Use this category is for recurrences that have not been confirmed by pathology but where serial imaging studies (serial is defined as similar scans performed more than 30 days apart) indicate tumor.
Clinical Evaluation:	Use this category for recurrences that have not been confirmed by pathology or serial imaging studies but are manifest on physical exam or compelling imaging studies (absent serial images).

11.5.2.3 Second primary colorectal cancer (2PC)

Second primary cancers are those that arise anywhere in the colon. Tumors involving the surgical anastamosis or arising from the pelvis are to be categorized as recurrent disease.

12.0 DESCRIPTIVE FACTORS AT BASELINE

- **Clinical Stage at Baseline Based on Pelvic MRI**: cT2N1 vs. cT3N0 vs. cT3N1 vs. pelvic MRI not done
- **Clinical Stage at Baseline Based on ERUS and Pelvic CT**: cT2N1 vs. cT3N0 vs. cT3N1 vs. ERUS and pelvic CT not done
- **History of Diabetes:** Yes vs. No
- **History of Cardiovascular Disease:** Yes vs. No
- **Highest Education Level:** Less than high school vs. High school graduate or GED vs. Some college vs. College graduate or more

13.0 TREATMENT/FOLLOW–UP DECISION

This section describes how to follow patients who are deemed ineligible, refuse treatment assignments; withdraw consent or who have violations or progression/recurrent disease.

Cancel	A patient is deemed a cancel if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted.
Ineligible	A patient is deemed ineligible if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study. If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. If the patient undergoes surgery, the surgery data must be submitted. Event monitoring will be required per Section 17.0 of the protocol. If the patient never received treatment, on-study material must be submitted. Event monitoring will be required per Section 17.0 of the protocol.
Refusal	Patients who refuse a treatment assignment after started the study treatment will go to the event-monitoring phase of the study. All data up until the point of refusal and surgery data (if the patient undergoes surgery) must be submitted. End of Active Treatment/Cancel Notification Form must be submitted.
Withdrawal From Study Treatment but Not Consent	Patients who withdraw from study treatment will go to event monitoring. If the patient undergoes surgery, the surgery data must be submitted.
Withdrawal of Consent for Participation	Patients who withdraw consent completely will be taken off study; study staff cannot collect any more study data on patient. If/when this occurs, site should notify the Data Manager (see Protocol Resources).
Major Violation	A patient is deemed a major violation, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 17.0 of the protocol.
Minor Violation	A patient is deemed a minor violation, if protocol requirements regarding treatment in cycle 1 of the initial therapy were violated such that evaluability for primary end point is nevertheless reasonable. For example, if baseline blood test fell outside the prescribed range, but all other criteria were met, the violation would be deemed minor. For minor violations, protocol directed treatment and observation should proceed.
Progression Before Surgery	Patients with disease progression preoperatively will continue with evaluation and treatment as outlined in Section 4.0. All patients should continue treatment per protocol and will continue to undergo observation.
Persistent Disease at Surgery	Rare patients in this study will have persistent disease at surgery. Persistent disease is defined as R1 or R2 resection. Patients who have persistent disease should continue observation until if and when there is progressive disease.
Recurrence or Progression After Surgery	Patients in this study will be rendered disease free after surgical resection. Patients who develop progression after surgery, which is new evidence of disease should be categorized as having local or pelvic recurrence. Subsequent to recurrence, patients should undergo event monitoring for survival.
Failure to Complete Treatment	Group 1 patients who fail to complete neoadjuvant FOLFOX x 6 will go to 5FUCMT. Group 2 patients who fail to complete neoadjuvant 5FUCMT will go to surgery. Group 1 or Group 2 patients who do not complete any component of postoperative therapy will go to observation. If the patient undergoes surgery, the surgery data must be submitted.

14.0 BIOSPECIMENS

For SAKK sites, please refer to the Swiss Specific Appendix for information regarding translational research.

14.1 Biospecimens Acquisition Schedule

Type of biospecimen to submit	Indicate if specimen is mandatory or optional	Collection tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes to be collected)	**Both Groups 1 and 2:** baseline (≤ 28 days prior to start of treatment)	**Both Groups 1 and 2:** after completion of neoadjuvant treatment	Shipment precautions
Tumor block[1] from baseline proctoscopic **biopsy** or outside tissue specimen	Mandatory	FFPE		X[4]		
Tumor block[1] from TME **surgical** resection	Mandatory	FFPE			X (at surgery)	
Whole blood[2]	Mandatory	Red/grey or gold-topped Serum Separator Tube	10 mL (1)	X	X (pre-op)	Cool pack
Whole blood[3]	Mandatory	EDTA (purple top)	10 mL (1)	X	X (pre-op)	Cool pack

1. If tumor block is unavailable, the site may instead submit 4 2mm tissue cores, 15 unstained slides at 4 microns thick, 4 unstained slides at 10 microns, and 1 H&E. If the site cannot send this many slides, the site may submit a total of 10 slides –5 slides at 4 microns thick, 4 slides at 10 microns, and 1 H&E stained slide. Submission of a block (or alternative) from the surgical resection is required even if no residual tumor is found in the resected specimen.
2. For serum to be isolated from whole blood and used for immunology studies.
3. For DNA to be isolated from whole blood and used for genotyping.
4. Rectal tumor biopsy may be performed within 60 days before registration OR between registration and the start of treatment

14.2 Specimen Registration and Tracking

Use of the Alliance Biospecimen Management System (BioMS) is mandatory and all specimens must be logged and shipped via this system.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: [redacted] using most standard web browsers (Safari, Firefox, and Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training

videos. To report technical problems, such as login issues or application errors, or for assistance in using the application, or questions or problems related to specific specimen logging, please contact: 855-55BIOMS.

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens. Instructions for the collection of samples are included below.

14.3 Biospecimens Submission Schedule

Label all biospecimens with the following identification:

1) N1048 Protocol
2) N1048 Protocol Study Number
3) Date of Specimen Collection
4) Patient's Initials
5) Type of Specimen Collected
6) Institutional Surgical Pathology # (for Pathology Specimens)

Whole blood specimens need to be mailed as soon as feasible following blood draw (preferably within 24 hours of collection; preferably mailed in a cool pack; no additional processing is required prior to shipment). Tumor blocks from the proctoscopic biopsy and the TME surgical specimen may be batched and sent together as soon as is feasible postoperatively. Tumor blocks should be sent within 4 weeks of TME resection.

Biospecimens Submission Instructions

Kits will NOT be provided for this study; sites should use institutional supplies. Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and trackable. Extreme heat precautions should be taken. Corresponding de-identified pathology reports should accompany any tissue specimen submitted.

Shipment on Monday through Friday by overnight service to assure receipt is encouraged. Do not ship specimens the day before a holiday. The Alliance Biorepository at OSU does not accept Saturday deliveries.

Ship all specimens with BioMS shipping manifest and pathology reports (if applicable) to the following address:

[redacted]

For Argentine Sites:

In addition to utilizing BioMS for specimen registration and tracking (as described in Section 14.2), the N1048 Study-Specific Requisition Form must be completed. The local Courier Company "MARKEN" will perform shipment of samples.

14.4 Blood Sample Submission

The samples collected in 1) red/grey or gold top tubes (Serum Separator) and 2) purple top (EDTA) tubes should be collected at baseline (≤ 28 days of start of FOLFOX [Group 1] or 5FUCMT [Group 2]) and ≤ 28 days prior to surgery for both Groups 1 and 2. Collect 10mL peripheral venous blood in a non-heparinized "red/grey or gold top" tube. Also collect 10 mL of peripheral venous blood in an EDTA "purple top" tube. The tubes should be refrigerated until shipped on cool pack by overnight mail to the Alliance Biorepository at OSU. The samples should be shipped as soon as is feasible, ideally, the same day that the blood is drawn; no additional processing is required prior to shipment.

14.5 Paraffin Block Submission

Submit one formalin fixed paraffin embedded tissue block with representative primary tumor from the pre-treatment proctoscopic biopsy and one FFPE tissue block with representative primary tumor from the TME surgical specimen.

The Alliance has instituted special considerations for institutions whose policies prohibits release or long-term storage of tissue blocks. If, due to institutional policy, a block cannot be sent, please submit 4 2mm cores, 15 unstained slides at 4 microns thick, 4 unstained slides at 10 microns, and 1 H & E slide. If the site cannot send this many slides, the site may submit a total of 10 slides – 5 slides at 4 microns thick, 4 slides at 10 microns thick, and 1 H & E stained slide.

The goal of the Alliance Biorepository at OSU is to provide investigators with quality histology sections for their research while maintaining the integrity of the tissue. All paraffin blocks that are to be stored at the Alliance Biorepository at OSU will be vacuum packed to prevent oxidation and will be stored at 4ºC to minimize degradation of cellular antigens. For these reasons it is preferred that the Alliance Biorepository at OSU bank the tissue block until the study investigator requests thin sections. Please contact the Alliance Biorepository at OSU if additional assurances are required.

14.6 Study Methodology and Storage Information

14.6.1 Analysis of Tissue Samples

FFPE tumor tissue blocks will be collected in order to assess correlation of responses to treatment with FOLFOX by genome sequencing. Banking of tumor tissue, according to the patient consent permission, is for future research. As protocols are developed, they will be presented for Alliance IRB review and approval.

Genomic Characterization of Rectal Tumors Using Molecular Inversion Probe (MIP) Assay and Mass Spectrometry based Genotyping

The MIP array technology will be used to identify prognostic and/or predictive, potentially druggable mutations involving MEK, AKT, PIK3CA, and BRAF, as well as others, and copy number alterations, such as ERBB2 amplification, using FFPE material. Mutations in KRAS, NRAS, BRAF and PIK3CA will be detected using the iPLEX assay and analyzed by the MassARRAY system is based on matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS). In these assays, the mutant and germline alleles for a given point mutation produce single-allele base extension reaction products of different masses that are then resolved by MALDI-TOF MS. For further information, refer to Appendix X.

14.6.2 Analysis of Blood Samples

Indicators of Immunologic Activation

Measurement of serum cytokines (IFN- γ, IL-2, IL-4, IL-5, IL-10, tumor necrosis factor-α, VEGF, basic fibroblast growth factor (bFGF), and IL-8 may be performed using bead array and ELISA kits. ELISA will also be used to measure antibody response to classes of cancer-testes antigens notably LAGE-1, MAGE, CT-7, CT-47, Sox-2, XAGE-1 or others. Last, specifically bound serum IgG will be assayed by protein microarrays. For further information, refer to Appendix XI.

Assessment of Germline Variation as a Predictor of Response and Toxicity to Platinum-based Chemotherapy and Radiation Therapy

We will perform genotyping of DNA on all patients randomized to receive neoadjuvant chemotherapy with FOLFOX using genetic variants to evaluate if germline genetic variants in candidate genes of interest are associated with response and/or toxicity to platinum and radiation therapy. We will also evaluate whether genetic risk variants identified in genome-wide association studies of colorectal cancer susceptibility are associated with rectal cancer clinical outcome and response to therapy. For further information, refer to Appendix XII.

14.7 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

If at any time, genetic results are obtained that may have clinical relevance, IRB review and approval will be sought regarding the most appropriate manner of disclosure and whether or not validation in a CLIA-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

15.0 DRUG INFORMATION

For SAKK sites, please refer to the Swiss Specific Appendix for information regarding drug supply and handling.

15.1 Oxaliplatin (Eloxatin®, OXAL)

15.1.1 Background: Oxaliplatin, a platinum derivative, is an alkylating agent. Following intracellular hydrolysis, the platinum compound binds to DNA forming cross-links which inhibit DNA replication and transcription, resulting in cell death. Cytotoxicity is cell-cycle nonspecific.

15.1.2 Formulation: Commercially available for injection as: Solution [preservative free]: 5 mg/mL (10 mL, 20 mL, 40 mL)

15.1.3 Preparation, Storage, and Stability: Refer to package insert for complete preparation and dispensing instructions. Store intact vials in original outer carton at room temperature and do not freeze. According to the manufacturer, solutions diluted for infusion are stable up to 6 hours at room temperature or up to 24hours under refrigeration. Oxaliplatin solution diluted with D_5W to a final concentration of 0.7 mg/mL (polyolefin container) has been shown to retain > 90% of its original concentration for up to 30 days when stored at room temperature or refrigerated; artificial light did not affect the concentration (Andre, 2007). As this study did not examine sterility, refrigeration would be preferred to limit microbial growth. Do not prepare using a chloride-containing solution (e.g., NaCl). Dilution with

D_5W (250 or 500 mL) is required prior to administration. Infusion solutions do not require protection from light.

15.1.4 Administration: Refer to the treatment section for specific administration instructions. Administer as I.V. infusion over 2-6 hours. Flush infusion line with D5W prior to administration of any concomitant medication. Patients should receive an antiemetic premedication regimen. Cold temperature may exacerbate acute neuropathy. Avoid mucositis prophylaxis with ice chips during oxaliplatin infusion.

15.1.5 Pharmacokinetic Information:

Distribution: V_d: 440 L
Protein Binding: > 90% primarily albumin and gamma globulin (irreversible binding to platinum)
Metabolism: Nonenzymatic (rapid and extensive), forms active and inactive derivatives
Half-life Elimination: Terminal: 391 hours; Distribution: Alpha phase: 0.4 hours,
Beta Phase: 16.8 hours
Excretion: Primarily urine (~ 54%); feces (~ 2%)

15.1.6 Potential Drug Interactions:

Increased Effect/Toxicity: Nephrotoxic agents may increase oxaliplatin toxicity. When administered as sequential infusions, observational studies indicate a potential for increased toxicity when platinum derivatives (carboplatin, cisplatin, oxaliplatin) are administered before taxane derivatives (docetaxel, paclitaxel).

Decreased Effect: Oxaliplatin may decrease plasma levels of digoxin.

15.1.7 Known Potential Adverse Events:

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single 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 Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' [redacted] for further clarification. *Frequency is provided based on 1141 patients.* Below is the CAEPR for oxaliplatin.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, November 1, 2011[1]

Adverse Events with Possible Relationship to Oxaliplatin (CTCAE 4.0 Term) [n= 1141]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)** (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
	Disseminated intravascular coagulation		***Disseminated intravascular coagulation (Gr 2)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
	Hemolysis		***Hemolysis (Gr 2)***
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
	Atrial fibrillation		***Atrial fibrillation (Gr 2)***
	Atrial flutter		***Atrial flutter (Gr 2)***
	Paroxysmal atrial tachycardia		***Paroxysmal atrial tachycardia (Gr 2)***
	Sinus bradycardia		***Sinus bradycardia (Gr 2)***
	Sinus tachycardia		***Sinus tachycardia (Gr 2)***
	Supraventricular tachycardia		***Supraventricular tachycardia (Gr 2)***
	Ventricular arrhythmia		***Ventricular arrhythmia (Gr 2)***
	Ventricular fibrillation		***Ventricular fibrillation (Gr 2)***
	Ventricular tachycardia		***Ventricular tachycardia (Gr 2)***
EAR AND LABYRINTH DISORDERS			
	Hearing impaired		***Hearing impaired (Gr 2)***
	Middle ear inflammation		***Middle ear inflammation (Gr 2)***
EYE DISORDERS			
	Conjunctivitis		***Conjunctivitis (Gr 2)***
	Dry eye		***Dry eye (Gr 2)***
	Eye disorders - Other (amaurosis fugax)		***Eye disorders - Other (amaurosis fugax) (Gr 2)***
	Eye disorders - Other (cold-induced transient visual abnormalities)		***Eye disorders - Other (cold-induced transient visual abnormalities) (Gr 2)***
	Eyelid function disorder		***Eyelid function disorder (Gr 2)***
	Papilledema		***Papilledema (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Ascites		***Ascites (Gr 2)***
	Colitis		***Colitis (Gr 3)***
	Constipation		***Constipation (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Dysphagia		***Dysphagia (Gr 2)***
	Enterocolitis		***Enterocolitis (Gr 3)***

	Esophagitis		***Esophagitis (Gr 3)***
	Flatulence		***Flatulence (Gr 2)***
	Gastritis		***Gastritis (Gr 2)***
		Gastrointestinal disorders – Other (pneumatosis intestinalis)	
	Gastrointestinal hemorrhage[2]		***Gastrointestinal hemorrhage[2] (Gr 3)***
	Gastrointestinal necrosis[3]		***Gastrointestinal necrosis[3] (Gr 2)***
	Gastrointestinal ulcer[4]		***Gastrointestinal ulcer[4](Gr 2)***
	Ileus		***Ileus (Gr 3)***
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Pancreatitis		***Pancreatitis (Gr 2)***
	Small intestinal obstruction		***Small intestinal obstruction (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema face		***Edema face (Gr 2)***
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Gait disturbance		***Gait disturbance (Gr 2)***
	General disorders and administration site conditions - Other (Hepato-renal syndrome)		***General disorders and administration site conditions - Other (Hepato-renal syndrome) (Gr 2)***
	Injection site reaction		***Injection site reaction (Gr 2)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 2)***
HEPATOBILIARY DISORDERS			
		Cholecystitis	
	Hepatic failure		***Hepatic failure (Gr 2)***
	Hepatobiliary disorders - Other (hepatic enlargement)		***Hepatobiliary disorders - Other (hepatic enlargement) (Gr 2)***
	Hepatobiliary disorders - Other (veno-occlusive liver disease)		***Hepatobiliary disorders - Other (veno-occlusive liver disease) (Gr 2)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Infection[5]		***Infection[5] (Gr 3)***
INVESTIGATIONS			
	Activated partial thromboplastin time prolonged		***Activated partial thromboplastin time prolonged (Gr 2)***
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
Aspartate aminotransferase			***Aspartate aminotransferase increased (Gr 3)***

increased			
	Blood bilirubin increased		***Blood bilirubin increased (Gr 3)***
	Creatinine increased		***Creatinine increased (Gr 3)***
	GGT increased		***GGT increased (Gr 2)***
	INR increased		***INR increased (Gr 2)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 3)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight gain		***Weight gain (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Acidosis		***Acidosis (Gr 4)***
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hyperglycemia		***Hyperglycemia (Gr 2)***
	Hyperuricemia		***Hyperuricemia (Gr 2)***
	Hypoalbuminemia		***Hypoalbuminemia (Gr 3)***
	Hypocalcemia		***Hypocalcemia (Gr 3)***
	Hypoglycemia		***Hypoglycemia (Gr 2)***
	Hypokalemia		***Hypokalemia (Gr 4)***
	Hypomagnesemia		***Hypomagnesemia (Gr 4)***
	Hyponatremia		***Hyponatremia (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
	Bone pain		***Bone pain (Gr 2)***
	Myalgia		***Myalgia (Gr 2)***
	Trismus		***Trismus (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Ataxia		***Ataxia (Gr 3)***
	Depressed level of consciousness		***Depressed level of consciousness (Gr 2)***
	Dizziness		***Dizziness (Gr 3)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Dysphasia		***Dysphasia (Gr 2)***
	Extrapyramidal disorder		***Extrapyramidal disorder (Gr 2)***
	Headache		***Headache (Gr 2)***
	Intracranial hemorrhage		***Intracranial hemorrhage (Gr 2)***
	Ischemia cerebrovascular		***Ischemia cerebrovascular (Gr 2)***
	Nerve disorder[6]		***Nerve disorder[6] (Gr 2)***
	Nervous system disorders - Other (multiple cranial nerve palsies)		***Nervous system disorders - Other (multiple cranial nerve palsies) (Gr 2)***

	Peripheral motor neuropathy		***Peripheral motor neuropathy (Gr 3)***
Peripheral sensory neuropathy			***Peripheral sensory neuropathy (Gr 3)***
	Seizure		***Seizure (Gr 2)***
PSYCHIATRIC DISORDERS			
	Anxiety		***Anxiety (Gr 2)***
	Confusion		***Confusion (Gr 3)***
	Depression		***Depression (Gr 2)***
	Insomnia		***Insomnia (Gr 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury	***Acute kidney injury (Gr 3)***
	Hematuria		***Hematuria (Gr 2)***
	Renal hemorrhage		***Renal hemorrhage (Gr 2)***
	Urinary frequency		***Urinary frequency (Gr 2)***
	Urinary retention		***Urinary retention (Gr 2)***
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
	Hematosalpinx		***Hematosalpinx (Gr 2)***
	Ovarian hemorrhage		***Ovarian hemorrhage (Gr 2)***
	Prostatic hemorrhage		***Prostatic hemorrhage (Gr 2)***
	Spermatic cord hemorrhage		***Spermatic cord hemorrhage (Gr 2)***
	Testicular hemorrhage		***Testicular hemorrhage (Gr 2)***
	Uterine hemorrhage		***Uterine hemorrhage (Gr 2)***
	Vaginal hemorrhage		***Vaginal hemorrhage (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Adult respiratory distress syndrome	***Adult respiratory distress syndrome (Gr 2)***
	Allergic rhinitis		***Allergic rhinitis (Gr 2)***
	Bronchopulmonary hemorrhage		***Bronchopulmonary hemorrhage (Gr 2)***
	Bronchospasm		***Bronchospasm (Gr 2)***
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 4)***
	Hiccups		***Hiccups (Gr 2)***
	Pneumonitis		***Pneumonitis (Gr 3)***
	Pulmonary fibrosis		***Pulmonary fibrosis (Gr 4)***
	Sinus disorder		***Sinus disorder (Gr 2)***
	Voice alteration		***Voice alteration (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
	Hyperhidrosis		***Hyperhidrosis (Gr 2)***
		Palmar-plantar erythrodysesthesia syndrome	***Palmar-plantar erythrodysesthesia syndrome (Gr 2)***
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Urticaria		***Urticaria (Gr 2)***
VASCULAR DISORDERS			
	Flushing		***Flushing (Gr 2)***

	Hot flashes		***Hot flashes (Gr 2)***
	Hypertension		***Hypertension (Gr 2)***
	Hypotension		***Hypotension (Gr 3)***
	Phlebitis		***Phlebitis (Gr 2)***
	Thromboembolic event		***Thromboembolic event (Gr 4)***
	Vascular disorders - Other (hemorrhage with thrombocytopenia)		***Vascular disorders - Other (hemorrhage with thrombocytopenia) (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.
[2]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Doudenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.
[3]Gastrointestinal necrosis includes Anal necrosis, Esophageal necrosis, Gastric necrosis, Pancreatic necrosis, Peritoneal necrosis, and Rectal necrosis under the GASTROINTESTINAL DISORDERS SOC.
[4]Gastrointestinal ulcer includes Anal ulcer, Colonic ulcer, Duodenal ulcer, Esophageal ulcer, Gastric ulcer, Ileal ulcer, Jejunal ulcer, Rectal ulcer, and Small intestine ulcer under the GASTROINTESTINAL DISORDERS SOC.
[5]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.
[6]Nerve disorder includes Abducens nerve disorder, Accessory nerve disorder, Acoustic nerve disorder NOS, Facial nerve disorder, Glossopharyngeal nerve disorder, Hypoglossal nerve disorder, IVth nerve disorder, Oculomotor nerve disorder, Olfactory nerve disorder, Trigeminal nerve disorder, and Vagus nerve disorder under the NERVOUS SYSTEM DISORDERS SOC.
[7]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.
Also reported on oxaliplatin trials but with the relationship to oxaliplatin still undetermined:
CARDIAC DISORDERS - Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Pericardial effusion
EYE DISORDERS - Eye pain
GASTROINTESTINAL DISORDERS – Gastrointestinal perforation[7]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Injury to superior vena cava; Vascular access complication
INVESTIGATIONS - Cardiac troponin I increased; Lipase increased; Serum amylase increased
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness
NERVOUS SYSTEM DISORDERS - Syncope
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Hypoxia
VASCULAR DISORDERS - Visceral arterial ischemia
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.

15.1.8 Drug Procurement: Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.1.9 Nursing Guidelines:

15.1.9.1 GI adverse events similar to cisplatin occurs with doses above 30 mg/m^2. It can be almost constant and frequently severe, but not always dose limiting. Monitor for nausea and vomiting and treat accordingly.

15.1.9.2 Dose-limiting side effects can be paresthesias of hands, fingers, toes, pharynx, and occasionally cramps which develops with a dose-related frequency (>90 mg/m^2). Duration of symptoms tend to be brief (less than a week) with the first course, but longer with subsequent courses. Phase I patients have reported exacerbation of paresthesias by touching cold surfaces or exposure to cold. Advise patient of these possibilities and instruct patient to report these symptoms to the health care team.

Also advise patient to refrain from operating dangerous machinery that requires fine sensory-motor coordination, if symptoms appear.

15.1.9.3 These sensory neuropathies developed after subsequent courses with increasing intensity (Grade 3 toxicity after the fourth course) and with increasing duration. In 63% of the patients tested in Phase I at high doses (135-200 mg/m2), neuropathies became long-term with slow reversal over several months. Disabling walking and handwriting difficulties, as well as mouth and throat dysesthesias and laryngospasms were seen. Instruct patient to report any swallowing difficulties or gait changes.

15.1.9.4 Oxaliplatin is incompatible with NS. Flush lines with D5W prior to and following oxaliplatin infusion.

15.1.9.5 Low back pain is a common side effect, perhaps a form of hypersensitivity reaction. Instruct patient in good body mechanics, advise light massage, heat, etc.

15.1.9.6 Laryngopharyngeal dysesthesia (LPD) occurs in about 15% of patients and is acute, sporadic, and self-limited. It usually occurs within hours of infusion, is induced or exacerbated by exposure to cold, and presents with dyspnea and dysphagia. The incidence and severity appear to be reduced by prolonging infusion time. Instruct patient to avoid ice and cold drinks the day of infusion. If ≥ Grade 2 laryngopharyngeal dysesthesia occurs during the administration of oxaliplatin, do the following:

- Stop oxaliplatin infusion
- Administer benzodiazepine and give patient reassurance
- Test oxygen saturation via a pulse oximeter
- At the discretion of the investigator, the infusion can be restarted at 1/3 the original rate of infusion.
- Rapid resolution is typical within minutes to a few hours. Can recur with retreatment.

Comparison of the Symptoms and Treatment of Laryngopharyngeal Dysesthesias and Platinum Hypersensitivity Reactions		
Clinical Symptoms	**Laryngopharyngeal Dysesthesias**	**Platinum Hypersensitivity**
Dyspnea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
Oxygen saturation	Normal	Decreased
Difficulty swallowing	Present	Absent
Pruritus	Absent	Present
Urticaria/rash	Absent	Present
Cold-induced symptoms	Yes	No
Blood pressure	Normal or increased	Normal or decreased
Treatment	Anxiolytics, observation in a controlled clinical setting until symptoms abate or at the physicians' discretion	Oxygen, steroids, epinephrine, bronchodilators; fluids and vasopressors, if appropriate

15.1.9.7 Alopecia is rare with oxaliplatin alone, but is seen with 5-FU and oxaliplatin combination. Advise patient.

15.1.9.8 Mild-to-moderate diarrhea has been seen -- usually of short duration. Treat accordingly with loperamide and according to standard practice.

15.1.9.9a Respiratory problems (i.e., pulmonary fibrosis, cough, dyspnea, rales, pulmonary infiltrates, hypoxia, air hunger and tachypnea) have been observed in patients administered oxaliplatin. In rare cases, death has occurred due to pulmonary fibrosis. Please monitor and instruct the patient to report any respiratory difficulties and hold oxaliplatin until interstitial lung disease is ruled out for cases of Grade ≥ 3. If patient is experiencing shortness of breath, a chest x-ray and assessment of oxygenation via either finger oximetry or arterial blood gas evaluation are required to confirm the absence or presence of pulmonary infiltrates and/or hypoxia (treat accordingly: no intervention, steroids, diuretics, oxygen, or assisted ventilation).

15.19.9b Veno-occlusive disease (VOD) is a rare but serious complication that has been reported in patients receiving oxaliplatin in combination with 5-FU. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Instruct patients to report any jaundice, ascites, or hematemesis to the MD immediately as these could be a sign of VOD or other serious condition.

15.1.9.9c Acute vein irritation can occur with infusion. Apply heat to arm of infusion if you are using a peripheral line. However, extravasation of drug can cause severe pain, redness, soreness, and exfoliation of the skin in the affected area with loss of affected vein for a long period. If a patient has a problem with pain or sclerosis when chemotherapy is given by a peripheral line, then placement of a central line should be considered.

15.1.9.9d Hemolytic Uremic Syndrome (HUS) may result in kidney damage. Oxaliplatin is to be discontinued in cases where hematocrit is < 25%, thrombocytopenia < 100,000, and creatinine ≥ 1.6 mg/dL.

15.1.9.9e Patients may experience sleep disturbances, specifically insomnia. Encourage good sleep hygiene and instruct patient to report any problems with sleep to the MD, to assess for the potential use of sleeping aids.

15.1.9.9f Cold-induced transient visual abnormalities can be experienced by patients while receiving oxaliplatin, although the relationship to oxaliplatin has not been completely determined. Instruct patient to report any problems with vision to the MD.

15.1.9.9g Extrapyramidal side effects and/or involuntary limb movement has been seen with oxaliplatin administration. Patients may also experience restlessness. Instruct patient to report any of these side effects to the MD.

Use the following if a bolus infusion is being used:

15.1.9.9h A bolus infusion of oxaliplatin/capecitabine may increase the risk of developing life-threatening enteric sepsis secondary to neutropenia and diarrhea. Patients with Grade 4 ANC and Grade 3 diarrhea should be closely monitored and condition reported to MD for possible hospitalization for appropriate hydration and treatment with antibiotics, appropriate for gram negative or anaerobic sepsis. Patients should be monitored closely and provided with aggressive supportive care until neutropenia and diarrhea resolve.

15.2 Leucovorin Calcium (CF)

15.2.1 Background: A reduced form of folic acid, leucovorin supplies the necessary cofactor blocked by methotrexate, enters the cells via the same active transport system as methotrexate. Stabilizes the binding of 5-dUMP and thymidylate synthetase, enhancing the activity of fluorouracil.

15.2.2 Formulation: Commercially available as powder for reconstitution: 50 mg, 100 mg, 200 mg, 350 mg. Injection, solution: 10 mg/mL (50 mL)

15.2.3 Preparation, Storage, and Stability:

Powder for injection: Store at room temperature, protect from light. Reconstitute with sterile water for injection or bacteriostatic water for injection; dilute in 100-1000 mL 0.9% NaCl or D_5W. When doses > 10 mg/m^2 are required, reconstitute using sterile water for injection, not a solution containing benzyl alcohol. Solutions reconstituted with bacteriostatic water for injection must be used within 7 days. Solutions reconstituted with sterile water for injection must be used immediately. Parenteral admixture is stable for 24 hours stored at room temperature and for 4 days when stored under refrigeration. Solution for injection: Prior to dilution, store vials under refrigeration, protect from light.

15.2.4 Administration:

Due to calcium content, do not administer I.V. solutions at a rate > 160 mg/minute. Refer to individual protocols for specific administration instructions. Leucovorin should be administered I.V. push or I.V. infusion (15 minutes to 2 hours).

In combination with fluorouracil: The fluorouracil is usually given after the leucovorin infusion. Leucovorin is usually administered by I.V. bolus injection or short (10-120 minutes) I.V. infusion. Other administration schedules have been used; refer to the treatment section of the protocol for specific directions. In combination with oxaliplatin: Leucovorin is compatible with oxaliplatin and may be administered concurrently via Y-connector at normal doses. Oxaliplatin is incompatible with 0.9% NaCl. Leucovorin must be diluted in D_5W when administered with oxaliplatin. In combination with irinotecan: Leucovorin is compatible with irinotecan via Y-site injection.

15.2.5 Pharmacokinetic Information:

Metabolism: Intestinal mucosa and hepatically to 5-methyl-tetrahydrofolate (5MTHF; active)
Half-life Elimination: ~4-8 hours
Time to Peak: I.V.: Total folates: 10 minutes; 5MTHF: ~1 hour
Excretion: Urine (primarily); feces

15.2.6 Potential Drug Interactions:

Decreased Effect: May decrease efficacy of trimethoprim/sulfamethoxazole against Pneumocystis carinii pneumonia.

15.2.7 Known Potential Adverse Events: Consult the package insert for the most current and complete information.

Common known potential toxicities, > 10%: None
Less common known potential toxicities, 1% - 10%:
Dermatologic: Rash, pruritus, erythema, urticaria
Gastrointestinal: Nausea, vomiting
Rare known potential toxicities, <1% (Limited to important or life-threatening):
allergic reactions, anaphylactoid reactions, dyspnea, thrombocytosis

15.2.8 Drug Procurement: Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.2.9 Nursing Guidelines:

15.2.9.1 Headache may occur. Advise patient analgesics such as Tylenol may help. Instruct patient to report any headache that is unrelieved.

15.2.9.2 Observe for sensitization reaction (rash, hives, pruritus, facial flushing and wheezing).

15.2.9.3 May potentiate the toxic effects of fluoropyrimidine (5-FU) therapy, resulting in increased hematologic and gastrointestinal side effects (diarrhea, stomatitis). Monitor closely.

15.2.9.4 May cause mild nausea or upset stomach. Administer antiemetics if necessary and evaluate for their effectiveness.

15.3 Fluorouracil (Adrucil, Efudex, [5FU])

15.3.1 Background: Antineoplastic Agent, Antimetabolite (Pyrimidine Analog). Fluorouracil is a fluorinated pyrimidine antimetabolite that inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, interfering with DNA, and to a lesser degree, RNA synthesis. Fluorouracil appears to be phase specific for the G_1 and S phases of the cell cycle.

15.3.2 Formulation: Commercially available for injection 50 mg/mL (10 mL, 20 mL, 50 mL, and 100 mL).

15.3.3 Preparation, Storage, and Stability: Store intact vials at room temperature and protect from light. A slight discoloration may occur with storage but usually does not denote decomposition. Dilute in 50 – 1000 mL of 0.9% NaCl or D5W. If exposed to cold, a precipitate may form; gentle heating to 60ºC will dissolve the precipitate without impairing the potency. Solutions in 50 – 1000 mL 0.9% NaCl or D5W or undiluted solutions in syringes are stable for 72 hours at room temperature. Fluorouracil should not be co-

administered with diazepam, doxorubicin, daunorubicin, idarubicin, cisplatin, or cytarabine. However, fluorouracil and leucovorin are compatible for 14 days at room temperature. Fluorouracil is compatible with vincristine, methotrexate, and cyclophosphamide.

15.3.4 Administration: Fluorouracil may be given IV push, IV infusion. Refer to Section 7.0 (treatment) administration instructions specific to the protocol.

15.3.5 Pharmacokinetic Information:

Distribution: V_d ~ 22% of total body water; penetrates extracellular fluid, CSF and third space fluids (e.g., pleural effusions and ascitic fluid)
Metabolism: Hepatic (90%); via a dehydrogenase enzyme; Fluorouracil must be metabolized to be active.
Half-life Elimination: Biphasic: Initial: 6-20 minutes; two metabolites, FdUMP and FUTP, have prolonged half-lives depending on the type of tissue.
Excretion: Lung (large amounts as CO_2); urine (5% as unchanged drug) in 6 hours.

15.3.6 Potential Drug Interactions: Fluorouracil may increase effects of warfarin. Avoid ethanol (due to GI irritation).

15.3.7 Known Potential Adverse Events: Consult the package insert for the most current and complete information. Counsel patients to use protective wear and avoid excessive sun exposure as direct sun exposure during 5FU or capecitabine therapy may be associated with severe sunburn.

Common Known Potential Toxicities, >10%:
Dermatologic: Dermatitis, pruritic maculopapular rash, alopecia.
Gastrointestinal (route and schedule dependent): Heartburn, nausea, vomiting, anorexia, stomatitis, esophagitis, anorexia, diarrhea. GI toxicity (anorexia, nausea, and vomiting) is generally more severe with continuous-infusion schedules.
Emetic potential: <1000 mg: Moderately low (10% to 30%) ≥ 1000 mg:
Hematologic: Leukopenia; Myelosuppressive (tends to be more pronounced in patients receiving bolus dosing of FU). Decreased white blood cell count with increased risk of infection; decreased platelet count with increased risk of bleeding.
Local: Irritant chemotherapy.
Less Common Known Potential Toxicities, 1% - 10%:
Dermatologic: Dry skin.
Gastrointestinal: GI ulceration
Rare Known Potential Toxicities, <1% (Limited to Important or Life-threatening):
Cardiac enzyme abnormalities, chest pain, coagulopathy, dyspnea, ECG changes similar to ischemic changes, hepatotoxicity; hyperpigmentation of nail beds, face, hands, and veins used in infusion; hypotension, palmar-plantar syndrome (hand-foot syndrome), photosensitization. Cerebellar ataxia, headache, somnolence, ataxia are seen primarily in intracarotid arterial infusions for head and neck tumors.

15.3.8 Drug Procurement: Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.3.9 Nursing Guidelines:

15.3.9.1 Monitor complete blood count and platelet count. Instruct patient to report signs and symptoms of infection, unusual bruising or bleeding to the physician.

15.3.9.2 Administer antiemetics as indicated.

15.3.9.3 Diarrhea may be dose-limiting; encourage fluids and treat symptomatically.

15.3.9.4 Assess for stomatitis; oral care measures as indicated.

15.3.9.5 Monitor for neurological symptoms (headache, ataxia).

15.3.9.6 Inform patient of potential alopecia.

15.3.9.7 Those patients on continuous infusion may need instruction regarding central intravenous catheters and portable intravenous or IA infusion devices.

15.3.9.8 5-FU-induced conjunctivitis is a common problem. Advise patient to report any eye soreness or redness to the healthcare team.

15.3.9.9 Photosensitivity may occur. Instruct patients to wear sunblock when outdoors.

15.4 Capecitabine (Xeloda®)

15.4.1 Background: Capecitabine is classified as an antineoplastic agent, antimetabolite (pyrimidine analog). Capecitabine is a prodrug of fluorouracil. It undergoes hydrolysis in the liver and tissues to form fluorouracil which is the active moiety. Fluorouracil is a fluorinated pyrimidine antimetabolite that inhibits thymidylate synthetase, blocking the methylation of deoxyuridylic acid to thymidylic acid, interfering with DNA, and to a lesser degree, RNA synthesis. Fluorouracil appears to be phase specific for the G_1 and S phases of the cell cycle.

15.4.2 Formulation: Commercially available in 150 mg and 500 mg tablets for oral administration.

15.4.3 Preparation, Storage, and Stability: Store at room temperature of 25°C with excursions between 15°C and 30°C permitted.

15.4.4 Administration: Usually administered in 2 divided doses taken 12 hours apart. Doses should be taken with water within 30 minutes after a meal (Because current safety and efficacy data are based upon administration with food, it is recommended that capecitabine be administered with food. In all clinical trials, patients are instructed to take with water within 30 minutes after a meal).

15.4.5 Pharmacokinetic Information:
Absorption: Rapid and extensive
Protein Binding: <60%; ~35% to albumin
Metabolism:
Hepatic: Inactive metabolites
Tissue, Active metabolite, Fluorouracil
Distribution: $V_{d:}$ 46 mL/kg
Half-life Elimination: 0.5-1 hour
Time to Peak: 1.5 hours; Fluorouracil, 2 hours
Excretion: Urine (96%), Feces (<3%)

15.4.6 Potential Drug Interactions:

Increased Effect/Toxicity: Phenytoin and warfarin levels or effects may be increased. **[U.S. Boxed Warning] Capecitabine may increase the anticoagulant effects of warfarin; monitor closely.**

Nutrition Interactions: Food reduced the rate and extent of absorption of capecitabine.

15.4.7 Known Potential Adverse Events:

Consult the package insert for the most current and complete information. Frequency listed derived from Monotherapy trials.

Common Known Potential Toxicities, > 10%:

Cardiovascular: Edema
Central nervous system: Fatigue, fever, pain
Dermatologic: Palmar-plantar erythrodysethesia (hand-and-foot syndrome), dermatitis.
Gastrointestinal: Diarrhea may be dose limiting, nausea, vomiting, abdominal pain, stomatitis, appetite decreased, anorexia, constipation.
Hematologic: Lymphopenia, anemia, neutropenia, thrombocytopenia.
Hepatic: Bilirubin increased.
Neuromuscular & skeletal: Paresthesia.
Ocular: Eye irritation.
Respiratory: Dyspnea.

Less Common Known Potential Toxicities, 5% - 10%:

Cardiovascular: Venous thrombosis, chest pain.
Central Nervous System: Headache, lethargy, dizziness, insomnia, mood alteration, depression.
Dermatologic: Nail disorder, rash, skin discoloration, alopecia, Erythema.
Endocrine& metabolic: Dehydration.
Gastrointestinal: Motility disorder, oral discomfort, dyspepsia, upper GI inflammatory disorders, hemorrhage, ileus, taste perversion.
Neuromuscular & skeletal: Back pain, weakness, neuropathy, myalgia, arthralgia, limb pain
Ocular: Abnormal vision, conjunctivitis.
Respiratory: Cough.
Miscellaneous: Viral infection.

Rare Known Potential Toxicities, <5% (Limited to Important or Life-threatening):

Angina, ascites, asthma, atrial fibrillation, Bradycardia, bronchitis, bronchopneumonia, bronchospasm, cachexia, cardiac arrest, cardiac failure, cardiomyopathy, cerebral vascular accident, cholestasis, coagulation disorder, colitis, deep vein thrombosis, diaphoresis, duodenitis, dysphagia, dysrhythmia, ECG changes, encephalopathy, epistaxis, fungal infection, gastric ulcer, gastroenteritis, hematemesis, hemoptysis, hepatic failure, hepatic fibrosis, hepatitis, Hypokalemia, hypomagnesemia, hyper-/hypotension, hypersensitivity, hpertriglyceridemia, idiopathic thrombocytopenia purpura, ileus, infection, intestinal obstruction, keratoconjunctivitis, lacrimal duct stenosis, leukopenia, loss of consciousness, lymphedema, MI, multifocal leukoencephalopathy, myocardial ischemia, myocarditis, necrotizing enterocolitis (typhlitis), oral candidiasis, pericardial effusion, thrombocytopenic purpura, pancytopenia, photosensitivity reaction, pneumonia, pruritus, pulmonary embolism, radiation recall syndrome, renal impairment, respiratory distress, sedation, sepsis, skin ulceration, tachycardia, thrombophlebitis, toxic megacolon, tremor, ventricular extrasystoles.

15.4.7 Drug Procurement: Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.4.8 Nursing Guidelines:

15.4.8.1 Instruct patients to take the tablets within 30 minutes of a meal (breakfast and dinner). Tablets should be swallowed with 6-8 oz. of water.

15.4.8.2 Instruct patient to avoid taking a missed dose, to never double up on a dose, and to notify the health care team if a dose has been missed.

15.4.8.3 Diarrhea can be severe and dose limiting. Instruct patient to contact the health care team immediately if they experience > 4 BMs/day and/or nocturnal diarrhea above baseline. Monitor carefully for dehydration and need for fluid and electrolyte replacement. Standard anti-diarrheal treatment, e.g., loperamide is recommended.

15.4.8.4 Nausea and vomiting can be severe and dose-limiting. Instruct patient to report nausea and vomiting to the health care team if they experience > 2 episodes of emesis in a 24-hour period. Initiate symptomatic treatment.

15.4.8.5 Hand and Foot Syndrome is common and dose-limiting (redness, swelling, pain, numbness, tingling, blistering, and moist desquamation). Instruct patient to notify health care team immediately if symptoms appear. Chemotherapy may have to be discontinued until symptoms subside with future dose reduction initiated. The syndrome may recur with a rechallenge.

- Advise patient to apply cool compress for comfort.
- Advise patient to avoid harsh soaps and to use alcohol-free emollients.
- Administer analgesics as prescribed.
- Administer systemic steroids and pyridoxine as prescribed.

15.4.8.6 Treat stomatitis symptomatically -- may try dabbing vitamin E oil on lesions. Do not swallow oil. Advise frequent and careful oral hygiene.

15.4.8.7 Assess for warfarin use. Patients taking coumadin-derivative anticoagulants concomitantly with capecitabine should be monitored regularly for alterations in their coagulation parameters (PT or INR).

15.4.8.8 Carefully assess patient's understanding and need of instruction in adequate birth control measures. Discuss importance of avoiding pregnancy. Periodically re-assess.

15.4.8.9a The use of Sorivudine or its analogue, Birivudine, is contraindicated for this study due to a possible, even fatal, drug reaction. Assess patient's drug use. Impress on patients the importance of avoiding these drugs while on study.

15.4.8.9b Cardiotoxicity (including MI, angina, dysrhythmias, and cardiac arrest) has been seen with capecitabine. Observe patients closely for signs of cardiac dysfunction. Instruct patient to report any chest pain or palpitations to the health care team immediately or seek emergency medical attention.

15.4.8.9c Monitor patient closely who are taking concomitant phenytoin therapy. There have been reports of increased levels of phenytoin in patients who are also taking capecitabine. These patients may require more frequent monitoring of their phenytoin levels and dose adjustments as necessary.

15.4.8.9d Cimetidine may alter the clearance of capecitabine and cause toxic levels. Cimetidine should be avoided while taking capecitabine.

16.0 STATISTICAL CONSIDERATIONS AND METHODOLOGY

16.1 Study Overview

This is a two-group randomized phase II/III trial of the selective use of radiation therapy in intermediate risk rectal cancer. Patients will be randomized to either neo-adjuvant combined modality therapy (treat all group, Group 2) or to initial pre-op chemotherapy with selected use of radiation depending on response to chemotherapy (selected use group, Group 1). Subject to passing all safety and initial efficacy stopping rules, accrual will continue uninterrupted between the phase II and phase III portions of the trial. This phase II/III design is highly efficient in that all patients are randomized and are able to be included in the phase III comparison. The main objective of the phase III component is to evaluate whether clinical outcomes for the selected use group are non-inferior to those of the treat all group based on a sequential decision strategy regarding co-primary endpoints of disease-free survival (DFS) and time to local recurrence (TLR). In the phase II component, the main objective is to closely monitor the safety and early evidence of inferiority of selected use group compared to treat all group based on the pelvic R0 resection rate (RRR) and TLR. The study will not proceed to phase III component if there is evidence that either RRR in the selected use group is lower than in the treat all group, or TLR in the selected use group is shorter than in the treat all group.

Addendum 10 of the N1048 protocol modified the phase III portion to evaluate a single primary endpoint of DFS (see Section 16.3.3).

16.2 Sample Size, Accrual Time, and Study Duration

16.2.1 Sample Size: The study design to be utilized is fully described in Section 16.3. There will be total of 500 evaluable patients randomized to each group of this study (total of 1000 evaluable patients) if the trial completes the full phase III accrual. The phase II portion is defined as the first 366 randomized patients. Current data shows the rate of patients who are not evaluable for primary endpoint to be about 15%. Therefore, we anticipate accruing an additional 90 patients in each group to account for cancellations, major violations, and ineligibility deemed by central imaging review. Thus the maximum accrual is 1180 patients in total.

16.2.2 Accrual Time: Because this study does not involve novel agents, therapies or techniques, we anticipate this study to be straightforward to launch and conduct across sites. The observed accrual rate in the ongoing ACOSOG study (Z6051) in this patient population is about 100 patients per year. This study will be open to Alliance and CTSU sites. We estimate the accrual rate for this study is 200 patients per year. With this accrual rate we plan to accrual the required 1180 patients for the trial in 6 years, which includes the time period for achieving IRB approvals at treating sites after activation of the study.

16.2.3 Primary Endpoint Completion Time Estimation: For the primary endpoint analysis, 3 years of minimum follow-up is required. All patients will be followed for local recurrence, disease-free survival and overall survival for 8 years. Based on statistical design described in Section 16.3, we estimate the primary endpoint data will be mature 8.5 years after the activation of the study, and the results on primary endpoints will be reported 9 years after the activation of the study which includes time for quality control review of the case report forms and data analysis.

16.3 Statistical Design for Primary Endpoints

16.3.1 Primary Endpoints

16.3.1.1 Phase II Component

16.3.1.1.1 The Pelvic R0 Resection Rate (RRR): A pelvic R0 resection is defined in Section 11.0. The pelvic RRR is defined as the number of patients with pelvic R0 resection divided by total number of patients included in the analysis population (see definition in Section 16.3.3.1) in each group. A patient who undergoes a TME and has no tumor identified in the rectal cancer surgical specimen, but is found to have a focus of distant metastatic disease (must be outside the pelvis) such as a microscopic (R1) or macroscopic (R2) focus of liver metastasis would be considered to have a pelvic R0 resection.

16.3.1.1.2 Time to Local Recurrence (TLR): TLR is defined as the time from randomization to the date of the first documentation of local recurrence.

16.3.1.2 Phase III Component

16.3.1.2.1 Time to Local Recurrence (TLR): See Section 16.3.1.1.2. Removed per Addendum 10.

16.3.1.2.2 Disease-free Survival (DFS): DFS is defined as the time from randomization to the date of local recurrence, distant recurrence or death due to all causes whichever comes first. Patients who fail to return for evaluation after beginning therapy will be censored for DFS on the last day of therapy.

16.3.2 Decision Rules and Power Consideration (Original Design)

16.3.2.1 Phase II Component:

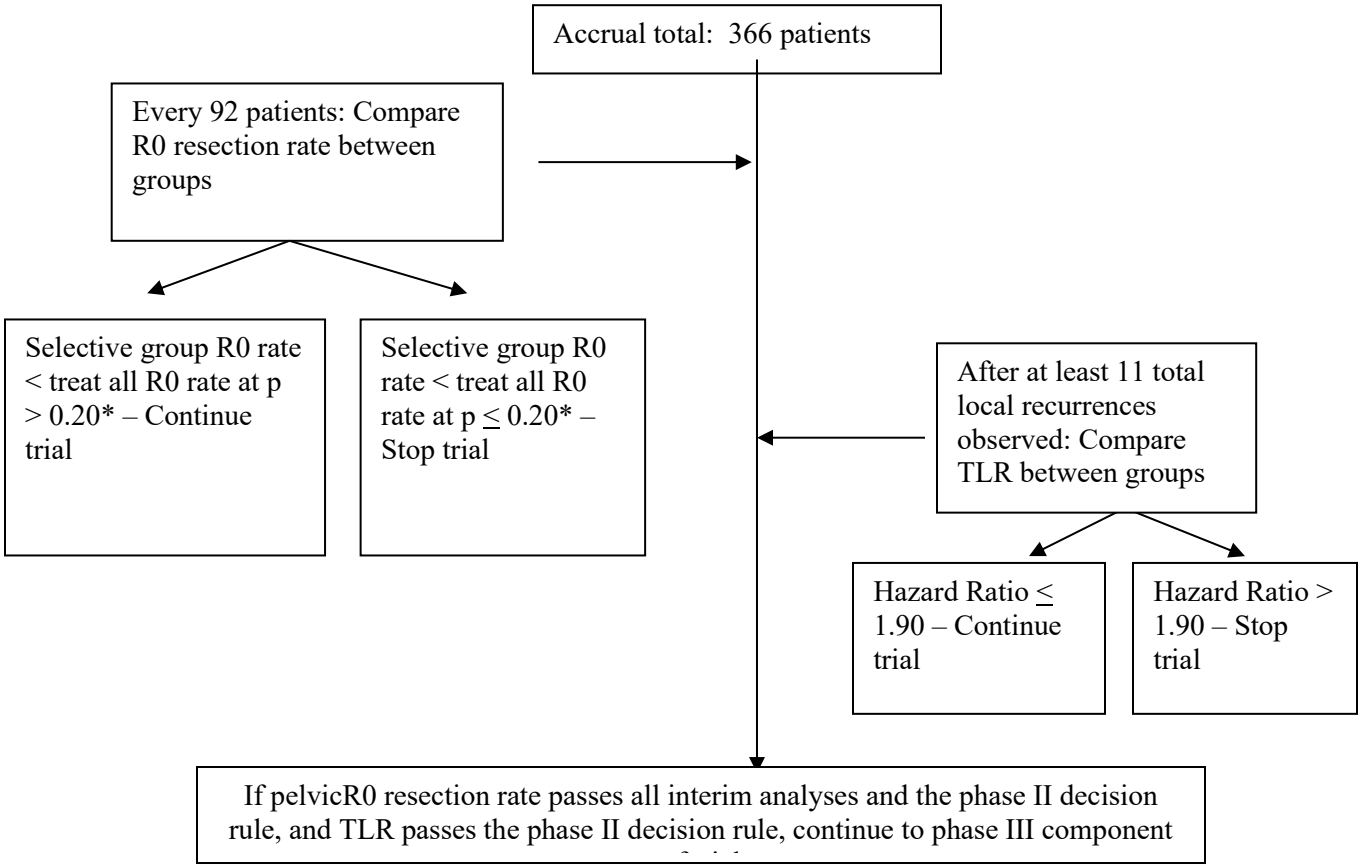
The primary goal of the phase II component of this trial is to 1) assure that the selective use RT group achieves acceptable pelvic R0 resection rate compared to the treat all group and 2) assure that the selective use RT group does not result in inferior TLR. The testing for non-inferiority for the TLR endpoint in the phase II portion will be conducted as an interim analysis integrated into the phase III component at the time of the last pelvic R0 resection rate analysis. DFS will not be considered as an endpoint for testing in the phase II portion. Therefore, the power and sample size considerations are only presented for RRR.

It is expected that the pelvic R0 resection rate will be approximately 90% on each group. A sample size of 366 patients will provide 82% power to detect that the RRR in the treat all group is higher than RRR in selective use group by at least 0.06 (absolute percentage difference) assuming the RRR in selective use group is 87%, based on one-sided test at significance level of 0.20. After the surgery data are available on all 366 patients, the final phase II analysis regarding RRR will be conducted. If the p-value is less than or equal to 0.114, then we will terminate the study and not proceed to phase III component, and conclude that the treat all group is preferred. Three interim analyses will be performed when surgery data are available on the first 92, 184 and 274 patients. The Pocock version of the Lan Demets stopping rules will be used to allow monitoring with a greater likelihood of early stopping for poor results on the selected use group for the RRR endpoint. If p-value is less than or equal to 0.072, 0.088, and 0.102 at three interim looks, respectively, accrual will be suspended and a determination will be made upon review of the data, whether to terminate the trial.

For TLR, the phase II decision-making analysis will be conducted when at least 11 events are observed (approximately 2.4 years after the first patient enrolled). If the HR (selective use vs. treat all) for TLR is less than or equal to 1.90, we will proceed

to phase III component if all RRR conditions are satisfied. Otherwise, we will terminate the study and conclude that treat all group is preferred.

Phase II Analytic Schema:



*p-values adjusted at each look for multiple comparisons based on Pocock stopping boundaries (0.072, 0.088, 0.102, and 0.114)

16.3.2.2 **Phase III Component:**

The primary goal of the phase III component of this trial is to compare combined modality neoadjuvant chemoradiation to the selective use of chemoradiation with respect to the co-primary endpoints of the Disease Free Survival (DFS) and time to local recurrence (TLR). Co-primary endpoints are chosen due to the particularly devastating nature of local recurrence in rectal cancer.

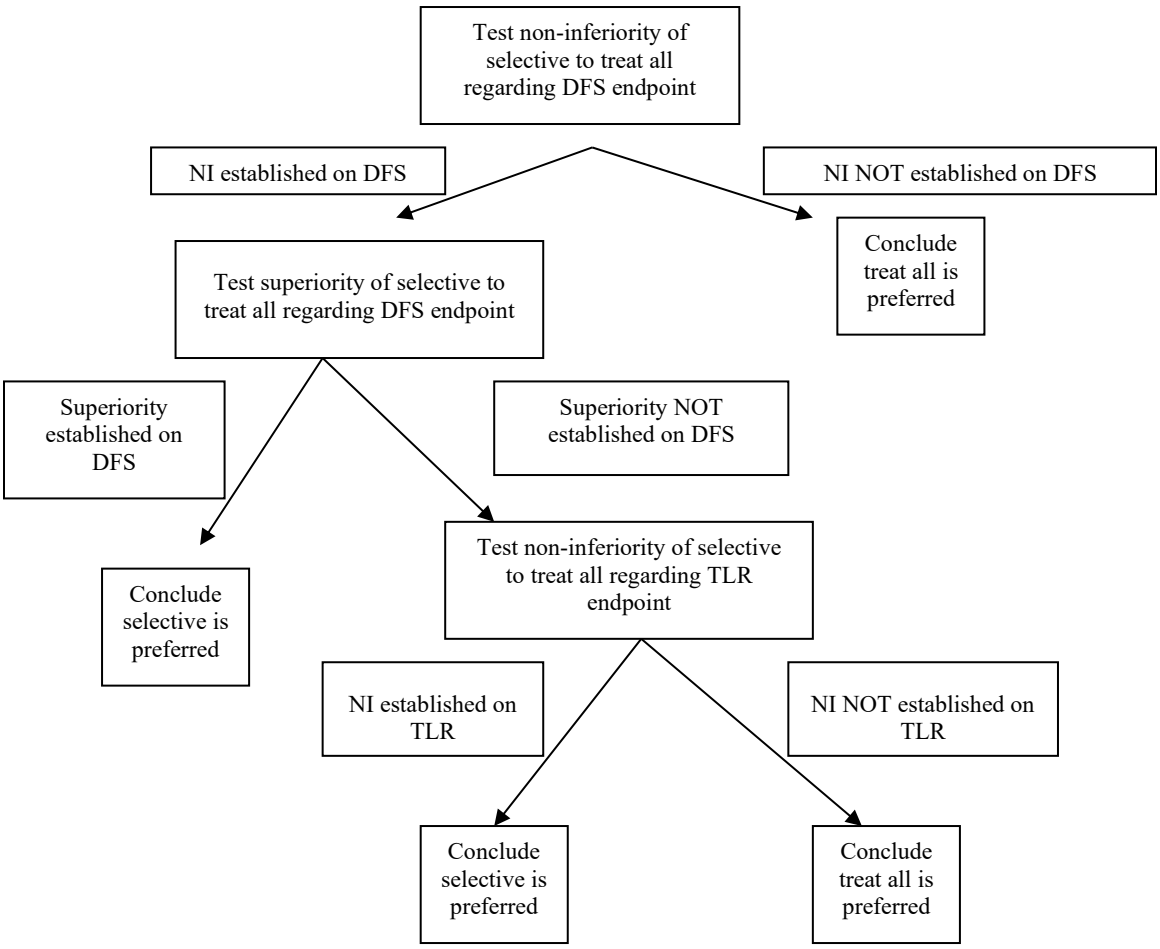
The two co-primary endpoints will be considered jointly based on a sequential decision strategy in the final determination of which approach (selective use versus treat all) is preferred. The selective use group will be favored if either:

1. The selective use group results in superior DFS compared to the treat-all group (regardless of the TLR results), or
2. If the selective use group is at least non-inferior to the treat all group on both DFS and TLR.

The final sequential hypothesis testing procedure for the phase III component will proceed as follows (outlined in Figure 1). First, DFS will be compared between the two groups for non-inferiority of the selective RT use group. If non-inferiority is supported, then the selective use group will be tested for superiority regarding to DFS based on a one-sided test. If non-inferiority is not demonstrated, the treat all group will be declared to be the preferred group. If superiority of the selective use

group on the DFS endpoint is determined, further formal testing will stop for the primary aims and we will conclude that selective use group is preferred. If however non-inferiority but not formal superiority of the selective use group is found based on decision rules for the DFS endpoint, then the co-primary endpoint of TLR will be tested for non-inferiority. If non-inferiority in TLR is supported, the selective use group will be declared to be the preferred group. Otherwise, the treat all group will be declared to be the preferred group. The testing algorithm is outlined in Figure 1 below.

Figure 1: Sequential Hypothesis Testing Plan for Phase III Component



Based on preliminary data and literature review, the expected 3 year DFS rate in the treat-all group is 74%, and the expected 3 year local recurrence rate in the treat all group is 4% (local recurrence-free rate of 96%). The sequential hypotheses testing are designed to test the null hypotheses:

- DFS: the hazard ratio comparing the DFS in selective groups to the treat all group is ≥1.23. This is equivalent, based on design assumptions, to a 3 year DFS rate in the selective use group of 69% vs. 74% in the treat all group.
- TLR: the hazard ratio comparing the time to local recurrence in the selective use group is to the treat all group is ≥1.775. This is equivalent to a 3 year recurrence free rate of 93% in the selective use group vs. 96% in the treat all group.

This level of non-inferiority margin is necessary in order to justify the additional toxicity, long-term complications, and expense of the radiation component of therapy for all patients. We note that rates are quoted here but that all statistical testing will use the full time to event variables of DFS and TLR.

Assuming an accrual rate of 200 patients per year with 3 years of minimum follow-up, 1000 total patients provides 85% power to detect non-inferiority of the DFS and TLR jointly at the overall alpha level of 0.05, if the true DFS in the selective use group is slightly superior (approximately 2% absolute percentage superior at 3 years) to the treat all approach (equivalent to HR=0.91), and the true local recurrence-free in the selective use group is the same as in the treat all group (equivalent to HR = 1). These joint power and overall type I error rate calculations are based on simulation studies with 10,000 replicates, assuming an exponential survival function and a constant accrual rate, including 3 interim analyses for DFS and phase II decision-making (as outlined in Section 16.3.2.1) for TLR. The data generation process in the simulation studies also incorporates the correlation between DFS and TLR, as local recurrence is one component of the composite DFS endpoint.

The final analysis will be conducted when there are at least 406 and 75 events observed for DFS and TLR, respectively. The final sequential decision rules are listed as following:

1. If the HR comparing DFS in the selective use group to the treat all group is greater than 1.115 (in favor of the treat all group), then the treat all group is declared to be preferred, otherwise proceed to the following steps:
2. If the HR comparing DFS in selective use group to treat all group is less than 0.8367, then selective use group is declared to be preferred, otherwise proceed to the following step:
3. If the HR comparing TLR in selective use group to treat all group is less than or equal to 1.44, then the selective use group is declared to be preferred, otherwise the treat all group is declared to be preferred.

EAST version 5 was used to set up the initial decision rules for DFS and TLR separately. For the TLR phase II decision rule, which is equivalent to one interim analysis in phase III portion, was determined using EAST version 5 based on O'Brien-Fleming version of the Lan-Demets stopping rules. Simulation studies were further performed to refine the decision rules according to the joint-testing nature of the final sequential hypothesis testing procedure, and incorporating all the interim analyses in phase II and III portion for DFS and TLR.

Three interim analyses testing for superiority in DFS (selective use vs. treat all, two-sided log-rank test) will be conducted when 102, 230, and 305 have been events observed. The O'Brien-Fleming version of the Lan-Demets stopping rules will be implemented for the DFS interim analyses. If the p-value of the two-sided log-rank test is less than or equal to 0.001, 0.0077, 0.0246 at the three interim looks, respectively, the study will be stopped early and we will conclude that the selective use group is preferred if the HR is less than 1, or the treat all group is preferred if the HR is greater than 1.

All patients enrolled in phase II and III component will be used in the phase III analysis and decision-making. In order to protect the phase III comparison, the

results of the phase II portion will not be released beyond the DMC until all phase III patients have been randomized and have undergone surgery. The independent Data Monitoring Committee will only report whether the criteria for continuation have been satisfied, not any of the actual results.

16.3.2.3 **Study Operating Characteristics:**

The table below shows the study operating characteristics assuming the time-to-event outcomes of DFS and TLR follow exponential survival functions. Table 1 includes the operating characteristics according to the monitoring plan outlined in previous sections. The proportion of times that 1) the study would conclude that the selective use group is preferred at the final analysis of phase III portion, 2) the study would stop early at phase II analysis due to inferiority regarding TLR, 3) the study would stop early at interim analyses due to significant difference in hazard rates between two treatment groups regarding DFS if the study proceeds to phase III portion, are tabulated by true 3-year rates for TLR and DFS by treatment groups.

Table 1: Study Operating Characteristics When Jointly Assessing DFS and TLR

True 3-year rates†				%‡ of times that the study will be stopped early			
LR-free		DFS		%‡ of times that SUA is preferred at the final analysis	Phase II TLR	Phase III DFS interim analyses, if the study proceeds to phase III portion	
TAA	SUA	TAA	SUA		Due to SUA is inferior to TAA	Due to SUA is inferior to TAA	Due to SUA is superior to TAA
0.96	0.93	0.74	0.69	0.045	0.387	0.183	0.000
0.96	0.93	0.74	0.76	0.209	0.385	0.000	0.060
0.96	0.96	0.74	0.69	0.129	0.112	0.289	0.000
0.96	0.96	0.74	0.76	0.846	0.108	0.001	0.080

Abbreviations: LR, local recurrence; DFS, disease-free survival; TAA, treat all group; SUA, selective use group; † Although we use the 3-year rates to illustrate each scenario, the hypothesis testing is based on the entire survival curve. ‡ Proportions are based on 10,000 replicates in the simulation study.

From this table, we see when both LR-free and DFS 3-year rates are at the non-inferiority margin (null hypotheses), there is a 4.5% chance of concluding the selective use group is preferred incorrectly. This is the overall alpha level. When the both true rates of LR-free and DFS are under the non-inferiority alternatives, i.e., the selective use group performs as well as the treat all group on both endpoints, we have 84.6% power to conclude that selective use group is preferred correctly. When either of two endpoints follows the null hypothesis but the other follows the alternative, there is a relatively small chance (12.9% to 20.9%) to conclude that the selective use group is preferred. There is a 57.0% chance that the study will stop early (either at phase II stage or phase III interim looks) due to inferiority of selective use group when both endpoints follow the null hypotheses. There is a 10.9% chance of stopping early due to inferiority of selective use group when both endpoints follow the alternative hypotheses. There is a 38.5% to 40.1% chance that the study will stop early due to inferiority of selective use group when either of the two endpoints follows the null but the other the alternative.

The marginal alpha and power for DFS following the same final non-inferiority testing decision rule with the same interim analyses decision rules, ignoring inference on TLR, are 15.9% and 98.1%, respectively. The marginal alpha and power for TLR following the same final non-inferiority test decision rule with the same phase II decision rule, ignoring inference on DFS, are 15.3% and 85.3%, respectively. We note that the marginal alpha level for each of the endpoints, DFS and TLR, is > 0.05. This is acceptable as for the selective use group to be considered the preferred approach; it must satisfy the non-inferiority bounds for both endpoints. The procedure outlined maintains the overall type I error rate of ≤ 0.05 with acceptable joint power.

16.3.3 Major Re-Design

16.3.3.1 Background:

N1048 (PROSPECT) study was designed with disease-free survival (DFS) and time to local recurrence (TLR) as co-primary endpoints for the phase III portion of the study. The original design was based on the best available information from the literature, expert opinion, and historical data which were accessible prior to 2012. The protocol specified that the primary analyses will be performed after observing at least 406 and 75 events observed for DFS and TLR, respectively to ensure 85% power.

The first patient was randomized on June 11, 2012. Phase II analyses were completed in February 2018, and the study was open to phase III portion. The first Phase III DFS interim analysis per original design was completed in August 2018 when 102 DFS events were observed, and the study continued accrual. The alpha spent was 0.001. The last patient was randomized on December 28, 2018 and the phase III full accrual was reached. The median follow-up time as of February 2021 is 39 months for all evaluable patients (N = 1023, according to the definition in the protocol version 9.0 and prior versions). As of February 2021, the planned 406 DFS events and 75 TLR events have not yet been reached likely due to the higher than expected 3-year DFS rates.

A review of blinded N1048 data revealed that the 3-year DFS rate (combining two treatment arms) is much higher than what was expected in the original design (69%). Recent data reported in January 2021 by Schmoll et al from the PETACC trial also showed higher 3-year DFS rate in the similar disease population. In order to preserve the scientific goal of the trial, a major statistical redesign request was submitted to Group Statistician, [redacted] on Feb 11, 2021. An independent statistician, [redacted] from NRG, was appointed to perform the major redesign in collaboration of CTEP statistician, [redacted] and the study chair. The study statistician, [redacted] was blinded to all redesign conversations. The proposed re-design was completed by [redacted]

16.3.3.2 Updated Statisticial Design for Phase III Portion:

To ensure the timely reporting of the trial results, the following simplifications are made to the statistical design of Phase III portion to reduce the number of DFS events needed while maintaining the overall type I error rate and power.

1) Reduce the number of hypotheses to be tested:

- Remove TLR as one of the co-primary endpoints and include it as one of the secondary endpoints, so the alpha can be preserved solely for the DFS primary analysis.
- Remove the 2nd and 3rd interim analyses in the original design, so the remaining alpha (0.049) can be preserved for the DFS primary analysis.

2) Modify the relative effect sizes (hazard ratio) for the primary DFS non-inferiority hypotheses, but keep the prior absolute effect size in terms of DFS:

- Null hypothesis: The 5-year DFS rate in the selective use group is 75% vs. 80% in treat all group. Same 5% absolute delta as the original protocol but based on 5-year DFS instead of 3. This is equivalent to a non-inferiority margin of hazard ratio (HR) = 1.29, assuming exponential survival functions.
- Alternative hypothesis: The 5-year DFS rate in the selective use group is 82% vs. 80% in treat all group. Same 2% absolute delta as the original protocol but based on 5-year DFS instead of 3. This is equivalent to HR = 0.89, assuming exponential survival functions.

Assuming a lost-to-follow-up rate of 8% annually, a minimal of 210 DFS events are required to achieve 85% power to test the alternative hypothesis against the null hypothesis incidated above.

16.3.3.3 Updated Analysis Timing and Decision Rule for Phase III Portion:

The primary analysis for the single endpoint of DFS will be conducted at the either occurrence of the following:

- Observe at least total of 210 DFS events pooling two arms.
- December 31, 2022 (i.e. 10.5 and 3.5 years after the first and last patient was randomized, respectively) using whatever events are available and possibly accepting reduced power.

At the final analysis, the p-value of testing non-inferiority (against null hypothesis of HR = 1.29) will be calculated based on a stratified Cox model. If this p-value is < 0.049, then the selective use of chemoRT treatment will be considered non-inferior to the treat all approach.

16.3.4 General Analysis Plan

16.3.4.1 **Definition of Analysis Population:**

16.3.4.1.1 Per-Protocol (PP) Population: All randomized patients who received any quantity of the initial chemotherapy FOLFOX or chemoradiation (5FUCMT) before surgery and did not have major treatment violation. Patients will be included in the analysis in the group closest in principle to the initial treatment they actually received. Because the primary testing procedure is non-inferiority testing, the primary analyses of phase II and III component will be conducted based on the PP population.

16.3.4.1.2 Intention-to-treat (ITT) Population: All randomized patients regardless whether received any treatment. Patients will be included in the analysis in the group they

are randomized. ITT population will be used only for sensitivity analysis for primary and/or secondary endpoints when it is applicable.

16.3.4.1.3 Safety Population: All randomized patients who received any quantity of study drug. Patients will be grouped according to treatment received. Safety population will be used for safety related analyses.

16.3.4.2 **General Analysis Plan for Primary Endpoints:**

The analysis plans outlined in this section refer to marginal analysis, i.e., examining each primary endpoint individually.

16.3.4.2.1 Pelvic R0 Resection Rate (RRR): Point estimate and confidence interval (according to approach of Duffy and Santner) will be calculated by treatment groups. The Chi-square test will be used to compare the RRR between groups. Logistic regression will be used for multivariate analysis.

16.3.4.2.2 Disease-free Survival (DFS): The distribution of DFS by group will be estimated using the method of Kaplan-Meier. 3 and 5 year disease free rates by treatment group with confidence intervals based on Kaplan-Meier curves will be reported. Log-rank test will be used to compare DFS between two treatment groups. Hazard ratio with confidence interval will be estimated based on Cox proportional hazard model. The Cox proportional hazard model will be used for multivariate analysis.

16.4 Supplementary Analysis Plans

16.4.1 Secondary Endpoints:

All analyses on secondary endpoints will be conducted on PP population, except Safety population for safety endpoints. ITT population will be used for sensitivity analyses if it is applicable.

16.4.1.1 Time to Local Recurrence (TLR): The distribution of TLR by group will be estimated using the method of Kaplan-Meier. 3 and 5 year local recurrence free rates by treatment group with confidence intervals based on Kaplan-Meier curves will be reported. The comparison of the cumulative incidence of local recurrence between groups, treating distant recurrence and death as competing risks using the test of Gray (Annals of Statistics, 1988) will be conducted.

16.4.1.2 Pathologic Complete Response (pCR): The pCR rate is defined as number of patients who achieve pCR divided by total number of patients included in the analysis population (see definition in Section 16.3.3.1) in each group. Patients who didn't undergo surgery will be classified as non-pCR. Point estimate and confidence interval (according to approach of Duffy and Santner) will be calculated by treatment groups. Chi-square test will be used to compare the pCR rates between groups.

16.4.1.3 Overall Survival (OS): OS is defined as time from randomization to the date of death due to all causes. The distribution of OS by group will be estimated using the method of Kaplan-Meier. Three and five year survival rates by treatment group with confidence intervals based on Kaplan-Meier curves will be reported. Log-rank test will be used to compare OS between two treatment groups. Hazard ratio with confidence interval will be estimated based on Cox proportional hazard model. The Cox proportional hazard model will be used for multivariate analysis.

16.4.1.4 Adverse Event (AE) Profiles: The maximum grade for each type of adverse events during neoadjuvant chemotherapy and chemoradiation therapy, and surgical

complications will be recorded for each patient. The frequency tables will be reviewed to determine patterns. The overall AE rates for Grade3 or higher events, Grade 4 or higher events will be compared between two treatment groups using Chi-square test.

16.4.1.5 Rates of Receiving 5FUCMT: For selective group patients, the proportion of patients who received 1) pre-operative 5FUCMT, 2) post-operative 5FUCMT, 3) either pre or post-operative 5FUCMT, and confidence intervals (according to approach of Duffy and Santner) will be reported.

16.4.1.6 Neoadjuvant Response Score: The Neoadjuvant Response (NAR) score is defined based on the formula devised by George, Allegra, and Yothers (George et al., 2015). The NAR scores between between the two treatment groups will be compared using the Wilcoxon Rank Sum test (continues version) and Chi-square test (categorical version). (The NAR is defined in Section 11.3.3.3).

16.4.2 Clinical and Biological Correlative Studies

The details of the statistical analysis plan for the QOL, PRO-CTCAE, genomic characterization, immunologic and pharmacogenomics studies are contained in Appendices VI, VII, XII, XIII, and XIV.

16.5 Adverse Event Stopping Rule

The study PI, statistician and Research Base Adverse Event Coordinator review all Serious Adverse Events occurring on both groups of the trial on an ongoing basis. In addition, the independent Data Monitoring Committee (DMC) reviews all safety data every 6 months and may convene for a special session when necessary. In addition to this standard safety monitoring we have developed a formal monitoring plan for treatment-related toxicity.

- The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.
- Based on previous experience with this disease, we expect approximately 3% of patients to experience at least one Grade 4+ non-hematologic adverse event which is at least possibly related to the treatment. Therefore, accrual will be temporarily suspended to the study (both Groups) to allow for a full review of data, if any time, we observe events that satisfy either of the following:
    - After 10 patients are randomized to each group (total of 20 patients enrolled), if at any time, in patients who have completed all protocol-specified treatment, the rate of any Grade 4+ adverse events in either group is higher than 15%. All treatment includes preoperative treatment, surgery and postoperative chemotherapy.
    - OR if at any time the 80% two-sided confidence interval for the rate of on study death combining both groups excludes 5% to the right (i.e., includes only values greater than 5%).
- After consideration by the study team (study chair[s], statistician[s], etc.) and DMC, a decision will be made as to whether accrual can be resumed or whether protocol modifications are necessary.

16.6 Accrual Monitoring Stopping Rule

Accrual will be monitored closely. The Investigators including study statisticians and the data monitoring committee will convene monthly conference calls. Input from NCI leadership, the Rectal Anal Task Force, GI Steering Committee, Cooperative Group leadership and Patient Advocates will be obtained on an ongoing basis. During the first 4 months, the team will carefully review the lists of sites that have activated the study and will engage in outreach to sites to understand potential obstacles to activation. After the trial has been open for 4 months, investigators will carefully review accrual based on feedback from sites and will consider whether any amendments need to be made. These amendments will be submitted no later than 6 months from activation. Investigators will evaluate accrual within the 5th to 6th quarter from activation (months 12 to 18). If accrual during this time period is less than 20% of what was projected to meet accrual goals, the study will automatically be closed. If accrual is >20% but less than 50% of what was projected, working together with the Data Monitoring Committee and the National Cancer Institute, we will plan modifications including the potential for closure.

16.7 Study Monitoring

16.7.1 This study will be monitored by the independent Data Monitoring Committee (DMC), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DMC every six months as per NCI guidelines.

16.7.2 This study will be monitored by the Clinical Data Update System (CDUS) version 3. Cumulative Abbreviated CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

16.8 Women and Minorities Distributions

16.8.1 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.8.2 There is no information currently available regarding differential effects of study regimens in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groups, the sample size is not increased in order to provide additional power for subset analysis.

16.8.3 Based on prior studies involving similar disease sites, we expect about 10% patients will be classified as minorities by race and about 45% patients to be women. Expected size of racial by gender subsets are shown in the following table:

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	2	3	0	0	5
Asian	5	7	0	0	12
Native Hawaiian or Other Pacific Islander	31	42	1	1	75
Black or African American	2	3	0	0	5
White	424	529	9	9	971
More Than One	0	0	0	0	0

Race					
Total	464	584	10	10	1068

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	1	1	0	0	2
Native Hawaiian or Other Pacific Islander	3	5	0	0	8
Black or African American	0	0	0	0	0
White	44	56	1	1	102
More Than One Race	0	0	0	0	0
Total	48	62	1	1	112

Ethnic Categories: **Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
Not Hispanic or Latino

Racial Categories: **American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."
Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 RECORDS AND DATA COLLECTION PROCEDURES

For SAKK sites, please refer to the Swiss Specific Appendix for information regarding documentation.

17.1 Data Submission Using RAVE

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to [redacted] for registration types and documentation required.Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at [redacted] or by contacting the [redacted]

For questions regarding forms completion and submission, please contact the Data Manager listed on the Protocol Resources page of the protocol.

17.2 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, ~~and~~ DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

17.3 Submission Timetable

Please refer to the forms packet found on the N1048 study page on the Alliance for Clinical Trials in Oncology and/or the CTSU web site for the most up to date data submission requirements.

18.0 BUDGET

18.1 Costs Charged to Patient

Routine clinical care, all study procedures but the tissue and blood biospecimens required for correlative studies. NOTE: all imaging scans, biopsies, and treatment regimens should be billed

to the patient's insurance company. FOLFOX is standard of care and is incorporated into many practice guidelines for rectal cancer including those put forth by the NCCN.

18.2 Reimbursement

The most up to date details regarding the per-case funding available for patients enrolled onto N1048 may be found on the study funding sheet available on the N1048 study page on the Alliance and CTSU web sites.

18.3 MRI Reimbursement

Pelvic MRIs are standard of care and procedures should be reimbursed by the patients' insurance companies. Every effort will be made to appeal to insurance companies on patient's behalf.

18.4 Correlative Science Funding

Study investigators will seek independent NIH funding to support the correlative science work as well as analyses of QOL assessments. The PRO-CTCAE component is funded under an existing NCI contract (HHS-N261201000063C; PI: Basch).

For more information about per patient reimbursement to sites, please see the Funding Memo available on [redacted] under protocol N1048.

For SAKK sites, please refer to the Swiss Specific Appendix for information regarding translational research costs.

19.0 REFERENCES

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APPENDIX I: PATIENT INFORMED CONSENT VISUAL PRESENTATION

The Patient Informed Consent Visual Presentation can be found as a separate document on the N1048 study-specific webpage on the Alliance and CTSU websites.

APPENDIX II: PATIENT FAQ- PROSPECT RECTAL CANCER STUDY

The Patient Guide for the PROSPECT Rectal Cancer Study can be found as a separate document on the N1048 study-specific webpage on the Alliance and CTSU websites.

APPENDIX III: OPTIONAL PATIENT CAPECITABINE MEDICATION DIARY

Optional Patient Capecitabine Medication Diary (Optional; does not need to be submitted to the Alliance)

Patient Capecitabine Medication Diary
PROSPECT (N1048)

Study ID#: _____

Patients Initials: _____

Starting Dose: _____

INSTRUCTIONS TO PATIENT:

1. Complete on form for the entire period during which you receive radiation therapy and capecitabine. The duration of treatment is usually 5.5 weeks but may be a bit longer if treatment is interrupted for any reasons.
2. Please follow the dosing instructions carefully.
3. Please record the date and approximate times you take the capecitabine tablets. Your physician or nurse will write down your dose and explain to you how many tablets are in your dose.
4. Start taking capecitabine on day 1 and take Monday through Friday while you are receiving radiation treatment.
5. You should take the capecitabine dose prescribed for you by mouth twice a day on Days 1-5, 8-12, 15-19, 22-26, 29-33, and 36-38. Take a dose every morning and a dose every evening, about 12 hours apart. Take the dose with 8 ounces of water each time. It is best to take the dose within 30 minutes after eating food.
6. If you vomit after taking a dose, or if you forget to take a dose, please note it on this diary, and do not take capecitabine again until your next scheduled dose.
7. The use of a daily moisturizer to hands, feet and face are commended. Please use sunscreen if you are going outdoors.
8. Please contact your health care team with any questions or for help understanding exactly how to take your medicine.
9. Bring this Medication diary with you when you meet with your doctor each week.

PLEASE CONTINUE TO PAGE 2

Day	Date	Approximate times tablets taken	
		a.m.	p.m.
1			
2			
3			
4			
5			
6	**Do not take capecitabine tablets today**	--	--
7	**Do not take capecitabine tablets today**	--	--
8			
9			
10			
11			

12			
13	**Do not take capecitabine tablets today**	--	--
14	**Do not take capecitabine tablets today**	--	--
15			
16			
17			
18			
19			
20	**Do not take capecitabine tablets today**	--	--
21	**Do not take capecitabine tablets today**	--	--
22			
23			
24			
25			
26			
27	**Do not take capecitabine tablets today**	--	--
28	**Do not take capecitabine tablets today**	--	--
29			
30			
31			
32			
33			
34	**Do not take capecitabine tablets today**		
35	**Do not take capecitabine tablets today**		
36			
37			
38			
39	**Do not take capecitabine tablets today**		

_____ _____

Patient signature **Date**

Physician's office will complete this section:

1. Date patient started radiation therapy: _____
2. Date patient completed radiation therapy: _____
3. Date patient started capecitabine: _____
4. Date patient finished capecitabine: _____

Physician/Nurse/Data Manager's signature _____Date_____

APPENDIX IV: SUGGESTED DOSE MODIFICATION OF CAPECITABINE

Dose Modification of Capecitabine During 5FUCMT

Capecitabine tablets are available as 150mg and 500mg sizes and doses therefore need to be rounded since splitting tablets is difficult and imprecise. The following tables are provided for the convenience of treating clinicians in order to provide patients with clear dosing instructions based on BSA and total daily dose. The need to provide patients with clear written instructions and of monitoring adherence is an essential component of dispensing oral chemotherapy such as capecitabine.

Dosing Table Based Upon Body Surface Area Calculation:
Capecitabine Starting Dose

Dose level 1650mg/m^2/d		AM 150 mg	AM 500mg	PM 150mg	PM 500mg
BSA (m^2)	Total Daily Dose (mg)				
<1.24	2000	0	2	0	2
1.25-1.36	2150	1	2	0	2
1.37-1.51	2300	1	2	1	2
1.52-1.64	2600	2	2	2	2
1.65-1.76	2800	1	3	1	2
1.77-1.91	3000	0	3	0	3
1.92-2.04	3150	1	3	0	3
2.05-2.17	3300	1	3	1	3
>2.18	3600	2	3	2	3

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

Dose 1237 mg/m^2/d		AM 150 mg	AM 500mg	PM 150mg	PM 500mg
BSA (m^2)	Total Daily Dose (mg)				
<1.24	1500	0	2	0	1
1.25-1.36	1650	1	2	0	1
1.37-1.51	1800	1	2	1	1
1.52-1.64	1950	2	2	1	1
1.65-1.76	2150	1	2	0	2
1.77-1.91	2300	1	2	1	2
1.92-2.04	2450	2	2	1	2
2.05-2.17	2500	0	3	0	2
>2.18	2650	1	3	0	2

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

Dose level 825 mg/m^2/d		AM 150 mg	AM 500mg	PM 150mg	PM 500mg
BSA (m^2)	Total Daily Dose (mg)				
<1.24	1000	0	1	0	1
1.25-1.36	1150	1	1	0	1
1.37-1.51	1150	1	1	0	1
1.52-1.64	1300	1	1	1	1
1.65-1.76	1450	2	1	1	1
1.77-1.91	1500	0	2	0	1
1.92-2.04	1650	1	2	0	1
2.05-2.17	1650	1	2	0	1
>2.18	1800	1	2	1	1

Adapted from RTOG study 0247 “A Randomized Phase II Trial of Neoadjuvant Combined Modality Therapy for Locally Advanced Rectal Cancer”

APPENDIX V: PATIENT-REPORTED OUTCOMES

Patient-Reported Outcomes: Evaluation of the Clinical Value and Feasibility of the Patient-reported Outcomes Version of the Common Terminology Criteria (PRO-CTCAE)

1. Correlative Study Background

The PRO-CTCAE is a group of items currently being developed by the NCI for direct electronic patient-reporting of adverse symptoms via the Web or automated telephone system, in order to complement the CTCAE (Basch, 2010). Development and testing of the PRO-CTCAE is funded under an NCI contract (HHS-N261201000063C). This contract includes assessment of the feasibility of implementing the PRO-CTCAE in cooperative group treatment trials, which is the primary aim of the PRO-CTCAE correlate in this trial. To date, 78 symptoms in the CTCAE have been developed for patient self-reporting via the PRO-CTCAE, and have undergone refinement in a cognitive testing study (Hay, 2010). A validation study of the PRO-CTCAE is near completion, with interim descriptive statistics supporting validity of the items, and a final analysis planned for December 2011. The items are now ready for assessment of feasibility of electronic implementation in a cooperative group trial, in order to assess the ability and effort at sites to use the system, and the extent to which study participants are willing and able to use the system throughout treatment.

In this correlative study, all patients enrolling in the phase II and phase III portions of the clinical trial will be required to self-report selected PRO-CTCAE symptoms at baseline, once every week during active treatment, and once every 6 months for three years following surgery, via an automated electronic system.

Patients will be given a choice to report either via an automated telephone system (interactive voice response system [IVRS]), or via Web. The electronic system for administering the PRO-CTCAE items has previously been developed, is hosted and maintained on servers at the NCI, and has undergone rigorous safety and privacy assessment per NCI requirements. This reporting will be completed by patients from home. It will be made clear in the training and software that the PRO-CTCAE information being collected is for research purposes only, and is not being monitored by a clinician. Therefore, patients will be advised to directly contact their doctor's office for any symptoms of concern.

The work for site personnel will consist of training patients to use the system; registering patients into the system; printing PRO-CTCAE patient symptom reports at preoperative visits for reference when documenting study AEs (Sites will be randomly assigned at the time of training by the PRO-CTCAE Coordinator to report adverse events either by: a) using the Solicited AE Form from the paper forms packet posted on the CTSU website or: b) using a Solicited AE Form generated from the PRO-CTCAE system which contains the patient's PRO-CTCAE scores); and completing a feasibility survey/discussion about experiences using the system.

2. Specific Hypotheses

The primary hypothesis of this correlative study is that study sites will be willing and able to register patients to use the PRO-CTCAE; that this activity will incur a minimal incremental effort; and that patients will be willing and able to self-report via the PRO-CTCAE throughout treatment.

The secondary hypothesis of this correlative study is that patient-reported PRO-CTCAE data will be able to detect differences in symptoms between study groups.

The exploratory hypothesis of this correlative study is that exposure to printed patient-reported symptoms

will increase the severity of symptom reporting by research staff for symptoms known to be associated with the trial's neoadjuvant treatments.

3. PRO-CTCAE Training and Reporting for Site Study Staff and Patients

Note: At least one staff personnel from the site study team should be credentialed to perform patient PRO-CTCAE training and registration before the first study participant's baseline visit.

For further information about site credentialing for PRO-CTCAE, site training and reporting and patient training and reporting, please refer to protocol Section 4.4.

4. Statistics

For the primary hypothesis, descriptive statistics will be used to characterize the proportion of sites where patients are enrolled onto this correlative study and the proportion of participating patients adhering to scheduled self reports at each time point during the trial. Qualitative information about the feasibility of implementing the PRO-CTCAE at sites will be collected via a survey of study personnel and clinical research staff at participating sites. Moreover, site personnel will be asked in the survey if they are willing to participate in a brief semi-structured discussion by telephone or in person regarding their experiences with this new system (including effort/cost, technical issues, and administrative burden). These discussions will be conducted with staff members of the PRO-CTCAE project. In addition, the frequency of backup reminders and success of backup reminders for questionnaire completion will be evaluated.

For the secondary hypothesis, the patient-reported maximum score (post baseline) for each frequency/severity/interference item for each patient will be computed and compared between groups using a two-sample independent samples t-test. Present/absent items will be analyzed similarly, however, using a chi-squared test. Multiple testing will be handled using Hochberg's step-up method.

Power (gender-neutral t-tests): Assuming that 70% patients are eligible to participate in this correlative study and provide data (i.e., N= 700 with reported scores for a given gender-neutral frequency/severity/interference question), we will have 80 % power to detect a 0.30 standard deviation difference between groups using a t-test. With this sample size, we will have 90 % power to detect a 0.34 standard deviation difference between groups using a t-test. Estimates are based on a two-sided $\alpha=0.05/30=0.00167$ two-sample t-test using a Bonferonni correction. We base calculations on the more conservative Bonferonni correction but plan to handle multiple testing using Hochberg's step-up method. With 70 % participation, this study will be able to detect small (0.2 standard deviations) to moderate (0.5 standard deviations) effect size differences between groups (Cohen, 1988).

Power (gender-neutral chi-squared tests): With N=700, we have 80 % and 90 % power to detect a Cohen's w of 0.15 or 0.17, respectively, using a chi-squared test in testing for association between "present" vs. "not present" and group. Cohen's w of 0.3 is considered a moderate effect size (Cohen, 1988). If the number of responders is somewhat less than N=700, a sample size of N=500 provides 80 % and 90% power to detect a Cohen's w of 0.18 and 0.20, respectively.

Power (gender-specific t-tests): For gender-specific t-tests, we assume that approximately 65% of patients will be male. With N=455 males agreeing to participate in this correlative study and providing data, we will have 80 % and 90 % power to detect a 0.38 and 0.42 standard deviation difference between groups using a t-test, respectively. With N=245 females agreeing to participate in this correlative study and providing data, we will have 80 % and 90 % power to detect a 0.52 and 0.57 standard deviation difference between groups using a t-test, respectively. If the number of responders is somewhat less (e.g., for sexual functioning questions), a sample size of N=325 males provides 80 % and 90 % power to detect

a 0.45 and 0.50 standard deviation difference between groups using a t-test, respectively; and N=175 females provides 80 % and 90 % power to detect a 0.61 and 0.68 standard deviation difference between groups using a t-test, respectively.

Power (gender-specific chi-squared tests): Present/absent gender-specific questions are only assessed for females so power is provided for N=245 females. A sample size of N=245 females provides 80% and 90% power to detect a Cohen's w of 0.25 and 0.28, respectively. If the number of responders is somewhat less, a sample size of N=175 females provides 80 % and 90 % power to detect a Cohen's w of 0.30 and 0.33, respectively.

Additional analyses will include a comparison of the incidence of patient-reported maximum score ≥3 (i.e., severity reported as "severe" or "very severe"; frequency reported as "frequently" or "almost constantly"; or interference reported as "quite a bit" or "very much") between groups using chi-squared testing for each item; and a comparison of the time to patient-reported score ≥3 between groups using Kaplan-Meier and log-rank analyses. Further, these three endpoints (maximum score/grade, incidence of score/grade ≥3, and time to score/grade ≥3) will be compared between patient- and clinician-report overall and within groups using appropriate paired analyses. The PRO-CTCAE items related to bowel and genitourinary function will be further validated by computing Pearson correlations between each of these items and associated patient-reported outcomes (bowel, bladder, and sexual function, pain, and health-related quality of life) collected as part of the Quality of Life study at the 12-month and 24-month post-surgery assessment time points.

Anticipated differences in toxicities between arms which we hypothesize the PRO-CTCAE system will detect include: 1) In the control arm, toxicities related to chemoradiation during the first 6 weeks will include increasing perineal pain, diarrhea, and fatigue which should improve by week 9; no peripheral neuropathy is anticipated due to lack of oxaliplatin. 2) In the intervention arm including FOLFOX, more of a steady state pattern is expected with relatively less diarrhea and less pain, but more nausea and more peripheral neuropathy.

For the exploratory analysis involving a comparison of symptom severities between patients at sites randomized to (1) printing of PRO-CTCAE responses vs. (2) no printing of PRO-CTCAE responses, the clinician-reported maximum grade (post baseline) for each AE for each patient will be computed and compared between groups using a generalized linear mixed model including a fixed effect for randomized group (print vs. no print) and a random effect for site-specific mean intercepts (sites are nested within the randomized arm). Similar models will also be developed to compare AE severity over time between the randomized groups. Assuming that 70 % of patients agree to participate in this correlative study and have reported data (i.e., N=700 with reported clinician grades for a given AE), we have 80% power to detect a 0.42 standard deviation difference between groups without adjustment for multiple AE comparisons. This power calculation assumes that 5 patients will be accrued at each site and conservatively that the intracluster correlation coefficient is strong (= 0.7).

5. PRO-CTCAE Question Bank

1. In the last 7 days, what was the SEVERITY of your **NUMBNESS OR TINGLING IN YOUR HANDS OR FEET** at its WORST:
    - None / Mild / Moderate / Severe / Very severe

2. In the last 7 days, how much did **NUMBNESS OR TINGLING IN YOUR HANDS OR FEET** INTERFERE with your usual or daily activities:
    - Not at all / A little bit / Somewhat / Quite a bit / Very much

3. In the last 7 days, how OFTEN did you have **LOOSE OR WATERY STOOLS (DIARRHEA)**:
    - Never / Rarely / Occasionally / Frequently / Almost constantly

4. In the last 7 days, did you have any RASH:
    - Yes / No

5. In the last 7 days, what was the SEVERITY of your **CONSTIPATION** at its WORST:
    - None / Mild / Moderate / Severe / Very severe

6. In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST:
    - None / Mild / Moderate / Severe / Very severe

1. In the last 7 days, how much did **MOUTH OR THROAT SORES** INTERFERE with your usual or daily activities:
    - Not at all / A little bit / Somewhat / Quite a bit / Very much

2. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST:
    - None / Mild / Moderate / Severe / Very severe

3. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities:
    - Not at all / A little bit / Somewhat / Quite a bit / Very much

4. In the last 7 days, how OFTEN did you have PAIN:
    - Never / Rarely / Occasionally / Frequently / Almost constantly

5. In the last 7 days, what was the SEVERITY of your PAIN at its WORST:
    - None / Mild / Moderate / Severe / Very severe

6. In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities:
    - Not at all / A little bit / Somewhat / Quite a bit / Very much

7. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST:
    - None / Mild / Moderate / Severe / Very severe

8. In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities:
    - Not at all / A little bit / Somewhat / Quite a bit / Very much

9. In the last 7 days, how OFTEN did you have NAUSEA:
    - Never / Rarely / Occasionally / Frequently / Almost constantly

10. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST:
    - None / Mild / Moderate / Severe / Very severe

11. In the last 7 days, how OFTEN did you have **VOMITING**:
    - Never / Rarely / Occasionally / Frequently / Almost constantly

12. In the last 7 days, what was the SEVERITY of your **VOMITING** at its WORST:
    - None / Mild / Moderate / Severe / Very severe

13. In the last 7 days, what was the SEVERITY of your **DIFFICULTY SWALLOWING** at its WORST:
    - None / Mild / Moderate / Severe / Very severe

14. In the last 7 days, what was the SEVERITY of your **SHORTNESS OF BREATH** at its WORST:
    - None / Mild / Moderate / Severe / Very severe

15. In the last 7 days, how much did **SHORTNESS OF BREATH** INTERFERE with your usual or daily activities:
    - Not at all / A little bit / Somewhat / Quite a bit / Very much

16. In the last 7 days, how OFTEN did you FEEL **ANXIETY**:
    - Never / Rarely / Occasionally / Frequently / Almost constantly

17. In the last 7 days, what was the SEVERITY of your **ANXIETY** at its WORST:
    - None / Mild / Moderate / Severe / Very severe

18. In the last 7 days, how much did **ANXIETY** INTERFERE with your usual or daily activities:
    - Not at all / A little bit / Somewhat / Quite a bit / Very much

19. In the last 7 days, how OFTEN did you **FEEL THAT NOTHING COULD CHEER YOU** UP:
    - Never / Rarely / Occasionally / Frequently / Almost constantly

20. In the last 7 days, what was the SEVERITY of your **FEELINGS THAT NOTHING COULD CHEER YOU UP** at their WORST:
    - None / Mild / Moderate / Severe / Very severe

21. In the last 7 days, how much did **FEELING THAT NOTHING COULD CHEER YOU UP** INTERFERE with your usual or daily activities:
    - Not at all / A little bit / Somewhat / Quite a bit / Very much

22. In the last 7 days, how OFTEN did you have **ARM OR LEG SWELLING**:
    - Never / Rarely / Occasionally / Frequently / Almost constantly

23. In the last 7 days, what was the SEVERITY of your **ARM OR LEG SWELLING** at its WORST:
    - None / Mild / Moderate / Severe / Very severe

24. In the last 7 days, how much did **ARM OR LEG SWELLING** INTERFERE with your usual or daily activities:
    - Not at all / A little bit / Somewhat / Quite a bit / Very much

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APPENDIX VI: FUNCTIONAL OUTCOMES AND QUALITY OF LIFE

Functional Outcomes and Quality of Life after Rectal Cancer Therapy: A Comparison Between Patients Randomized to Selective Pre-operative Radiation vs. Traditional Pre-operative Chemoradiation

Background

Significant long term sequelae of rectal cancer therapy exist and alterations in bowel, bladder and sexual function are prevalent. Many factors (i.e., age, gender, level of tumor, level of anastomosis, reconstructive techniques, timing of radiation, temporary diversion) are frequently reported to affect long term outcomes. The data almost uniformly suggest that radiation significantly impacts function (Temple et al., 2003; Thong et al., 2011). In a recent prospective longitudinal study of 168 patients treated for rectal cancer, there was significant bowel and sexual dysfunction at 12 months, particularly amongst patients treated with pre-operative radiation (Lee et al., 2010; Temple et al.., 2010). While measurement has varied, RCTs and population based studies comparing pre-operative short course radiation results in worse bowel, bladder and sexual function (Bruheim et al., 2010b; Bruheim et al., 2010a; Murata et al., 2008; Stephens et al., 2010; Lange and van de Velde et al., 2008; Lange et al., 2008).when compared to surgery alone. Although no comparisons have been made between short and long course RT, function is also significantly affected by standard long course radiation (Sauer et al., 2004; Pucciarelli et al., 2011; Parc et al., 2009; Wilson and Alexander, 2008; Hoerske et al., 2010).

While it is clear that radiation impacts long term outcomes, there are many unanswered questions. To date, there has been no single institution, cohort or randomized trial that has evaluated the functional outcomes of a selective approach to chemoradiation. Most studies report bowel function symptoms (i.e., incontinence) rather than a global score so that it is difficult to determine the actual overall effect of radiation. When studies report global bowel function, they typically use an EORTC-CRC38 subscale which may not be a sensitive enough measure to assess issues faced in patients with sphincter preserving surgery (Neuman et al., 2007). Some studies did not require TME (Sebag-Montefiore et al., 2009) and as such surgical injury to the nerves may have confounded the results, particularly with respect to sexual function. Sexual function has been infrequently studied, particularly in women. When studied, response rates in women are often so low that data were not meaningful (Ho et al., 2011). There are several studies that have demonstrated that global QOL is high after treatment for rectal cancer (Thoneg et al. 2011; Wilson et al., 2008; Engel et al., 2003; Camilleri-Brennan and Steele, 2001; Savatta and Teple, 2005; Jess et al., 2002). However, there has been little work done to evaluate the relationship between QOL and function. While there are some data that suggest that QOL can be affected by function (Bruheim et al., 2010; Stephens et al., 2010; Wilson and Alexander, 2008; Hoerske et al., 2010), it has never been studied in a systematic manner and the studies have been small. Systematic collection of rectal cancer related QOL data will permit comparison of the neoadjuvant combined modality therapy approach and the selective approach. This will permit evaluation of the impact of pelvic radiation on long term QOL.

The functional and quality of life outcomes in this trial would influence the preferred treatment group, particularly if survival and recurrence outcomes are similar. If oncologic non-inferiority is established between selective vs. standard 5FUCMT, then the rationale supporting selective use of 5FUCMT may be that long term disease specific quality of life is better. While we hypothesize that the patients in the selective radiation group will have better function than patients with upfront chemoradiation, there will be patients in the selective 5FUCMT who will require post-operative radiation. The European trial which compared pre and postoperative chemoradiation included a QOL component and the QOL results influenced the overall interpretation that favors preoperative treatment approach (Sauer et al., 2004). Thus, the benefit of selective radiation may be mitigated by the detrimental effect of post operative radiation in the selective group. Depending on the number

of patients and the actual detrimental effect of post operative radiation, the overall function in the selective pre-operative radiation group could be worse. Thus, in establishing a new paradigm for the treatment of rectal cancer, it is very important to compare the functional outcomes and quality of life outcomes using these treatment strategies. The QOL companion to this study will use validated instruments to compare overall health related quality of life (HRQOL) as well as disease specific quality of life with emphasis on the specific domains of interest in rectal cancer, bowel, bladder and sexual function.

Objectives

Primary Objective:
To compare bowel function in patients randomized to selective pre-operative radiation vs. traditional pre-operative radiation at 12 and 24 months post-operatively. We hypothesize that patients randomized to the selective RT group will have superior bowel function at each of these time points compared to patients randomized to the traditional pre-operative radiation.

Secondary Objective:

1. To compare sexual function separately within men and within women between groups at 12 and 24 months post-operatively. We hypothesize that men and women randomized to the selective RT group will have superior sexual function at each of the post-operative time points compared to patients randomized to the traditional CMT group.
2. To compare bladder function between groups at 12 and 24 months post-operatively. We hypothesize that bladder function will be superior in patients randomized to the selective RT compared to patients randomized to the traditional CMT group at each of the post operative time points.
3. To compare health-related quality of life between groups at 12 and 24 months post-operatively. We hypothesize that patients randomized to the selective RT group will not have inferior health-related quality of life at each of these time points compared to patients randomized to the traditional CMT group.

Exploratory Objectives:
To assess the correlation between bladder, bowel, and sexual function and quality of life; to investigate factors associated with bladder, bowel, and sexual dysfunction; to compare bladder and bowel function over time between genders; and to perform subgroup analysis by language.

Methods

All patients randomized in the phase II or phase III component of the study who are fluent (reading/speaking) in English will be asked to participate in this correlative study until the target number of patients has been accrued. Patients will complete a booklet on paper during a clinic visit at designated time points. Patients must use pre-printed questionnaire booklets ordered from the CTSU website. (Note: There are 2 versions of the QOL booklet. One for males and one for females. Be sure to order both male and female QOL booklets from CTSU.) Study booklets will be completed in clinic at the time of study consent prior to neoadjuvant therapy, 1-2 weeks prior to surgery (after neo-adjuvant therapy is completed, ideally, at time of surgical consent) and post-operatively at approximately 12 months +/- 6 weeks and 24 months +/- 6 weeks after rectal resection. The post-operative time points will be anchored to rectal resection and in general, correspond to approximately 15-18 and 27-30 months after randomization depending on the neoadjuvant therapy and rectal resection. In the event that the patient has a stoma at the 12 and/or 24 month intervals, given the nature of the bowel function items, they will be deemed ineligible to complete the survey for that time point. The booklets will be administered by the site research staff. For sites using RAVE, enter the patient responses from the QOL booklet into RAVE and keep the original QOL booklet that contains patient responses at your site. If a patient does not have an appointment, misses a clinic visit and/or is missed by the study staff at the designated time points, the study center research coordinator will contact the patient via telephone and will ask the patient to complete the booklet by telephone/mail. In the event that the patient completes the survey via telephone, the sexual function

questions (items #20-34 MEN, #20-38 WOMEN) will not be asked. In the event that the patient chooses to complete the survey via mail, a stamped self addressed return envelope should be included with the booklet. In the event that the patient cannot be contacted by telephone, a booklet and stamped self addressed envelope should be mailed to the patient's home. If the coordinator is still not able to have the patient complete the booklet, a noncompliance form will be completed stating the reason for the missing assessment.

QOL Forms Employed

Patients will receive one survey packet that will include 42 (men) or 46 (women) items depending on the patient's gender. To assess bowel function, the19 item Bowel Function Index (Temple et al., 2005) will be used. To assess sexual function, we will use gender specific questionnaires: the International Index of Erectile Function (Rosen et al., 1997) and the Female Sexual Functioning Index (Rosen et al., 2000). Bladder function will be assessed using two items from validated questionnaires. We will assess global HRQL using the EuroQOL5D-5L which evaluates domains of pain, anxiety, physical function, ambulation and activities of daily living as well as the linear analogue scale. These instruments have been embedded in many prior NCCTG and CALGB clinical trials and reproducibly assess health related quality of life in a succinct manner. The entire functional assessment can be completed in less than 30 minutes with an average of 15-20 minutes per patient.

Bowel function will be measured using the 19 item Bowel Function Index (BFI). The BFI was developed to specifically assess bowel function after sphincter preserving surgery in patients treated for rectal cancer [25] and has recently been further validated in Europe (Zotti et al., 2011). It includes 18 items with three subscales and a total score and is written at an eighth-grade level. In addition, we will include an additional item in the BFI (question #19) that will ask patients about their global assessment of how much their bowel function changed in the last month using a 5 point Likert scale. This instrument takes no more than 5 minutes to complete.

Sexual function will be assessed with gender specific surveys. For men, the IIEF (Rosen et al., 1997) will be used. It consists of 15 questions with 5 domains (erectile function, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction), has good internal consistency (0.71-0.91) and test-retest reliability (0.71-0.84), and has been widely used. It takes about 10 minutes to complete. For women, the FSFI (Rosen et al., 2000) consists of 19 questions with 6 domains (desire, subjective arousal, lubrication, orgasm, satisfaction and pain). This instrument has demonstrated good internal consistency (0.89-0.96, 0.97), and high test-retest reliability for the 6 domains (0.79-0.86, 0.88) and global score, as well as good validity. It takes about 10 minutes to complete.

Bladder function will be assessed using 2 items from 2 well validated instruments, the Prostate Health Related QOL questionnaire (Befort et al., 2005) and the International Prostate Symptom Score (IPSS) (Barry et al., 1992). Given the problems associated with rectal cancer patients typically are urinary retention and continence, we have included questions about incomplete evacuation and leakage. The questions are specifically directed at bladder dysfunction, and are gender neutral. This takes less than 1 minute to complete.

Health-related quality of life will be assessed using the EuroQOL5D-5L (EQ5D) (euroqol website; Herdman et al., 2011). This is a widely used descriptive system of health-related quality of life states. It consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems or unable to function) within a particular EQ5D dimension. The EQ5D is almost always combined with a simple linear analogue scale that asks respondents to rate their overall health on a vertical scale of 0 to 100.

Statistical Considerations

All items/questionnaires will be scored according to published scoring guidelines. Descriptive statistics will include means, standard deviations, medians, and ranges for each continuous or ordinal scale/subscale/item by group at each

time point. Descriptive graphical techniques will include mean plots by group for each continuous or ordinal scale/subscale/item. Relative frequencies of responses for each ordinal item will also be generated at each time point by group.

Analyses

The primary analysis will compare bowel function between groups at 12 and 24 months. Specifically, the primary analysis will consist of two hypothesis tests and adjustment for multiple testing will employ the Bonferonni method. The hypothesis tests will use two-sided alpha=0.05/2=0.025 two-sample t-tests to compare the BFI overall score between groups at the 12-month and 24-month time points.

Supplement analyses to the primary analyses will include (1) analyses of covariance to compare means between groups or estimate confidence intervals for the mean difference between groups at the 12-month and 24-month time points while adjusting for the baseline value of the given score; (2) repeated measures analyses to compare scores over time; and (3) similar analyses as described for the primary analyses however applied to the other subscales/items of the BFI.

For the secondary objective, the total IIEF and FSFI score will be compared between groups (within males and within females, respectively) at 12 and 24 months using two-sample t-tests followed by analysis of covariance adjusting for the baseline value at each time point. Each ordinal score on the two bladder function items will be compared between groups at 12 and 24 months using two-sample t-tests followed by analysis of covariance adjusting for the baseline value at each time point. Health related quality of life comparisons will employ confidence intervals for the difference between groups (mean for the selective RT group minus the mean for the traditional CMT group) in mean EQ5D summary index at the 12-month and 24-month time points. If the lower limit of the two-sided 95% confidence limit falls above -0.05, then we will deem health related quality of life of patients in the selective RT group noninferior to that of patients in the traditional CMT group at the given time point. A difference of 0.05 is felt to be a conservative estimate of the minimally important difference in the EQ5D summary index based on a 0.33 standard deviation difference in N=534 US and English-speaking Canadian cancer patients when using ECOG performance status as an anchor (Pickard et al., 2007). If non-inferiority of health related quality of life in the selective RT group is concluded at a given time point, we will additionally test for superiority using a two-sample t-test followed by analysis of covariance adjusting for the baseline health related quality of life.

For the exploratory objective, Pearson correlations will be computed among each continuous or ordinal bowel, bladder, and sexual function scale/subscale/item, the EQ5D summary index, and EQ-VAS and at each time point. Correlations with sexual function scales/subscales/items will only be computed within gender subgroups. Regression models will be used to model each bowel, bladder, and sexual function scale/subscale/item at the 12-month and 24-month time points using baseline patient/disease characteristics and patient-reported outcomes at baseline. Repeated measures analyses will be used to compare bladder and bowel function over time between genders. Such analyses will be adjusted for group and will be supplemented with appropriate two-sample comparisons at each time point. Lastly, primary and secondary analyses will be repeated within subgroups according to language.

Missing data will be handled in a number of ways. Baseline patient/disease characteristics will be compared between responders and nonresponders for each endpoint. We will also graphically explore patterns of missing data. All analyses will be completed using all available data, followed by analyses completed using imputed data using the last observation carried forward. Lastly, we will employ pattern mixture models for longitudinal analyses. Output from all analyses will be compared to assess the degree to which missing data impacts study results.

For all statistical analyses other than the primary analyses, p-values <0.05 will be considered statistically significant. For interpreting the clinical significance of effects, 0.2, 0.5, and 0.8 SD effects will be considered as small, moderate, and large based on Cohen (Cohen, 1988) throughout.

Power: We will use Bonferonni adjustment for handling two primary hypothesis tests. We plan to accrue 460 patients to allow for missing data (25%) for reasons including patient refusal, administrative error (e.g., coordinator failed to give a booklet to a patient), missing items due to lack of applicability (e.g., if a patient does not have the temporary ileostomy reversed some bowel items may not be applicable), patient drop-out or death due to metastatic disease, and other reasons. Based on data from the validation of the BFI, patients not receiving pre-operative RT had a mean score of 54.8 (SD=9, n=45) and patients receiving pre-operative RT had a mean score of 48.6 (SD=10.2, n=67). In the current study, we do not expect as large a difference between groups but reasonably expect a mean score of about 48.6 in the traditional CMT group (similar to the pre-operative RT in the validation study) and a 60%/40% weighted average or a mean score of about 52.3 in the selective RT group with a pooled standard deviation of 9.7. With data for 344 patients (assuming a 25% missing data rate), we have 90% power to detect this 3.7 point difference between groups at a given time point using a two-sided alpha=0.025 two-sample t-test.

This sample size also gives reasonable power for the secondary comparison of sexual function between groups within men and non-inferiority assessment of health related quality of life between groups. Power for the secondary comparison of sexual function between groups within women is marginal and no power is computed for bladder function items due to lack of availability of preliminary data.

For comparison of sexual function between groups within gender subsets, we assume that 65% of patients will be men. Based on previous IIEF data in this population (also from the BFI validation study), men not receiving pre-operative RT had a mean score of 58.3 (SD=19.6, n=21) and men receiving pre-operative RT had a mean score of 34.8 (SD=22.4, n=46). In the current study, we do not expect as large a difference between groups but reasonably expect a mean score of about 34.8 in the traditional CMT group (similar to the pre-operative RT in the validation study) and a 60%/40% weighted average or a mean score of about 48.9 in the selective RT group with a pooled standard deviation of 21.5. With data for 224 men, we have >90% power to detect this 14.1 point difference between groups at a given time point using a two-sided alpha=0.05 two-sample t-test.

Based on previous FSFI data in this population (also from the BFI validation study), women not receiving pre-operative RT had a mean score of 21.4 (SD=10.8, n=15) and women receiving pre-operative RT had a mean score of 13.8 (SD=11.1, n=23). In the current study, we do not expect as large a difference between groups but reasonably expect a mean score of about 13.8 in the traditional CMT group (similar to the pre-operative RT in the validation study) and a 60%/40% weighted average or a mean score of about 18.4 in the selective RT group with a pooled standard deviation of 11.0. With data for 120 women, we have 62% power to detect this 4.6 point difference between groups at a given time point using a two-sided alpha=0.05 two-sample t-test.

Finally, for comparison of health related quality of life between groups, with data for 344 patients, the lower limit of the two-sided 95% confidence interval for the mean difference between groups in the EQ5D summary index has >90% likelihood of falling above -0.05 (i.e., above a 0.33 standard deviation difference) if the true difference between groups is 0.

PATIENT INFORMATION SHEET
Patient Completed Quality of Life Booklet FOR MEN

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. The booklet contains 4 sets of questions:
    a. Bowel Function Index (19 questions)
    b. Bladder Function Questions (2 questions)
    c. EuroQOL5D-5L (6 questions)
    d. International Index of Erectile Function (15 questions)

2. Directions on how to complete each set of questions are written on the top of each set.

3. If you were given this booklet during a clinical visit, please complete the booklet during your clinical visit and return it to your nurse or your physician.

4. If you received this booklet in the mail, please return the completed booklet in the provided envelope.

5. It is very important that you return the booklet to us, whether you finish the study or not.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

Thank you for taking the time to help us.

PATIENT INFORMATION SHEET
Patient Completed Quality of Life Booklet FOR WOMEN

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. The booklet contains 4 sets of questions:
    a. Bowel Function Index (19 questions)
    b. Bladder Function Questions (2 questions)
    c. EuroQOL5D-5L (6 questions)
    d. Female Sexual Functioning Index (19 questions)

2. Directions on how to complete each set of questions are written on the top of each set.

3. If you were given this booklet during a clinical visit, please complete the booklet during your clinical visit and return it to your nurse or your physician.

4. If you received this booklet in the mail, please return the completed booklet in the provided envelope.

5. It is very important that you return the booklet to us, whether you finish the study or not.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

Thank you for taking the time to help us.

QOL Assessment (Questions 1-19 are the same for both genders)

Directions: Please answer the following questions based on your experience <u>over the last 4 weeks</u>.

1. How many bowel movements did you generally have in 24 hours? _____ bowel movements/24 hours

	Always	Most of the time	Sometimes	Rarely	Never
2. Do certain solid foods increase the number of bowel movements in a day?					
3. Do certain liquids that you drink increase the number of bowel movements in a day?					
4. Do you feel like you have totally emptied your bowels after a bowel movement?					
5. Do you get to the toilet on time?					
6. Do you have another bowel movement within 15 minutes of your last bowel movement?					
7. Do you know the difference between having to pass gas (air) and needing to have a bowel movement?					
8. Have you used medicines to decrease the number of bowel movements (drugs like Imodium®, Lomotil®)?					
9. Have you had diarrhea (no form, watery stool)?					
10. Have you had loose stool (slight form, but mushy)?					
11. Have you been able to wait 15 minutes to get to the toilet when you feel like you are going to have a bowel movement?					

12. Have you been able to control the passage of gas (air)?

13. Have you limited the types of solid food you eat to control your bowel movements?

14. Have you limited the types of liquids you drink to control your bowel movements?

15. Have you had soilage (leakage of stool) of your undergarments during the day?

16. Have you used a tissue, napkin, and/or pad in your undergarments during the day in case of stool leakage?

17. Have you had soilage (leakage of stool) of your undergarments when you go to bed?

18. Have you had to alter your activities because of your bowel function?

19. Compared to 4 weeks ago, how would you rate your bowel function now?

- Much better than 4 weeks ago
- Somewhat better than 4 weeks ago
- About the same as 4 weeks ago
- Somewhat worse than 4 weeks ago
- Much worse than 4 weeks ago

For male patients ONLY

We would like to ask you questions about your sexual function.

International Index of Erectile Function

Directions: Circle the number that best describes your erectile function **for the past 4 weeks**.

20. Over the past 4 weeks, how often were you able to get an erection during sexual activity?

No sexual activity	Almost never or never	A few times (much less than half the time	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
1	2	3	4	5	6

21. Over the past 4 weeks, when you had erections with sexual stimulation, how often were your erections hard enough for penetration?

No sexual activity	Almost never or never	A few times (much less than half the time	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
1	2	3	4	5	6

22. Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?

Did not attempt	Almost never or never	A few times (much less than half the time	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
1	2	3	4	5	6

23. Over the past 4 weeks, during sexual intercourse how often were you able to maintain your erection after you had penetrated (entered) your partner?

Did not attempt	Almost never or never	A few times (much less than half the time	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
1	2	3	4	5	6

24. Over the past 4 weeks, during sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

Did not attempt	Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult
1	2	3	4	5	6

25. Over the past 4 weeks, how many times have you attempted sexual intercourse?

No attempts	One to two attempts	Three to four attempts	Five to six attempts	Seven to ten attempts	More than 11 attempts
1	2	3	4	5	6

26. Over the past 4 weeks, when you attempted sexual intercourse, how often was it satisfactory to you?

Did not attempt	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
1	2	3	4	5	6

27. Over the past 4 weeks, how much have you enjoyed sexual intercourse?

No intercourse	No enjoyment	Not very enjoyable	Fairly enjoyable	Highly enjoyable	Very highly enjoyable
1	2	3	4	5	6

28. Over the past 4 weeks, when you had sexual stimulation or intercourse, how often did you ejaculate?

No sexual stimulation/ intercourse	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
1	2	3	4	5	6

29. Over the past 4 weeks, when you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?

No sexual stimulation/ intercourse	Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
1	2	3	4	5	6

30. Over the past 4 weeks, how often have you felt sexual desire?

Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most times (much more than half the time)	Almost always or always
1	2	3	4	5

31. Over the past 4 weeks, how would you rate your level of sexual desire?

Very low/none at all	Low	Moderate	High	Very high
1	2	3	4	5

32. Over the past 4 weeks, how satisfied have you been with your overall sex life?

Very dissatisfied	Moderately dissatisfied	About equally satisfied and dissatisfied	Moderately satisfied	Very satisfied
1	2	3	4	5

33. Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?

Very dissatisfied	Moderately dissatisfied	About equally satisfied and dissatisfied	Moderately satisfied	Very satisfied
1	2	3	4	5

34. Over the past 4 weeks, how do you rate your confidence that you could get and keep an erection?

Very low	Low	Moderate	High	Very high
1	2	3	4	5

We would like to ask you some questions about your bladder function

35. Over the last 4 weeks, how often have you leaked urine?

Every day
About once a week
Less than once a week
Not at all

36. Over the last 4 weeks, how often have you had a sensation of not emptying your bladder completely after you finished urinating?

Not at all
Less than 1 time in 5
Less than half of the time
About half of the time
More than half of the time
Almost always

Under each heading, please tick the ONE box that best describes your health TODAY.

37. Mobility

I have no problems in walking about
I have slight problems in walking about
I have moderate problems in walking about
I have severe problems in walking about
I am unable to walk about

38. Self-Care

I have no problems washing or dressing myself
I have slight problems washing or dressing myself
I have moderate problems washing or dressing myself
I have severe problems washing or dressing myself
I am unable to wash or dress myself

39. Usual Activities (e.g. work, study, housework, family, or leisure activities)

I have no problems doing my usual activities
I have slight problems doing my usual activities
I have moderate problems doing my usual activities
I have severe problems doing my usual activities
I am unable to do my usual activities

40. Pain/Discomfort

I have no pain or discomfort
I have slight pain or discomfort
I have moderate pain or discomfort
I have severe pain or discomfort
I have extreme pain or discomfort

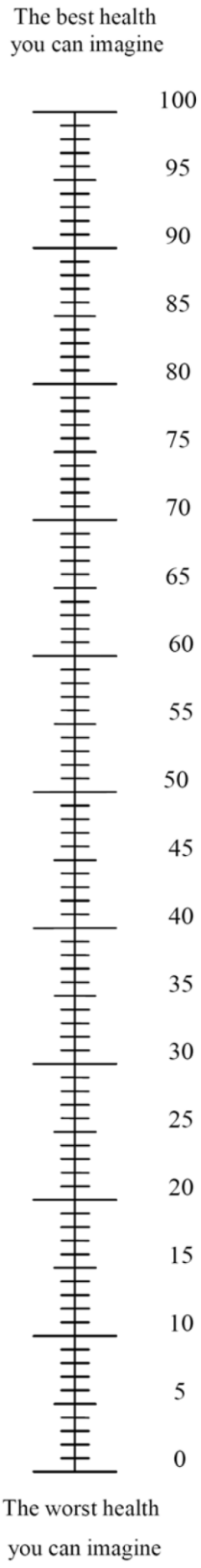
41. Anxiety/Depression

I am not anxious or depressed
I am slightly anxious or depressed
I am moderately anxious or depressed
I am severely anxious or depressed
I am extremely anxious or depressed

42. We would like to know how good or bad your health is TODAY.

- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
- 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



For male QOL, questions 1-19 are from Temple et al., 2005; question 20 from Sparngers et al., 1999; questions 21-23 from Basch et al., 2006; questions 25 and 26 are from Barry et al., 1992 and Befort et al., 2005; questions 27-32 are from the euroqol website and Herdman et al., 2011.

For female patients ONLY

We would like to ask you questions about your sexual function.

Female Sexual Function Index Questionnaire

Instructions: These questions ask you about your sexual feelings and responses during the past **4** weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential. In answering these questions the following definitions apply:
Sexual activity can include caressing, foreplay, masturbation and vaginal intercourse
Sexual intercourse is identified as penetration (entry) of the vagina.
Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.
Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.
CIRCLE ONLY ONE NUMBER PER QUESTION.

20. Over the past 4 weeks, how **often** did you feel sexual desire or interest?

Almost always or always	Most times (more than half the time)	Sometimes (about half the time)	A few times (less than half the time)	Almost never or never
1	2	3	4	5

21. Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?

Very high	High	Moderate	Low	Very low or none at all
1	2	3	4	5

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness) or muscle contractions.

22. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse?

No sexual activity	Almost always or always	Most times (more than half the time)	Sometimes (about half the time)	A few times (less than half the time)	Almost never or never
1	2	3	4	5	6

23. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?

No sexual activity	Very high	High	Moderate	Low	Very low or none at all
1	2	3	4	5	6

24. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?

No sexual activity	Very high confidence	High confidence	Moderate confidence	Low confidence	Very low or no confidence
1	2	3	4	5	6

25. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

No sexual activity	Almost always or always	Most times (more than half the time)	Sometimes (about half the time)	A few times (less than half the time)	Almost never or never
1	2	3	4	5	6

26. Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?

No sexual activity	Almost always or always	Most times (more than half the time)	Sometimes (about half the time)	A few times (less than half the time)	Almost never or never
1	2	3	4	5	6

27. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?

No sexual activity	Extremely difficult or impossible	Very difficult	Difficult	Slightly difficult	Not difficult
1	2	3	4	5	6

28. Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?

No sexual activity	Almost always or always	Most times (more than half the time)	Sometimes (about half the time)	A few times (less than half the time)	Almost never or never
1	2	3	4	5	6

29. Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

No sexual activity	Extremely difficult or impossible	Very difficult	Difficult	Slightly difficult	Not difficult
1	2	3	4	5	6

30. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?

No sexual activity	Almost always or always	Most times (more than half the time)	Sometimes (about half the time)	A few times (less than half the time)	Almost never or never
1	2	3	4	5	6

31. Over the past 4 weeks, when you have had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)?

No sexual activity	Extremely difficult or impossible	Very difficult	Difficult	Slightly difficult	Not difficult
1	2	3	4	5	6

32. Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

No sexual activity	Very satisfied	Moderately satisfied	About equally satisfied and dissatisfied	Moderately dissatisfied	Very dissatisfied
1	2	3	4	5	6

33. Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?

No sexual activity	Very satisfied	Moderately satisfied	About equally satisfied and dissatisfied	Moderately dissatisfied	Very dissatisfied
1	2	3	4	5	6

34. Over the past 4 weeks, how **satisfied** have you been with your sexual relationship with your partner?

No sexual activity	Very satisfied	Moderately satisfied	About equally satisfied and dissatisfied	Moderately dissatisfied	Very dissatisfied
1	2	3	4	5	6

35. Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?

No sexual activity	Very satisfied	Moderately satisfied	About equally satisfied and dissatisfied	Moderately dissatisfied	Very dissatisfied
1	2	3	4	5	6

36. Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration?

Did not attempt intercourse	Almost always or always	Most times (more than half the time)	Sometimes (about half the time)	A few times (less than half the time)	Almost never or never
1	2	3	4	5	6

37. Over the past 4 weeks, how **often** did you experience discomfort or pain following vaginal penetration?

Did not attempt intercourse	Almost always or always	Most times (more than half the time)	Sometimes (about half the time)	A few times (less than half the time)	Almost never or never
1	2	3	4	5	6

38. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?

Did not attempt intercourse	Very high	High	Moderate	Low	Very low or none at all
1	2	3	4	5	6

We would like to ask you some questions about your bladder function

39. Over the last 4 weeks, how often have you leaked urine?

Every day
About once a week
Less than once a week
Not at all

40. Over the last 4 weeks, how often have you had a sensation of not emptying your bladder completely after you finished urinating?

Not at all
Less than 1 time in 5
Less than half of the time
About half of the time
More than half of the time
Almost always

Under each heading, please tick the ONE box that best describes your health TODAY.

41. Mobility

I have no problems in walking about
I have slight problems in walking about
I have moderate problems in walking about
I have severe problems in walking about
I am unable to walk about

42. Self-Care

I have no problems washing or dressing myself
I have slight problems washing or dressing myself
I have moderate problems washing or dressing myself
I have severe problems washing or dressing myself
I am unable to wash or dress myself

43. Usual Activities (e.g. work, study, housework, family, or leisure activities)

I have no problems doing my usual activities
I have slight problems doing my usual activities
I have moderate problems doing my usual activities
I have severe problems doing my usual activities
I am unable to do my usual activities

44. Pain/Discomfort

I have no pain or discomfort
I have slight pain or discomfort
I have moderate pain or discomfort
I have severe pain or discomfort
I have extreme pain or discomfort

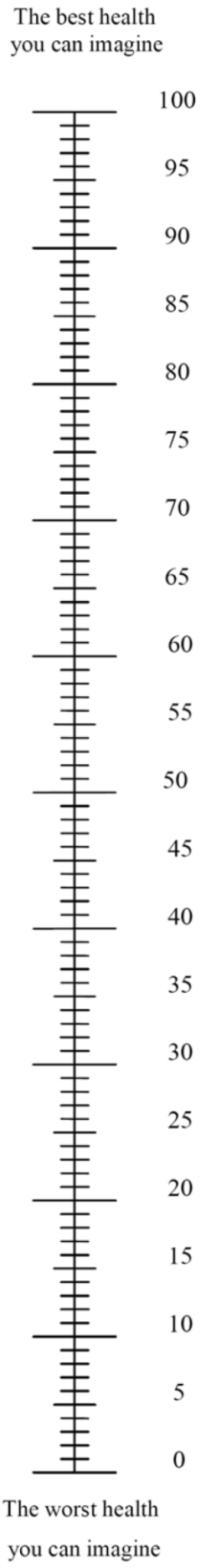
45. Anxiety/Depression

I am not anxious or depressed
I am slightly anxious or depressed
I am moderately anxious or depressed
I am severely anxious or depressed
I am extremely anxious or depressed

46. We would like to know how good or bad your health is TODAY.

- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
- 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



For female QOL, questions 1-19 are from Temple et al., 2005; question 20 from Sparngers et al., 1999; questions 21-23 from Basch et al., 2006; questions 25 and 26 are from Barry et al., 1992 and Befort et al., 2005; questions 27-32 are from the euroqol website and Herdman et al., 2011.

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APPENDIX VII: SURGICAL CONSIDERATIONS AND QUALITY ASSURANCE

Operative Technique

Treatment on this protocol must commence by the accruing membership under the supervision of a surgeon experienced in TME. **Note: To ensure proper stratification and consistency, the registering surgeon, assessing the inclusions parameters MUST be the surgeon intended to perform the assigned procedure.**

Operative procedures will include either laparascopic or open anterior/low anterior resection with a hand sewn or stapled anastomosis with or without temporary fecal diversion. The pelvic dissection must include the division of the inferior mesenteric pedicle, the transection of the specimen and the construction of the anastomosis. The mobilization of the proximal colon and splenic flexure may be performed by laparoscopic, laparoscopic-assisted, robotic-assisted or hand-assisted techniques to limit the incision to the lower abdomen. Although variation in technical approaches can be anticipated based on variation in patient's body habitus and surgical incision, the following technical descriptions will serve as guidelines.

Upon entering the abdominal cavity the abdomen will be explored for evidence of advanced disease including inspection of the liver, retroperitoneum, paraaortic nodes, ovaries and peritoneal surface. The site and location of the tumor relative to the peritoneal cavity and adjacent structures will be noted. Minimal tumor handling will be adhered to and contact of the tumor to the wound will be minimized. Mobilization of the left colon +/- splenic flexure, identification and protection of the left ureter, identification and ligation/division of inferior mesenteric vein and artery or superior hemorrhoidal vessels after bifurcation of the inferior mesenteric artery are essential features. Dissection of the rectum from the sacrum should occur in the avascular plane behind the fascia propria of the rectum and anterior to the presacral fascia in order to maintain intact the envelope containing the mesorectum. The pelvic nerves (right and left) at the pelvic brim should be identified and freed from the dissection plane unless dictated otherwise by tumor involvement. The dissection posteriorly is performed sharply (not blunt dissection) in the avascular areolar tissue plane and carried out through the rectosacral fascia to a level well below the tumor or all the way to the pelvic floor depending on tumor level in the rectum. The lateral peritoneal and anterior cul-de-sac incision should be made outside the area of the tumor and, if possible, within the pelvic confines to avoid the ureters, nerves, prostate, seminal vesicles, vagina, pelvic floor and side wall muscles. Retraction of the sigmoid and rectum should be accomplished in such a way that injury to that area is avoided and contamination limited.

The posterior mesorectum should be transected ideally 5 cm below the level of the tumor for upper rectal lesions or completely removed for mid to low rectal cancers (total mesorectal excision). Cautery, RF energy, clips, bipolar sealing devices or harmonic scalpel are all acceptable means of vascular control.

Transection of the distal rectum should be performed using the appropriate stapling instrument. For the anastomosis, the proximal bowel will be prepared for suturing or stapling. The anastomosis should be performed using standard techniques.

Minimal acceptable margins should be obtained at the time of transection and evaluated on the fresh, unstretched specimen. A proximal margin of greater than 5 cm and a clear 1 cm margin distally will be considered adequate for low rectal lesions in order to achieve sphincter preservation. The use of diverting loop ileostomy will be left to the surgeon’s discretion and recorded.

At the completion of the procedure photos of the anterior and posterior mesorectum on the fresh, unstretched specimen must be taken. Photographs of the open specimen are not required.

Extent and Technique of Resection
Extent of resection, including assessment of the margins and of completeness of TME will be documented for all procedures in the operative report and on data forms. Case report forms note the use of laparascopic assisted techniques as well as robotic assisted techniques.

Intraoperative Pathology and Pathologic Examination of Surgical Specimen
Pathologists will measure fresh, unstretched proximal and distal margins. The completeness of the TME resection will be assessed by the surgeon in the operating room and evaluated by the pathologist and categorized as defined in the Surgical QA Plan section. Prior to opening the specimen, it should be prepared by the pathologist to evaluate radial margins by applying ink to the mesorectal surface in the area of the tumor. **Note: The mesorectal specimen must be photographed with a digital camera with minimum of 2 megapixels to verify the quality of the dissection. Photos taken with an iPhone are accceptable. The anterior and posterior mesorectum should be photographed fresh. A photo of the open specimen is not required. The photo should be centered on the extraperitoneal mesorectal surphace and not the entire specimen (see figures at the end of this Appendix). The image files should not be compressed. These photographs should be retained in patient's research records and sent electronically within 2 weeks.** These photos should be sent to [redacted]

Morbidity and Mortality
Early, in hospital and late (within 30 days) morbidity and mortality will be closely monitored and recorded using the study data forms with the following definitions:

Pulmonary, urinary tract, and intraabdominal infections will be defined by the need for antibiotic treatment and/or interventional radiology drainage.

Abdominal wound infections will be defined by the location, extent and severity (i.e. superficial vs. deep space infection) and the need for wound opening and/or surgical intervention. Urinary retention will be defined as the condition of urinary dysfunction that occurs for greater than 5 days following surgery or that requires intervention, including replacement of Foley catheter, surgery, etc

Perioperative hemorrhage requiring blood transfusion(s) or reoperation will be considered as a complication. Correction of preoperative anemia will not be included as a complication. The decision to transfuse will be made at the surgeon's discretion.

Any documented medical or anesthetic complications that result in patient disability or that requires intervention will be recorded.

Problems with healing, function or management of the ostomy that requires intervention or additional hospital stay will be considered complication and recorded.

Surgical Complications
Perioperative and postoperative complications will be collected and submitted via CTEP-AERS; see Section 10.0, Adverse Event Reporting and Monitoring, for further instructions.

Perioperative Complications
Complications after rectal resections include:
Death after rectal resection (0-7.4%)
Anastomotic leak after recta1 resection (1-17%)
Abdominal wound infection (3-24%)
Stoma complications (4-10%)

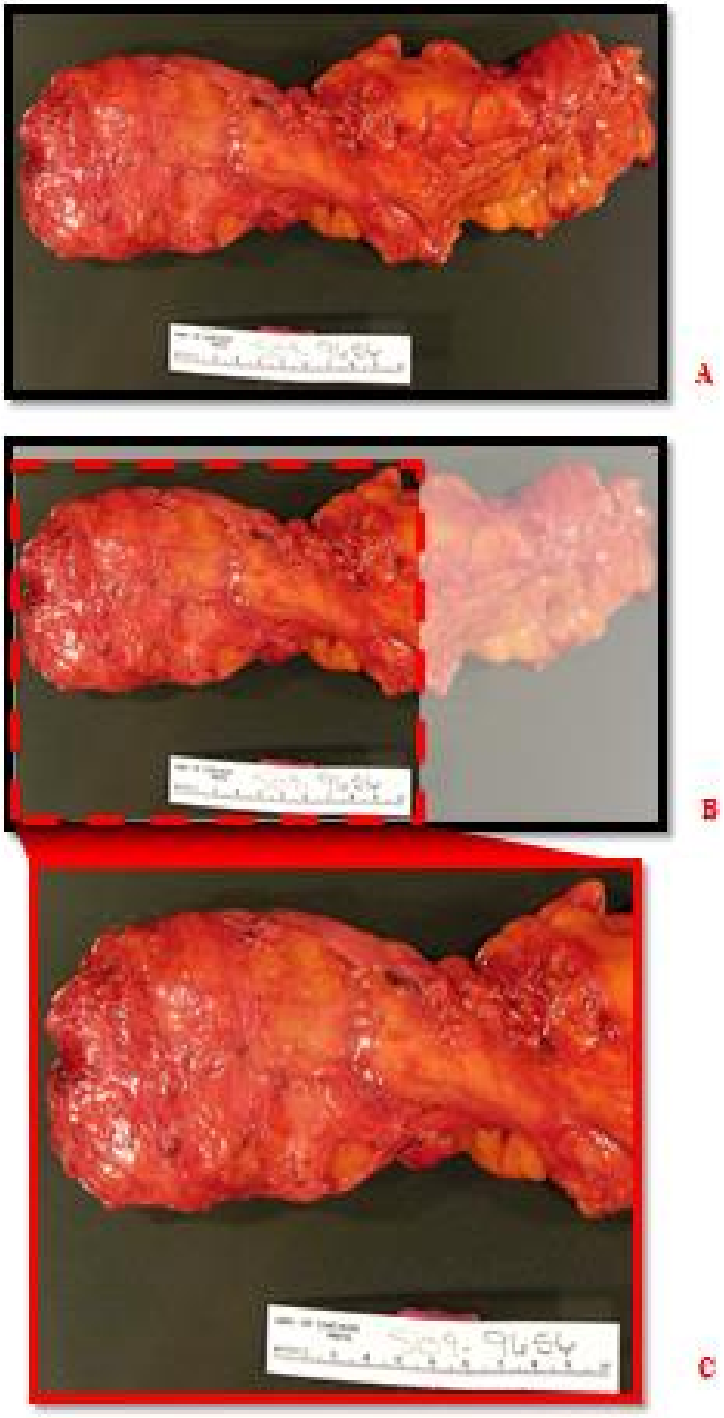
Late or Delayed Complications
Late or delayed complications such as bowel obstruction will be monitored and reported on data forms. Details of hospital admissions will be recorded in the patient's records, including dates, location, and admitting physician's name. The "reason for admission" will provide guidance as to whether the hospitalization was related to the cancer diagnosis and surgery or for other reasons. See Section 10.0, Adverse Event Reporting and Monitoring, for reporting guidelines for complications occurring > 30 days after surgery.

Surgical QA Plan
Evaluation at the Time of Surgery
• Intact TME resection as assessed by the surgeon, evaluated by the pathologists, documented on surgery and pathology intake forms and on the photo of the fresh specimen
• Circumferential margin positivity (< 1mm).
• Distal margin status (< 1cm).
• Lymph node harvest and number of positive lymph nodes
• Evaluation of surgical complications

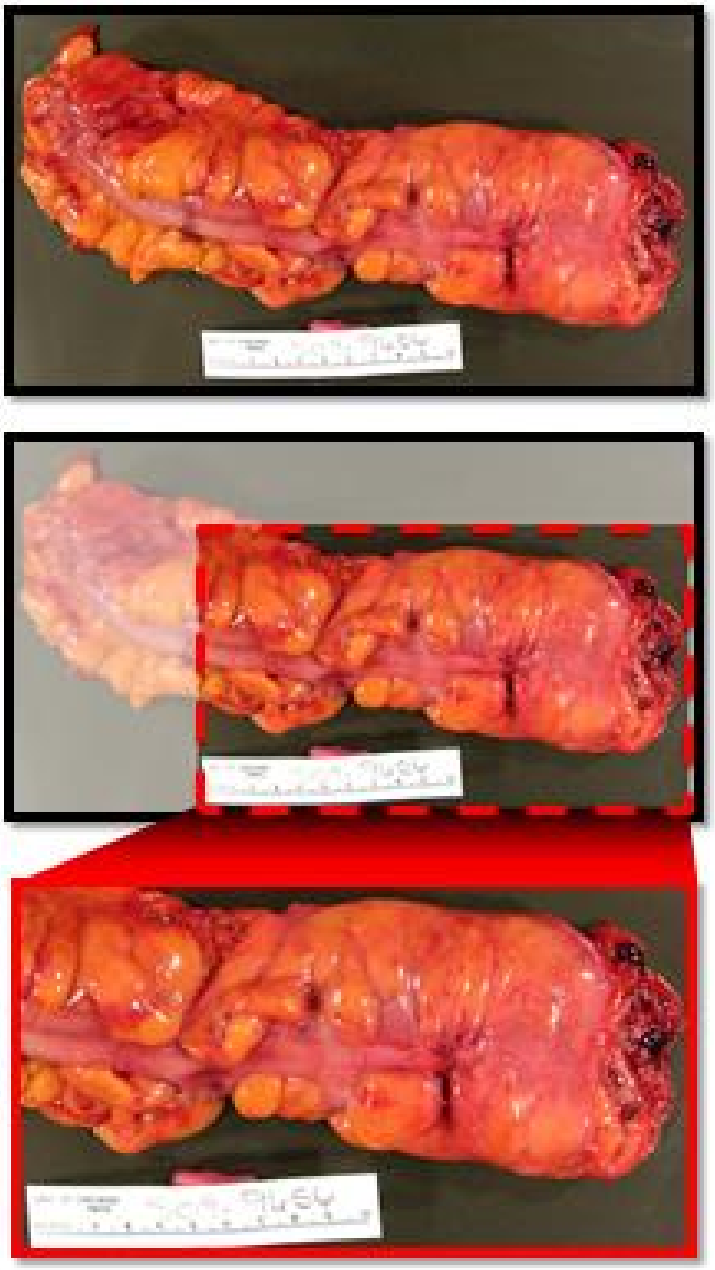
Performance Monitoring
Surgery PI Review
The Study Chairs will review each enrolled case for patient eligibility and intervention compliance. If an investigator has a possible performance issue, the Study Chairs will review the issue(s) and make recommendations to the investigator. It is expected that in most cases, the Study Chairs or designee will work with the investigator to improve performance. However, the Study Chairs are empowered to suspend protocol participation, if necessary.

Monitoring of Surgical Performance
Photo documentation of every TME specimen is required and will be reviewed by the Surgical Quality Committee. These photos should be sent to [redacted]

Please Note: Including a ruler in the photographs is preferred but NOT mandatory.



Do not include the whole specimen in the picture (A). The photo should be centered on the extraperitoneal portion of the rectum (B) with a ruler to allow measurements of any mesorectal defect (C).



Do not include the whole specimen in the picture (A). The photo should be centered on the extraperitoneal portion of the rectum (B) with a ruler to allow measurements of any mesorectal defect (C).

APPENDIX VIII: SUGGESTED MRI TECHNICAL AND QUALITY REQUIREMENTS

Suggested Technical and Quality Requirements for Rectal MRI Scans

MRI Field Strength: 1.0 T to 3.0 T, closed bore

Coil: Phased array: minimum 4 channels

IV Contrast: Optimal (preferred: 0.1mmol/kg Gadolinium), noncontrast acceptable

Spasmolytic: Glucagon optional: 1.0 mg IM, immediately before exam, no glucagon acceptable

Rectal Preparation: 1 Bisacodyl (Dulcolax) suppository inserted three hours prior to exam optimal, no prep acceptable.

Rectal Filling: 80-100 mL ultrasound transmission gel optimal (Kim et al., Eur Radiol 2011;21: 987-995).

Non-filling is acceptable as long as rectum is not collapsed, i.e. natural air or fluid distension [but not stool-distension] without gel insertion is acceptable.

1.5 Tesla Recommended Parameters

Plane:	Axial T1	Axial T2	Coronal T2	Sagittal T2	Oblique Axial T2*
Sequence:	2DF(R)SE/TSE for all planes				
Options:	no phase wrap	no phase wrap	no phase wrap	no phase wrap	no phase wrap
TE:	minimum/full	80-120	80-120	80-120	80-120
TR:	400-650	4000-6000	4000-6000	4000-6000	4000-6000
ETL:	4	18-26	18-26	18-26	18-26
Flip Angle:	90	90	90	90	90
Bandwidth:	32kHz	32kHz	32kHz	32kHz	32kHz
Sat. Pulse:	S/I/A	S/I/A	none	none	S/I/A
Field of View:	28-36	18-26	18-26	18-26	18-26
Slice Thick.:	5mm	2-4 mm	2-4mm	2-4 mm	2-4 mm
Gap:	1-2mm	1-2mm	1-2mm	1-2mm	1-2mm
Phase Enc.:	160	180-220	180-220	180-220	180-220
Frequency:	256	300-340	300-340	300-340	300-340
NEX:	2	3-4	3-4	3-4	3-4
Freq. Direction:	A/P	A/P	S/I	R/L	R/L
Comment:	no-breathhold	breathhold	no-breathhold	no-breathhold	no breathhold

Notes: ***Oblique Axial** is required. Angle is perpendicular to tumor. If tumor is long and follows curvature of rectum, re-angling is recommended, but rarely necessary.

Gadolinium-enhanced sequences (FSPGR, any plane) are optional and welcome

FAT SATURATION IS NOT ACCEPTABLE EXCEPT FOR GADOLINIUM SEQUENCES.

3.0 Tesla Recommended Parameters

Plane:	Axial T1	Axial T2	Coronal T2	Sagittal T2	Oblique Axial T2*
Sequence:	2DF(R)SE/TSE	for all phases			
Options:	no phase wrap	no phase wrap	no phase wrap	no phase wrap	no phase wrap
TE:	minimum/full	80-120	80-120	80-120	80-120
TR:	400-650	4000-6000	4000-6000	4000-6000	4000-6000
ETL:	3	18-26	18-26	18-26	18-26
Flip Angle:	90	90	90	90	90
Bandwidth:	32kHz	32kHz	32kHz	32kHz	32kHz
Sat. Pulse:	S/I/A	S/I/A	none	none	S/I/A
Field of View:	28-36	18-26	18-26	18-26	18-26
Slice Thick.:	5mm	2-4 mm	2-4mm	2-4 mm	2-4 mm
Gap:	1-2mm	1-2mm	1-2mm	1-2mm	1-2mm
Phase Enc.:	160	200-256	200-256	200-256	200-256
Frequency:	256	300-340	300-340	300-340	300-340
NEX:	2	4	4	4	4
Freq. Direction:	A/P	A/P	S/I	R/L	R/L
Comment:	no-breathhold	breathhold	no-breathhold	no-breathhold	no-breathhold

Notes: ***Oblique Axial** is required. Angle is perpendicular to tumor. If tumor is long and follows curvature of rectum, re-angling is recommended, but rarely necessary.

Gadolinium-enhanced sequences (FSPGR, any plane) are optional and welcome

FAT SATURATION IS NOT ACCEPTABLE EXCEPT FOR GADOLINIUM SEQUENCES.

APPENDIX IX: SCHEDULE AND PROCEDURE FOR IMAGING SUBMISSION

Schedule and Procedure for Image Submission to Central Review (Quality Assurance)

Procedure for Submitting Images to the Alliance Imaging Core Lab:

Imaging data shall be submitted to the Imaging Core Lab as promptly as is feasible.

Imaging studies listed in the following table must be **electronically** submitted to the Alliance Imaging Core Laboratory in digital DICOM format **only**; any other formats such as bitmap, JPG or hardcopies (scanned films) are unacceptable. The source data of the entire study should be saved until the images are accepted by the Imaging Core Lab. Remove all identifiers such as patient name and medical record number; the date of procurement should be kept. Be certain to include the patient study ID number and study protocol number.

Images may be securely transferred to the Imaging Core Laboratory by:

1. **Secure web transfer;**
2. **Secure FTP transfer;**

For web and FTP transfers, please contact the Imaging Core Lab at the e-mail address [redacted] to request a site-specific username and password that the site will use to log in at [redacted] In addition to the login credentials, detailed instructions how to upload the images will be sent. Once logged into the website ([redacted]), a tutorial folder will contain the upload instructions. A video demonstration of the transfer process is available for viewing or downloading. A live demonstration of the transfer process is available upon request.

Web Transfer

Any PC or workstation with Internet access and a web browser (such as Internet Explorer, Mozilla Firefox, etc.) can be used to securely upload/transfer DICOM images and other required files to the Imaging Core Lab. Enter "[redacted] into the address bar of the web browser and the PC will establish an encrypted connection (via Secure Sockets Layer – SSL) to the login page of the website. Once logged in, entire folders and subfolders can be securely transferred from a hard disk drive or from a CD/DVD. The scans are stored on the server using 256-bit AES encryption.

File Transfer

Any FTP software (such as WS_FTP, FileZilla, etc.) that is installed on a local PC or workstation can be used to securely connect to the FTP server. Start the program, enter the login credentials, and the PC can establish an encrypted connection via Secure Sockets Layer (SSL) or SSH. Once logged in, entire folders and subfolders can be securely transferred from a hard disk drive or from a CD/DVD. The scans are stored on the server using 256-bit AES encryption.

Important: Once the electronic imaging data submission is done, send an email to the Imaging Core Lab at [redacted] listing what images have been sent electronically. Please include the basic information of submitted data sets as follows:

1) N1048 Patient Study ID
2) Scan Time Point (Baseline, Restaging or Surveillance)
3) Type of Scans
4) Date of Scans
5) Date of First Day of Protocol Treatment
6) Institution Name

Shipment/Mail Transfer
If electronic transfer of data is not possible, the de-identified images in digital DICOM format should be burned to a CD/DVD then snail-mailed to the Imaging Core Lab at te address listed directly below. Please submit only one patient's imaging study per CD with the basic information listed above (#s 1-6). Multiple CDs can be sent together. Please note that the Imaging Core Lab does not accept deliveries on weekends and legal holidays.

For Questions or Concerns, Contact:

[redacted]

The Imaging Core Lab will acknowledge by email the receipt of the imaging data from the submitting site within 1 business day of receipt.

Schedule of Submission of Imaging Scans for Central Radiologic Review

	Submit electronically at [redacted] For help, email [redacted]	
Study Type	**Group 1: FOLFOX**	**Group 2: 5FUCMT**
If the patient receives an MRI and a CT at baseline, submit the **Baseline MRI** to Central Radiology for review	Submit as soon as feasible.	Submit as soon as feasible.
If the patient receives an ERUS and a CT at baseline, submit the **Baseline CT** to Central Radiology for review	Submit as soon as feasible.	Submit as soon as feasible.
If the patient receives an MRI at restaging*, submit the **Restaging MRI** to Central Radiology for review	Submit as soon as feasible.	Scan not required. If scan was performed, submit
If the patient receives an ERUS and a CT at restaging*, submit the **Restaging CT** to Central Radiology for review	Submit as soon as feasible.	Scan not required. If scan was performed, submit
Surveillance Imaging: **MRI, CT, PET-CT to identify recurrent disease**	Submit as soon as feasible.	Submit as soon as feasible.
*Note: At restaging, use the same imaging modality that was used at baseline for a given patient. ERUS studies do not need to be submitted. NOTE: Central Radiology Review is for quality assurance purposes and is not done in "real-time"; Decisions about clinical management based on interpretation of images rest with the accruing site and primary clinical team based on the best clinical interests of the patient.		

APPENDIX X: GENOMIC CHARACTERIZATION

Genomic Characterization of Rectal Tumors using Molecular Inversion Probe (MIP) Arrays and MALDI-TOF Mass Spectrometry.

Summary
Ongoing research is directed at developing patient-specific therapies by learning more about the molecular features of a tumor within an individual patient. Unlike normal cells, cancer cells are characterized by alterations in their molecular machinery related to damage or changes to their genetic material or DNA. Damage to the DNA can result in cancer-causing mutations; however, an alternative way for cancer cells to develop and grow is related to gains (amplifications) or losses (deletions) of genetic material referred to as copy number alterations. These mutations or copy number alterations can lead to uncontrolled cell growth, an inability to undergo normal cell death, and a propensity for cancerous cells to travel to other sites in the body, referred to as metastases.

We and others have previously demonstrated that colorectal cancer is more than one disease, as illustrated by the different somatic mutations that can occur in an individual's tumor involving genes such as KRAS, NRAS, BRAF, PIK3CA, AKT, PTEN, and TP53, as well as others. We hypothesize that pre-treatment determination of the molecular alterations that occur in an individual's rectal tumor will allow for patient- or tumor-specific therapies with a greater likelihood of a successful outcome.

A major challenge of a targeted approach to cancer therapy is the need for fresh-frozen tumor tissue for analysis in order to determine the genetic variants in a specific patient's tumor. Historically, most tumor tissue has been preserved by stabilizing it with formalin, a formaldehyde solution, and embedding it in paraffin. The result is known as formalin-fixed, paraffin-embedded (FFPE) tumor tissue. During this process, the DNA is degraded, limiting the ability to perform genetic analyses using currently available technologies. The objective of the current proposal is to prospectively determine mutations and copy number alterations in rectal tumors from patients participating in the current NCI cooperative group rectal cancer trial, using a novel technology called molecular inversion probe (MIP) arrays, which can be used on FFPE tumor tissue. The MIP technology allows for simultaneous assessment of copy number alterations and mutations at commonly altered locations using significantly less DNA than older technologies. We anticipate that this technology will greatly facilitate our ability to maximize the information we can obtain from the relatively small tissue samples anticipated from the pre-treatment rectal biopsies. The ability to obtain all of this information in a single assay using FFPE tumor tissue will allow us to identify genetic events that represent targets for current and novel therapeutics. We hypothesize that together, these data will act as an integrated biomarker that will be able to predict which patients are most likely to respond to which agents and treatment modalities. The knowledge obtained from this project is anticipated to be used to design prospective clinical trials of therapies for rectal cancer patients whose tumors posses the genetic profile predicted to be most likely to respond. By potentially individualizing treatment strategies to the patients who are most likely to respond, this approach is anticipated to accelerate the development of promising therapies.

Specific Aims
Aim 1: To prospectively use molecular inversion probe (MIP) array technology and mass spectrometry-based genotyping to identify copy number aberrations and somatic mutations that mediate tumor formation using formalin-fixed, paraffin-embedded (FFPE) tumor tissue from patients participating in the Alliance cooperative group rectal cancer neoadjuvant trial.

Aim 2: To correlate the MIP array copy number and mutational data collected from patients with locally advanced rectal cancer with clinical outcomes in each treatment cohort (pathologic complete response, recurrence-free, pelvic recurrence-free, and overall survival).

Background and Significance

Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer and the second leading cause of cancer death in the United States. CRC is not a single disease entity arising as a result of a single pathognomonic genetic alteration, but rather a collection of diseases with a common tissue of origin. Clinically this is demonstrated both by the heterogeneity of outcomes following surgical resection and by the heterogeneity of response of CRC patients to systemic agents. Given this clinical heterogeneity, strategies to increase the cure rate must focus on accurately predicting the likelihood of recurrence after resection. In an attempt to improve the likelihood of cure following complete resection of CRC, adjuvant systemic therapy is administered to those patients who are at a perceived high risk of recurrence. Current models employing clinicopathologic features, however, are imperfect in predicting cancer recurrence, which leads to potential overtreatment in a subset of patients, and under-treatment in others. A classification of colorectal cancer that incorporates both clinical and tumor genetic variables thus holds promise for improvement in prognostication and the development of more individualized treatment plans. For example, a reported 18 gene assay of tumor DNA has the ability to classify one clinicopathological subgroup, stage II disease, into higher and lower risk categories (Salazar et al., 2011). However, to really provide benefit, a classification scheme must be able to both accurately assign patients to low versus high risk cohorts, but also identify which if any systemic agents will significantly lower the risk of recurrence.

Although most cases of CRC seem to be sporadic, age-related cancers with a mean age at diagnosis of 64 years, approximately 10% of patients with colorectal cancer are diagnosed under the age of 50. In such early-onset cases, genetic over environmental risk factors are presumed to be implicated, and evaluation for underlying cancer predisposition syndromes is appropriate. In fact, according to the revised Bethesda guidelines, all patients with a diagnosis of colorectal cancer under the age of 50 should be evaluated for Lynch syndrome (Hereditary Non-polyposis Colorectal Cancer) regardless of family history (Umar, 2004). However, despite extensive genetic evaluation, a germline mutation in one of the known colon cancer susceptibility genes is identified in only about 10-20% of early-onset CRC patients, thereby leaving the etiology of the majority of early-onset CRC cases unexplained. While accounting for only a small fraction of CRCs, investigation of the genetic and/or epigenetic alterations that lead to tumor initiation in these early onset CRC patients may provide insight into pathways of carcinogenesis in common to all colorectal cancer patients.

Approximately 70% of CRC tumors have identifiable somatic mutations within the RAS/RAF and PIK3CA/AKT pathways. In CRC models harboring RAS and BRAF mutations, RAS-pathway mutations are required for tumor maintenance, suggesting that therapies that target RAS or its downstream effectors may represent a useful therapeutic strategy in this disease. Further, RAS pathway mutations are highly predictive of resistance to anti-EGFR targeted therapies such as cetuximab and panitumumab. Although typically assumed to confer overlapping downstream dependencies, our preliminary data suggest that individual RAS pathway mutations confer variable prognostic effects. Definitive elucidation of the prognostic value of individual mutant alleles has been hampered by an exclusive focus on only the most frequent “hot spot” mutations and the use of small datasets inadequate for analysis of low frequency mutations. Furthermore, little is known about the relative frequency of RAS pathway mutations in patients with early-onset CRC, and in minority populations, both of which exhibit a relatively poor outcome. A comprehensive effort to prospectively profile rectal tumors for both tumor-initiating alterations and those required for tumor maintenance may thus help explain the disparity in outcome seen in early-onset and in minority populations.

Significance

We strongly believe that stratification of patients with advanced rectal cancer by genotype, as compared to histological pathology, will lead to improved outcomes for our patients. This approach has demonstrated some positive results in non-small cell lung cancer with the use of epidermal growth factor receptor (EGFR)-targeted therapy and, more recently, ALK-targeted therapy in patients with genomic ALK alterations such as the EML4-ALK fusion. This proposal seeks to use the novel MIP array technology to characterize copy number alterations and mutations in FFPE tumor specimens to develop individualized treatment strategies for patients with locally advanced rectal cancer. The ability to obtain all of this information from a single assay that can be performed on FFPE tumor tissue represents a significant technological advance over currently available methods. Furthermore, the multiplexed nature of the MIP array will allow for the identification of actionable genetic alterations in the majority of patients with locally advanced rectal cancer. We believe that the current approach will rapidly improve outcomes in patients as many of the alterations that will be identified (BRAF mutation, etc.) have been validated as targets in other cancer types. FDA-approved drugs for such patients are available but not yet deployed in an individualized manner in locally advanced rectal cancer.

Preliminary Data

At MSKCC, we have embarked on a Colorectal Cancer Oncogenome Project (CCOP) with two main goals: 1) to identify known driver alterations for use in guiding treatment/trial selection; and 2) to identify genetic drivers in patients in whom no known driver alteration has yet been identified. The CCOP uses three complementary genomic approaches to characterize tumors for mutations (targeted sequencing), identification of structural variations (translocations, amplifications and deletions) and methylation events. These efforts have been closely coordinated with those of the Tumor Cancer Genome Atlas project of which we are an active participant.

In order to complement the TCGA efforts, we have compared the genomic profiles of primary and metastatic colorectal cancers (CRC). To date, we have analyzed 736 frozen CRC tumors samples from 613 patients. Annotated clinical data was available for all patients. The median age of the cohort was 62 years (mean 60 years, range 17-88 years); 23% of patients were less than 50 years old. Approximately half of the patients presented with metastatic disease. These patients had a 5-year disease specific survival of 24%. The mean follow-up time for all study patients was 4.5 years. Primary invasive carcinomas comprised 57% (n=406) of the specimens, while 291 were collected from metastatic foci and 39 were adenomas with or without high grade dysplasia/intramucosal carcinoma. The site of metastases included liver (n=227, 78%), lung (n=34), soft tissue (n=14), brain (n=7), ovary (n=5) and distant lymph nodes (n=4).

For all 613 patients, tumors were profiled for KRAS, NRAS, BRAF and TP53 mutations. To identify hotspot alterations in the KRAS, NRAS and BRAF genes, we used a mass spectrometry based (Sequenom) assay. As TP53 mutations are found scattered throughout the coding sequencing, to determine the mutational status of this gene, we performed Sanger sequencing of all TP53 coding exons. Mutations in KRAS were identified in 277 (45.1%) patients. 219 (35.7%) of the KRAS mutations were located at codons 12 or 13 whereas 58 (9.4%) patients had either NRAS (2.9%) mutation or mutations within exons 3 or 4 of KRAS (exon 3: 2%: exon 4: 4.6%). BRAF mutations were detected in 40 (6.5%) patients, PIK3CA mutations in 72 (11.7%) patients and TP53 mutations were identified in 247 (40.3%) patients. Consistent with prior series, mutations in KRAS, NRAS and BRAF were non-overlapping in distribution. PIK3CA and TP53 mutations were found to co-occurred with both RAS and BRAF mutations, although PIK3CA mutations were significantly more common in the KRAS mutant tumors (16.2% vs. 8.1%, p=0.001), while TP53 mutations were significantly more common in BRAF wild type cases (9% vs. 2.6%, p=0.002). In stages I-III disease, KRAS exon 2 and TP53 mutations were associated with a worse prognosis, while in metastatic (stage IV) disease all RAS and BRAF mutations were associated with significantly worse disease specific survival. In ongoing work, we are comparing the frequency of novel mutational events identified in the TCGA dataset by whole exome sequencing in our matched set of primary and metastatic samples.

The goal of these efforts will be to identify additional molecular events that correlate with clinical outcome.

On the basis of these preliminary findings, the current proposal seeks to use MIP array technology to identify prognostic and/or predictive, potentially druggable mutations involving MEK, AKT, PIK3CA, and BRAF, as well as others, and copy number alterations, such as ERBB2 amplification, using FFPE material. As only FFPE material is typically available for patients with locally advanced rectal cancer, the validation of this approach should pave the way for a biomarker-driven approach to individualized cancer treatment in patients with locally advanced rectal cancer. Molecular inversion probe technology has been successful in obtaining high-quality copy number and genotype data from both frozen and FFPE-derived DNA. Since the MIP probe requires only a small (~40 base pairs) target-binding site, it was hypothesized that it could be applied effectively to degraded FFPE DNA as well (Wang et al., 2009). As an example of the use of this technology, a MIP panel of 50,000 markers was performed on DNA derived from 93 FFPE tumor samples from patients with breast, colon, kidney, and liver cancers. A major advantage of this technology is that an input of only 37 ng of genomic DNA was required. High-quality copy number data was generated in 88% of the FFPE samples. In 38 samples with matched fresh-frozen tissue, the genotype concordance averaged 99.9%, with only a modest loss in performance in FFPE. In collaboration with Affymetrix, the laboratory of [redacted] at MSKCC has enhanced the platform by adding additional coverage to ~200 well-characterized cancer-associated genes, including those identified in our CCOG project and the TCGA. Furthermore, coverage of over 700 recurrent hotspot mutations, such as those in PIK3CA, and BRAF, were added to the revised cancer-specific assay.

Methods

Molecular Inversion Probe (MIP) Array Technology

Molecular inversion probe technology may offer a solution to the challenge of acquiring copy number and genotype data from limited quantities of FFPE-derived tumor samples (Wang et al., 2009). FFPE specimens represent a vast, underutilized resource for genomic characterization. Such samples suffer from a number of limitations, including DNA fragmentation and crosslinking (which are a consequence of the fixation process), low DNA yield, and age-related degradation, all of which impair their utility for use with array-based technologies, such as copy number and mutation profiling. The MIP array selectively amplifies a locus of interest using unique padlock primers that significantly enhance the specificity and sensitivity of single nucleotide polymorphism (SNP) and mutation detection. This technology requires only 40 base pairs of intact target DNA and 75 ng of input material, thereby overcoming the most common limitations of FFPE samples. Briefly, each padlock probe consists of two terminal regions complementary to the target sequence of interest, two universal polymerase chain reaction (PCR) primer regions, a DNA cleavage site, and a tag sequence used for identification on an array. Linear MIP probes hybridize and anneal to the target genomic DNA sequence, resulting in probe circularization (molecular inversion) with a single-nucleotide gap between the hybridized ends. Polymerization and ligation of the gap occurs in an allele-specific manner, resulting in a covalently closed circular probe hybridized to the genomic DNA region of interest. Exonucleolysis of excess linear probes and genomic DNA is followed by probe release through site-specific enzymatic cleavage. The common primer regions within the probe are then utilized to amplify the region of interest; fluorescent labels are additionally attached. Amplified products are subsequently hybridized onto DNA microarrays and the relative fluorescence signaling intensity discriminates between mutations and can also be used to detect copy number alterations. We have been involved in the design of a custom array that utilizes the multiplexing capabilities of MIP probes to detect 744 mutations across 72 genes within a single sample. The array was designed to have extremely high probe densities within known cancer associated genes, allowing for highly sensitive detection of oncogene amplification and intragenic deletions within tumor suppressor genes.

MALDI-TOF (Mass-Spectrometry-Based Genotyping; Sequenom)
Mutations in KRAS (codons 12, 13, 22, 61, 117, 146), NRAS (codons 12, 13, 61), BRAF (codon 600), and PIK3CA (codons 420, 542, 545, 546, 1043, 1047) will be detected using the iPLEX assay (Sequenom, Inc., San Diego, CA), which is based on a single-base primer extension assay, as previously described (Janakiraman et al., 2010). The Sequenom MassARRAY system is based on matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS). In these assays, the mutant and germline alleles for a given point mutation produce single-allele base extension reaction products of different masses that are then resolved by MALDI-TOF MS. Both the amplification and extension primers were designed using Sequenom Assay Designer software (Sequenom, San Diego, CA). The amplification primers were designed with a 10mer tag sequence to increase their mass so that they fall outside the range of detection of the MALDI-TOF mass spectrometer. Results were generated using the SpectroTYPER software (Sequenom, San Diego, CA). All the positive cases will be confirmed by visually reviewing the spectra. For the PCR amplification, a total of 15 ng of genomic DNA (in 1 μl) will be amplified in a 5 μl reaction mixture containing 0.1 μl (0.5 U) HotStarTaq enzyme (Qiagen, Valencia, CA), 0.625 μl of 10x HotStar buffer, 0.325 μl of 25 mM (total) MgCl2, 0.25 μl of 10mM (each) deoxynucleotide triphosphate, 1 μl of 100 nM of each forward and reverse primers and 1.7 μl of water. The PCR step is initiated with a 95°C soak for 15 min, followed by 45 cycles, consisting of 95°C for 20 sec, 56°C for 30 sec, 72°C for 60 sec, and a final extension of 3 min at 72°C. After PCR, the remaining unincorporated dNTPs were dephosphorylated by adding 2 μl of the SAP cocktail, containing 1.33 μl of water, 0.17 μl of reaction buffer (Sequenom, San Diego, CA) and 0.5 μl of SAP (Sequenom, San Diego, CA). The 384-well plate is then sealed and placed in a thermal cycler with the following conditions: 37°C for 40 min, 85°C for 5 min and then held at 4°C indefinitely. After the SAP treatment, a 2 μl cocktail, consisting of 0.755 μl water; 0.2 μl iPlex 10x buffer (Sequenom, San Diego, CA), 0.2 μl iPlex terminator mix (Sequenom, San Diego, CA); 0.804 μl of 7 M/ 14 M (depending on the low vs. high mass primers) extension primer mixture and 0.041 μl iPlex enzyme (Sequenom, San Diego, CA) is added. After the iPlex cocktail addition, the plate is again sealed and placed in a thermal cycler with the following program: 94°C for 2 min followed by 40 cycles of 94°C for 5 sec, [5 cycles (52°C for 5 sec, 80°C for 5 sec) and 72°C for 5 sec]. The reaction mixture is then desalted by adding 16 μl of water and 6 mg cationic resin mixture, SpectroCLEAN (Sequenom, San Diego, CA). The plate is then sealed and placed in a rotating shaker for 20 min to desalt the iPlex solution. Completed genotyping reactions are spotted in nanoliter volumes onto a matrix arrayed silicon chip with 384 elements (Sequenom SpectroCHIP) using the MassARRAY Nanodispenser. SpectroCHIPs were analyzed using the Bruker Autoflex MALDI-TOF mass spectrometer and the spectra are processed using the SpectroTYPER v3.4 software (Sequenom, San Diego, CA).

Aim 1: To prospectively use molecular inversion probe (MIP) array technology and mass spectrometry-based genotyping to identify copy number aberrations and somatic mutations that mediate tumor formation using formalin-fixed paraffin-embedded (FFPE) tumor tissue from patients enrolled on the NCI cooperative group neoadjuvant trial for patients with locally advanced rectal cancer. Patients must have FFPE tumor tissue available and have signed consent for use of this tissue. Since the MIP platform is relatively novel, we will first examine whether running arrays in different batches or using tumor sample stored for variable durations introduces any systematic differences in copy number profiles. If necessary, we will develop data normalization algorithms to remove these artifacts. Notably, in preliminary studies, FFPE samples more than 10 years old have been analyzed successfully. Prior to analysis, the MIP data will be normalized and segmented as previously described and placed in a format suitable for the Integrative Genomics Viewer. The segmented data will then be reviewed for focal copy number alterations in known cancer associated genes, including MET, NF1, PTEN, and others. Concurrently all samples will be run on our CLIA-approved mass spectrometry-based (Sequenom) genotyping platform. This assay assess for hotspot mutations in KRAS, NRAS, BRAF, PIK3CA and other genes. All mutations in the mass spectrometry based assay are also incorporated into the custom cancer MIP array developed in collaboration with Affymetrix. All mutation calls generated by the MIP array will be further validated using either Sanger sequencing or,

if the mutation is represented within our Sequenom assay, by mass spectrometry-based genotyping. Only those mutations that can be confirmed by an orthogonal method will be considered true positives. As the MIP array and the Sequenom assay may have greater sensitivity than the Sanger method, mutations that fail to be confirmed will be further assayed using next-generation sequencing methods on a case-by-case basis.

We will use hierarchical clustering to determine whether patients can be divided into subgroups defined by similar copy number profiles. These data will guide the formation of distinct subclasses of patients that are likely to respond to different treatments as described in Aim 3.

Aim 2: To correlate the MIP array copy number and mutational data collected from patients with locally advanced rectal cancer with clinical outcomes. For patients with locally advanced disease, the outcomes of interest will be complete pathologic response, pelvic recurrence-free, extra-pelvic recurrence-free, and overall survival. Patients will be followed for a minimum of 3 years in order to ensure that the majority of events have occurred before performing the initial test for association between mutational and copy number alteration status and outcome. Estimates of these endpoints will be calculated using the methods of Kaplan and Meier and comparisons between those with and without each mutation/copy number alteration will be examined using the log rank test. We will also correlate survival with the genomic subclasses discovered in Aim 1. The biomarker groups selected for the clinical trial should have similar clinical characteristics for all patients within this group; otherwise, subgroups will be redefined.

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APPENDIX XI: INDICATORS OF IMMUNOLOGIC ACTIVATION

Indicators of Immunologic Activation in Locally Advanced Rectal Cancer

Objectives:

(1) To identify immune markers for response to neoadjuvant chemotherapy or chemoradiation using very well established, validated immunologic assays.
(2) To investigate the ability of neoadjuvant FOLFOX or chemoradiation to augment anti-tumor immunity against rectal cancer.
(3) To identify novel immune targets in rectal cancer.

Specific Aims:

(1) To measure serum cytokine profiles before and after therapy.
(2) To determine the impact of chemotherapy or chemoradiation on antibody responses to cancer-testes antigens.
(3) To utilize recently developed protein array technology to simultaneously assay for induction of antibody responses to >8000 recombinant proteins as a tool for both correlation with clinical response as well as novel antigen discovery.

Significance and Background:

The rationale for immune recognition of colorectal cancer is based on several observations that effector/memory T cells infiltrate colorectal tumors, have prognostic value, and correlate with earlier disease stage and prolonged survival. This was furthermore shown in a retrospective analysis to be superior to and independent of the current TNM staging classification. Of particular relevance here, was the observation that the density of $CD3^+$ and $CD45RO^+$ T-cell density has prognostic value (Galon et al., 2006; Pages et al., 2005).

The core hypothesis that chemotherapy and radiation can both augment immunity is based on observations that genetic instability in cancer leads to a diverse number of mutations (Sjoblom et al.., 2006), and that such mutational diversity can provide novel targets that could be perceived by the immune system as non-self. As presented by [redacted] at the 2009 ASCO Plenary Session, we have confirmed that many candidate tumor antigens, that can bind to MHC class I, arise due to such mutational diversity (Segal et al., 2008). The important point is that each antigen recognized by the immune system is a potential target for a tumor-specific immune response. Therefore tumor cell destruction *in situ* by neoadjuvant FOLFOX or chemoradiation can provide a polyvalent tumor vaccine by causing cell death and liberating tumor antigens (Peggs et al., 2007)

This hypothesis has led to several studies combining standard chemotherapy with immune augmentation. At Memorial Sloan-Kettering Cancer, we are currently leading two multicenter immunotherapy clinical trials, studying (1) cetuximab plus Imprime-PGG; and, (2) FOLFOX with or without Programmed Death-1 (PD-1) blockade in patients with metastatic colorectal cancer, under the leadership of [redacted]

Similar studies have been done in melanoma with ipilimumab and dacarbazine (Hersh et al., 2011) and prostate cancer with radiation and ipilimumab (ASCO 2008). The success of immune augmentation using ipilimumab has led to its recent FDA approval in melanoma. Further studies toward immune therapy in colorectal cancer are warranted.

Recently the Immune Monitoring Facility (IMF) and the Ludwig Center for Cancer Immunotherapy at MSKCC has recently advanced the field of immune therapy and immune monitoring, under the leadership

of [redacted] in collaboration with the Cancer Vaccine Consortium, an international network of investigators who are focused on the conduct of clinical trials of novel immunotherapies for cancer. Our recent experience in tumor immunology with anti-PD-1 in colorectal cancer and melanoma, and CTLA-4 (Cytotoxic T-Lymphocyte Antigen 4) in melanoma has provided invaluable experience toward studying the immune response in cancer.

Specimens Required:
Mandatory research blood draws will be collected at baseline (≤ 28 days of start of FOLFOX or 5FUCMT) and ≤ 28 days before surgery. Specimens should be collected prior to drug administration or radiation on relevant days. See Section 14.0 for instructions regarding acquiring, processing, and shipping mandatory research blood specimens.

Specific Aim #1. **To measure serum cytokine profiles before and after therapy**.

Rationale and Design: Cytokine profiles provide insight in to the status of immune activation and whether there is predominance of a Th1 or Th2 tumor response. Th1 type immune responses are associated with cellular cytotoxicity and effective anti-tumor immunity. It has previously been shown that chemotherapy and radiation result in altered cytokine profiles in patients with colorectal cancer (Gremy et al., 2008; Tsavaris et al., 2010). Baseline and changes in cytokine profiles may be measured in patients treated with FOLFOX or chemoradiation. Matched Pre- and post-treatment patient sera may be assayed using the Human Th1/Th2 Cytokine Cytometric Bead Array Kit (BD Biosciences, San Jose, CA, USA) to measure serum levels of IFN- γ, IL-2, IL-4, IL-5, IL-10, and tumor necrosis factor-α according to the recommendations of the manufacturer. Serum may also be tested for VEGF, basic fibroblast growth factor (bFGF), and IL-8 using ELISA kits (R&D Systems, Minneapolis, MN, USA) according to the recommendations of the manufacturer.

Specific Aim #2. To determine the impact of chemotherapy or chemoradiation on antibody responses to the class of cancer-testes antigens.

Rationale and Design: Cancer-testis antigens are expressed in male germ cells, absent from adult somatic tissues, and are re-expressed in cancer due to disrupted gene regulation. Due to their restricted expression profile, these tumor antigens are ideal candidate tumor vaccines. More than 20 cancer-testes antigen families have been identified, including NY-ESO-1 and MAGE-A. Our previous studies in melanoma used ELISA to detect antibody responses to a panel of cancer-testis antigens. There is no clear consensus on the implication of these tumor antigens in patients with colorectal cancer and further work in this regard is warranted. We plan to study LAGE-1, MAGE, CT-7, CT-47, Sox-2, XAGE-1 or others.

Specific Aim #3: To utilize recently developed protein array technology to simultaneously assay for induction of antibody responses to >8000 recombinant proteins as a tool for both correlation with clinical response as well as novel antigen discovery.

Rationale and Design: Protein microarrays from Invitrogen allow for concurrent serological screening of >8000 full-length antigens with a single serum, on an unprecedented scale (termed seromics). We have performed a pilot study using serum from patients with colorectal cancer treated with chemotherapy and demonstrated seroreactivity against tumor antigens. In a study of melanoma before and after anti-cancer therapy, we demonstrated a relative increase in overall antibodies titers in patients with clinical response compared with patients that did not respond. While these numbers are small, we feel that these preliminary data justify further use of the seromics approach as an extremely powerful platform to study anti-tumor responses in colorectal cancer. We plan to apply seromics in patients treated with FOLFOX or chemoradiation. Matched Pre- and post-treatment patient sera will be assayed on one array each at an appropriate dilution to reveal specifically bound serum IgG.

The primary location of research will be within the Immune Monitoring Facility and the Ludwig Center for Cancer Immunotherapy, MSKCC. [redacted] from the department of epidemiology and biostatistics will perform statistical analysis on the data.

Interpretation of Data: Data analysis of resulting assays is expected to yield: **(1)** differences in immune activation after neoadjuvant chemotherapy or chemoradiation; **(2)** a limited number of antigens with significant changes in seroreactivity after each treatment, indicating potential targets "hit" as a result of treatment; and, **(3)** a profile of baseline immunoreactivity in these sera. Together, these studies will help identify prognostic and predictive markers of response to FOLFOX or chemoradiation, and identify antigens with that may be targets of future immune therapies in combination with chemotherapy or chemoradiation.

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APPENDIX XII: ASSESSMENT OF GERMLINE VARIATION

Assessment of Germline Variation as a Predictor of Response and Toxicity to Platinum-based Chemotherapy and to Radiation Therapy in Patients with Rectal Cancer

A major challenge in rectal cancer is that response, as well as treatment-related toxicity, is highly variable between patients. Pharmacogenomics has the potential to optimize, and personalize, the management of cancer patients by helping clinicians predict which individuals may be at increased risk of toxicity or resistance to a specific treatment modality. While response to chemotherapy and radiation therapy may be a function of an intrinsic biologic characteristic of the tumor itself (i.e., colorectal tumors with *KRAS* mutations are resistant to EGFR-inhibitors), host factors, as assessed through germline genetics, may influence pharmacokinetics of therapies and may thereby alter treatment efficacy and side effects. A small number of pharmacogenomic studies have already been performed in colorectal cancer but have largely been limited to single-institutions studies with small sample sizes, heterogeneous treatment groups, and/or consisted of the assessment of patients with metastatic, as opposed to early-stage, colorectal cancer. Furthermore, to our knowledge, the assessment of potential germline predictors of radiation response and toxicity in rectal cancer patients receiving radiation therapy has not been performed. The objective of this study is to identify germline genetic variants that may predict for chemotherapy and radiation sensitivity/toxicity which could potentially help tailor therapy according to individual host genetic factors.

Specific Aims:
1. To determine whether germline genetic variants in candidate genes of interest (Table1) are associated with response and/or toxicity to platinum and 5FU-based chemotherapy;

2. To determine whether germline genetic variants in candidate genes of interest (Table 2) are associated with response and/or toxicity to radiation therapy;

3. To assess whether genetic risk variants identified in genome-wide association studies of colorectal cancer susceptibility (Table 3) are associated with rectal cancer clinical outcome and response to therapy.

Aim 1

Rationale: Resistance to platinum agents has been attributed to enhanced tolerance to DNA adducts, decreased drug accumulation, and enhanced DNA repair. As such, the genes involved in some of these pathways have served as potential candidate genes for assessment in pharmacogenomic studies. In a number of small studies, functional polymorphisms in DNA-repair genes such as *XPD(ERCC2), ERCC1, XRCC1*, and metabolizing genes, glutathione S-transferase *GSTP1, GSTM1, and GSTT1* have been assessed for their ability to predict resistance/toxicity to oxaliplatin (Ruzzo et al., 2007; Pare et al., 2008a; Stoehlmacher et al., 2004; Lamas et al., 2011) In addition to these genes, for the combination of 5FU and oxaliplatin, germline genetic variants relevant to genes implicated in 5FU related function such as thymidylate synthase (TS), methylenetetrahydrofolate reductase (MTHFR), dihydropyrimidine dehydrogenase (DYPD) have also been assessed (Marsh et al., 2001; Etienne-Grimaldi et al., 2010 ; Pare et al., 2008b; Deenen et al., 2011; Salonga et al., 2000; Villafranca et al., 2001). Although results of such studies have identified a number of potential genetic variants predictive of outcome and toxicity, data have not been consistently replicable, due probably in part to cancer and treatment heterogeneity within the study group, and a limited sample size.

To date, there have been two large metastatic colorectal studies that have evaluated pharmacogenomic

associations with clinical outcomes and toxicity. In the NCI Intergroup N9741 trial, in which metastatic colorectal cancer patients were randomized to IFL, FOLFOX or IROX, a subgroup of patients were assessed for genetic predictors of chemotherapy response and adverse events (McLeod et al., 2010) Using a candidate gene approach, 34 germline genetic variants were assessed in 15 candidate genes, with the five genes of primary interest including *TYMS*, *DPYD, CYP3A4, UGT1A1* and *GSTM1*, for associations with adverse events or outcomes. The homozygous *UGT1A1*28* allele, observed in 9% of patients, was associated with a 55% risk of grade 4 neutropenia in the patients receiving IROX, while a deletion variant in *GSTM1* was associated with a 28% risk of grade 4 neutropenia in the FOLFOX group. For outcome, presence of the *CYP3A5* variant was significantly associated with response rate to IFL (29% versus 60%).

In the French FFCD 2000-05 randomized phase III trial, a subgroup of patients with metastatic colorectal cancer receiving either first-line LV5FU2 followed by second-line FOLFOX6, followed by third-line FOLFIRI (Group A) or first-line FOLFOX6 followed by second-line FOLFIRI (Group B) also underwent pharmacogenomic assessment (Boige et al., 2010) Genotyping for 20 polymorphisms from nine genes involved in the FU (*DPD, TS,* and *MTHFR*), oxaliplatin (*ERCC1, ERCC2, GSTT1, GSTM1* and *GSTP1*) and irinotecan (*UGT1A1*) pathways was performed. In this study, the *ERCC2*-K751QC allele was independently associated with risk of grade 3/4 hematologic toxicity to FOLFOX, while 3 genetic variants were associated with response to FOLFOX (*MTHFR*-1298C; *TS5-' UTR3RG*, and *GSTT1* alleles). Moreover, progression free survival from first-line FOLFOX was limited to patients with 2R/2R or the 2R/3R *TS-5'UTR* genotypes. It is notable that only a subgroup of patients in each of these studies underwent pharmacogenomic assessment limiting study results (for example, in N9741, informed consent for pharmacogenetic studies and blood sampling was added as an amendment midway through study accrual). On the other hand, these large metastatic colorectal studies clearly established that pharmacogenomic studies can be successfully conducted in large, multicenter research studies (Goldberg et al., 2010)

Our Genetics and GU oncology groups at MSKCC recently assessed whether germline variation in candidate genes predicted response to platinum-based chemotherapy in patients with urothelial carcinoma (*ASCO Genitourinary Cancer Symposium, February, 2011 Oral Presentation).* Our results showed that 4 SNPs retained associations with response. A greater number of "at-risk" alleles in an individual correlated with decreased response to platinum. In a multivariate model, that included a previously established MSKCC clinical risk score, each additional "at-risk" allele of the SNP score was associated with nearly 50% decrease in odds of response. The bootstrap-adjusted c-index (equivalent to AUC) of this model was 0.78, a marked improvement over 0.65 seen with the MSKCC clinical risk score alone. SNPs assessed, genotyping methods, and subsequent statistical analysis used in this prior study of platinum-sensitivity in urothelial carcinoma will be used as a source of reference for this study of platinum-based response/toxicity in rectal cancer.

In addition to hematologic toxicity, a major, often dose-limiting, side effect of oxaliplatin is the development of chronic sensory neuropathy, which appears to be cumulative, and in some cases results in permanent residual toxicity despite drug cessation. Studies aimed at preventing this life-altering side effect have been largely unsuccessful and the mechanism of neurotoxicity has not been clearly elucidated (McWhinney et al., 2009). The incidence of clinical neurotoxicity is not directly associated with tumor response. Pharmacogenomic studies assessing for predictors of neurotoxicity are limited. In smaller studies of colorectal cancer patients receiving oxaliplatin-based treatment, genetic variants in *ERCC1* and *GSTP1* predicted for earlier development of neurotoxicity.(Ruzzo et al., 2007; Inada et al., 2010]) In the aforementioned N9741 trial, patients with a homozygous variant genotype of *GSTP1* were more likely to discontinue FOLFOX due to neurotoxicity (24% versus 10%) (McLeod et al., 2010). Given the importance of this potentially irreversible toxicity, further pharmacogenomic studies to identify markers that predict for this toxicity are clearly needed.

Design: To determine whether germline genetic variants in candidate genes of interest are associated with

response and/or toxicity to platinum and 5FU-based chemotherapy.

Using the genetic variants within the listed candidate genes in Table 1 (other possible genetic variants/candidate genes may be added), we will perform genotyping (see Methods) using genomic DNA on all patients randomized to receive neoadjuvant chemotherapy with FOLFOX. Clinical outcome, as assessed by pathologic response to chemotherapy at time of surgical resection will be correlated with genotype for each SNP/genetic alteration. In addition, toxicity, using NCI-CTCAE, including but not limited to hematologic toxicity and neurotoxicity, will also be assessed and correlated with genotype.

Table 1. Genetic Variants Associated with Platinum and 5FU-based Chemotherapy Response or Toxicity

Candidate Genes	Polymorphism
5FU	
TS 5'-untranslated region (5'UTR)	VNTR
TS 3'-untranslated region (3'UTR)	6bp ins/del
TS 5'UTR	G/C
MTHFR	677 C>T
MTHFR	1298 A>C
MTHFR	1793 G>A
DPYD	1627 A>G
DPYD	2194 G>A
DPYD	85 T>C
DPYD	IVS14+1 G>A
Platinum	
ERCC1	IVS5+33 C>A
ERCC1	IVS3+74C>G
ERCC1	IVS4+86T>C
ERCC1	354 C>T
ERCC2	IVS19-70G>A
ERCC2	-1989A>G
ERCC2	2133 C>T
ERCC2	2251 A>G
GSTM1	del poly
GSTP1	2293 C>T
GSTP1	1578 A>G
XRCC1	1196 G>A
GSTT1	del poly

Table 1 candidate gene references: Wang et al., 2009; Berry et al., 2011; Zhou et al., 2008; Barker et al., 2009; Galon et al., 2006; Pages et al., 2005 ; Sjoblom et al., 2006; Segal et al., 2008; Peggs et al., 2007; Hersh et al., 2011; Gremy et al., 2008; Tsavaris et al., 2007.

Aim 2

Rationale: Response to radiation therapy varies widely, ranging from a complete response to virtually no response in the tumor, and from little toxicity to severe short- and/or long-term treatment related adverse reactions in normal tissue. Although clinical factors such as radiation dose, volume, and fraction certainly have an important impact on response and toxicity, it has been estimated that nearly 80% of inter-individual variation in normal tissue response to radiation may be due to genetic factors (Barnett et al., 2009). Given the relatively narrow therapeutic index for radiation therapy, understanding the underlying variation in response to radiation might help us maximize radiation efficacy in the tumor, while minimizing side effects in normal tissue. Genetic variants in a number of candidate genes in pathways that include endogenous oxidation stress defense, inflammatory response, cytokine activity related to fibrosis, DNA damage signaling, cell cycle control, and DNA repair have been associated with radiation response (Andreassen et al., 2009; Chistiakov et al., 2008; Popanda et al., 2009; Pugh et al., 2009) More recently, genome-wide basal gene expression profiles and genome-wide SNPs for 277 lymphoblastoid cell lines were used to identify SNPs/genes that might contribute to variation in radiation response (Niu et al., 2010). Using an integrated analysis that included genome-wide SNP data, basal expression and radiation AUC, 50 unique SNPs were identified with the most significant regions containing the *LRRN2, IL19, KCNK1, LDB2, NCRNA00290, DEPDC1B, PPIGP1* and *PLEKHF2* genes. Pharmacogenomic studies in radiation response and toxicity in rectal cancer have not been performed and, as such, this large adjuvant trial, will provide the platform for this novel study.

Design: Using the genetic variants within the listed candidate genes in Table 2 (other possible genetic variants/candidate genes may be added), we will perform genotyping (see Methods) using genomic DNA on all patients randomized to receive neoadjuvant radiation therapy. Clinical outcome, as assessed by pathologic response to radiation at time of surgical resection will be correlated with genotype for each SNP/genetic alteration. In addition, short-term radiation toxicity, using NCI-CTCAE, will also be assessed and correlated with genotype. Given that the radiation treatment will be receiving 5FU for radiosensitization, a subgroup of the SNPs listed in Aim1 that have been implicated in 5FU response/toxicity will also be assessed in this group.

Table 2. Genetic Variants Associated with Radiation Response or Toxicity

Candidate Genes	Polymorphism	Implications in Other Cancers
GSTP1	1578A>G	Skin Toxicity
TGFB1d	869 T>C	Subcutaneous fibrosis
ATM	5557G>A; IVS22-77 T>C; IVS48+238C>G	Late adverse normal tissue reaction; rectal bleeding (prostate cancer)
XRCC1c	rs25489	Late rectal bleeding; erectile dysfunction (prostate cancer)
LIG4	26C>T	Rectal and bladder toxicity (prostate cancer)
XRCC3a	5'UTR; 4541A>G; -1843A>G	Rectal and bladder toxicity (prostate cancer)
MLH1	rs1799977	Rectal and bladder toxicity (prostate cancer)
CYP2D6 4a	rs1800716	Rectal and bladder toxicity (prostate cancer)
XRCC3b	IVS5-14G	Gastrointestinal toxicity
IL12RB2a	rs3790566	Radiation dermatitis
RAD 21	rs1050838	Radiosensitivity
SMAD4	Multiple	Chemo and radioresistance
Candidate Genes from GWAS	**Polymorphism**	**Implication**
PLEKHF2	rs7000734	Radiosensitivity
TINAG	rs1685294	Radiosensitivity
PLEKHF2	rs1561715	Radiosensitivity
PLEKHF2	rs1610110	Radiosensitivity

Table 2 candidate genes from Andreassen et al., 2009; candidate genes from GWAS from Niu et al., 2010.

Aim 3

Rationale: Genome-wide association studies (GWAS) have identified at least 10 independent susceptibility loci associated with colorectal cancer risk (Table 3) (Stadler et al., 2010). The effect size for each of the identified risk SNPs is modest resulting in a 10-30% increase in the relative risk of CRC. While some of the risk SNPs map to genes of interest in colorectal cancer (*SMAD7, BMP4, CDH1*), several SNPs map to areas devoid of known genes. For the majority of risk SNPs, the causal variant(s) have not been identified and functional studies to determine how these risk variants may exert their effect are currently on-going. Also unknown are the possible gene-gene and gene-environment interactions that may further modify the effect of these risk alleles.

Our Genetics and GI Oncology groups at MSKCC recently completed a study to determine whether germline colorectal cancer risk variants (SNPs) discovered in recent GWAS are associated with cancer phenotype and outcome. Using an incident cohort of 891 colorectal cancer cases, we genotyped all cases for the eight independent colorectal risk SNPs (Table 2) and after adjusting for potential confounders and multiple comparisons, identified one SNP that predicted for an earlier age at disease onset as well as 2 SNPs that predicted for survival (*ESMO Annual Meeting Proceedings, October 2010, Oral Presentation; manuscript in preparation*). This incident cohort consisted of patients with stage I-IV disease receiving a variety of different treatment modalities. Although our group at MSKCC has looked at this heterogeneous incident group of colorectal cases for associations with clinicopathologic features, whether these colorectal cancer risk SNPs predict for clinical outcome and response to a specific treatment modality in a more homogenous population has not been assessed to date.

Design: To assess whether genetic risk variants identified in genome-wide association studies of colorectal cancer susceptibility are associated with rectal cancer clinical outcome and response to therapy

Using the colorectal cancer risk genetic variants listed in Table 3, we will perform genotyping (see Methods) using genomic DNA on all study patients. Clinical outcome, as assessed by pathologic response to chemotherapy or radiation therapy at time of surgical resection, will be correlated with genotype for each SNP/genetic alteration. In addition, the study end-points of TLR and DFS may also be used for correlation with genotype.

Table 3. Risk SNPs from GWAS of Colorectal Cancer

Locus	Implicated Gene	SNP	Per Allele OR Ranges
8q23.3	*EIF3H*	rs16892766	1.27
8q24.21	*LOC727677, POU5F1P1*	rs10505477	1.17
		rs6983267	1.17-1.27
		rs7014346	1.19
10p14	intergenic	rs10795668	1.12
11q23.3	intergenic	rs3802842	1.12
14q22-q23	*BMP4*	rs4444235	1.11
15q13	intergenic	rs4779584	1.23-1.26
15q13-q15	*GREM1*	rs10318	1.19
16q22.11	*CDH1*	rs9929218	1.10
18q21.1	*SMAD7*	rs4939827	1.16-1.20
20p12.3	intergenic	rs961253	1.12

Table 3 SNPs are from Stadler et al, 2010.

Methods: Informed consent for pharmacogenomic studies using blood sampling will be obtained from each study subject. Genomic DNA will be extracted from peripheral blood cells using standard techniques and will be stored at 4°C before use. Genotyping for the selected germline genetic variants will be performed using the Sequenom-iPLEX Gold System CC according to manufacturer's protocol (Sequenom, CA). The iPLEX Gold assay is based on multiplex PCR followed by a single base primer extension reaction. After the PCR, remaining nucleotides are deactivated by alkaline phosphatase (SAP) treatment. The single base primer extension step is performed, and the primer extension products analyzed using MALDI TOF MS. Alleles are distinguished on the basis of their masses and relative peak heights. The assay design is automated, all oligonucleotides are unlabeled and of standard quality. All primers and probes will be designed and multiplexed using Sequenom software and assistance through Sequenom web support ([redacted]).

It is important to note that as pharmacogenomics is a rapidly evolving field, additional genetic variant(s) in candidate gene(s) of interest are likely to be added to the current lists in the above tables. In addition, with the rapidly decreasing cost of genotyping, an agnostic approach to the identification of genetic variants that predict for platinum-based chemotherapy and radiation response/toxicity may be an alternative acceptable method for this correlative study.

Statistical Analysis: Univariate Cox proportional hazards regression will be used to investigate the association between each SNP and clinical endpoints of interest. Each SNP will be analyzed under a co-dominant model, with the association determined from a global test for differences in outcome between the 3 genotypes (common homozygote, heterozygote, and rare homozygote), commonly referred to as a "2 degree of freedom test". The probability of freedom from the various events will be estimated using Kaplan-Meier methods. For relevant clinical endpoints, time at risk will be calculated from the date of study registry

to the date of event or date of last contact, and patients without the event will be censored at their last follow up date. For SNPs significant at $p < 0.05$ under the co-dominant model, multivariable analyses will be conducted controlling for potential confounders. P values will be reported both with and without correction for multiple testing using a Bonferonni correction. The endpoints tested will include pathologic response to neoadjuvant chemotherapy and/or radiation therapy, NCI-CTCAE graded toxicities, including but not limited to hematologic toxicity, neurotoxicity and skin toxicity, and possibly LTR and DFS.

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APPENDIX XIII: AJCC 7TH EDITION RECTUM CANCER STAGING

AJCC 7th Edition Rectum Cancer Staging Definitions

Source: The AJCC Cancer Staging Manual, 7th Edition (2010) published by Springer New York, Inc.

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ: intraepithelial or invasion of lamina propria[1]
T1 Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades through the muscularis propria into pericolorectal tissues
T4a Tumor penetrates to the surface of the visceral peritoneum[2]
T4b Tumor directly invades or is adherent to other organs or structures [2, 3]

Regional Lymph Nodes (N) [4]

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1–3 regional lymph nodes
N1a Metastasis in one regional lymph node
N1b Metastasis in 2–3 regional lymph nodes
N1c Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2 Metastasis in 4 or more regional lymph nodes
N2a Metastasis in 4–6 regional lymph nodes
N2b Metastasis in 7 or more regional lymph nodes

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis
M1a Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
M1b Metastases in more than one organ/site or the peritoneum

Notes

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

2 Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (that is, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina).

3 Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion, whereas the PN site-specific factor should be used for perineural invasion.

4 A satellite peritumoral nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule may represent discontinuous spread, venous invasion with extravascular spread (V1/2), or a totally replaced lymph node (N1/2). Replaced nodes should be counted separately as positive nodes in the N category, whereas discontinuous spread or venous invasion should be classified and counted in the Site-Specific Factor category Tumor Deposits (TD).

Anatomic Stage/Prognostic Groups:

Stage	ypT	ypN	M
0	Tis	N0	M0
I	T1 T2	N0 N0	M0 M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2 T1	N1 or N1c N2a	M0 M0
IIIB	T3-T4a T2-T3 T1-T2	N1 or N1c N2a N2b	M0 M0 M0
IIIC	T4a T3-T4a T4b	N2a N2b N1-N2	M0 M0 M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

Note: cTNM is the clinical classification, pTNM is the pathologic classification.

APPENDIX XIV: INDEX OF ACRONYMS

Index of Acronyms (in alphabetical order):

2PC	Second primary colorectal cancer
5-FU	5-Fluorouracil
ACOSOG	American College of Surgeons Oncology Group
ADR	Adverse drug reaction
AE	Adverse Event
AERS	Adverse event reporting system
AJCC	American Joint Committee on Cancer
AKA	Also known as
AML	Acute Myelocytic Leukemia
ANC	Absolute neutrophil count
APR	Abdominaloperineal
ASCO	American Society of Clinical Oncology
ATC	Advanced Technology Consortium
BDP	Bi-dimensional product
BP	Blood pressure
BWH	Brigham and Women's Hospital
CALGB	Cancer and Leukemia Group B
CDUS	Clinical Data Update System
CEA	Carcinoembryonic antigen
CF	Leucovorin Calcium
CR	Complete Response
CRA	Clinical research associate
CRF	Case report form
CRM	Circumferential resection margin
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTEP-AERS	CTEP Adverse Event Reporting System
CTMS	Clinical trial management systems
CTSU	Cancer Trials Support Unit
CTV	Clinical target volume
DCTD	Division of Cancer Treatment and Diagnosis (NCI)
DFCI	Dana-Farber Cancer Institute
DFS	Disease Free Survival
DMC	Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
ERUS	Endorectal ultrasound
FAME	Foundation of Advanced Medical Education
FDA	Food and Drug Administration
FFPE	Formalin-Fixed, Paraffin-Embedded
FOLFOX	5FU + leucovorin + oxaliplatin

FSFI	Female Sexual Function Index
FTP	File Transfer Protocol
FUCMT	5FU combined modality therapy
GTV	Gross tumor volume
HRQL	Health-related quality of life
HUS	Hemolytic Uremic Syndrome
IIEF	International index of erectile function
IME	Important medical events
IMRT	Intensity Modulated Radiation Therapy
IND	Investigational new drug
IRB	Institutional review board
IROC	Imaging and Radiation Oncology Core
ITT	Intention-to-treat
IV	Intravenous
IVRS	Interactive voice response system
LAR	Low Anterior Resection
LLT	Lowest Level Term
LN	Lymph node(s)
MDS	Myelodysplastic syndrome
MIP	Molecular Inversion Probe
MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
NAR	Neoadjuvant Response Score
NCCTG	North Central Cancer Treatment Group
NCI	National Cancer Institute
NCTN	National Cancer Trials Network
NE	Not evaluated
NED	No evidence of disease
NOS	Not otherwise specified
NSABP	National Surgical Breast and Bowel Project
OAR	Organs at Risk
OPEN	Oncology Patient Enrollment Network
OS	Overall survival
OSU	Alliance Biorepository at Ohio State University
OXAL	Oxaliplatin
PACS	Picture archiving and communications system
PBDP	Post-Baseline Bi-Dimensional Product
pCR	Pathologic complete response
PD	Progressive disease
PET	Positron emission tomography
PMB	Pharmaceutical Management Branch
PP	Per-Protocol
PR	Partial Response
PRO-CTCAE	Patient-Reported Outcomes Version of the Common Terminology Criteria

PS	Performance status
PSR	Protocol Specific Requirement
PTV	Planning target volume
QARC	Quality Assurance Review Center
QOL	Quality of Life
REC	Recurrence of disease
RECIST	Response Evaluation Criteria in Solid Tumors
RPC	Radiological Physics Center
RRR	R0 Resection Rate
RSS	Regulatory Support System
RT	Radiation therapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
SD	Stable disease
SOC	SYSTEM/ORGAN/CLASS
SPEER	Specific Protocol Exceptions to Expedited Reporting
TLR	Time to local recurrence
TME	Total Mesorectal Excision
TRG	Tumor Regression Grade
UCSF	University of California San Francisco
ULN	Upper limit of normal
VOD	Veno-occlusive disease

APPENDIX XV: SITE PREPARATION CHECKLIST

Site Preparation Checklist

This preparation checklist is intended to be a resource for site study teams to be used in conjunction with the official protocol document; it **does not** replace the official protocol. References to where the information may be located are included in parenthesis.

- ☐ Is your site PI and study staff registered with CTEP and do they have active CTEP-IAM account(s)? (For assistance, please refer to protocol Section 6.0)

- ☐ Is your site investigator an NCI registered investigator with an NCI investigator number? (For assistance, please refer to protocol Section 6.1)

- ☐ Is your site IRB approved and activated? (Contact your site's IRB office with questions.)

- ☐ Did your site complete and submit documentation of the protocol specific requirement (PSR) to the CTSU Regulatory Office (one item is required BEFORE a site can open N1048)?
  - ☐ IRB approval of protocol (Section 6.2)

- ☐ Did your site complete and submit documentation of the following protocol specific requirements (PSRs) to the CTSU Regulatory Office (these two items can be done before OR after a site opens N1048)?
  - ☐ IMRT physics credentialing **and/or** 3D Conformal RT credentialing (Section 7.3)
  - ☐ PRO-CTCAE credentialing (Section 4.4.1 and Appendix V)

- ☐ Is your study site listed as 'approved' in the CTSU RSS? (Log into the CTSU website; click the blue 'protocols' tab. Click the beige 'site registration' tab. Enter your site CTEP code and the protocol number in the open text boxes and click GO. The website will indicate whether your site is approved or whether PSRs are still outstanding.)

- ☐ Is your study staff registered/active with OPEN? (Section 6.2)

- ☐ Has your study staff registered with and completed the training for RAVE? (You should automatically receive email invitations to activate your iMedidata account and/or join a site and study. Contact the CTSU Help Desk at [redacted] if you did not receive the email invitations.)

- ☐ Does your site have QOL Booklets on hand? (Please order these using the "CTSU Supply Request Form" available at [redacted]

- ☐ Does your site have a system in place to collect, process, and ship blood and tissue specimens at the necessary time points? (Please contact the clinical trial office at your site.)

- ☐ Have you emailed [redacted] to request log-in information for [redacted] the website that will enable you to electronically submit scans (MRI or CT) to the Alliance Imaging Core Lab?

APPENDIX XVI: IMAGE INTERPRETATION

The following instructions should aid in the consistent interpretation of images. It is recognized that assessment of clinical staging based on imaging is necessarily inexact and involves estimation. Clinical staging should be estimated using the AJCC 7th edition criteria. The criteria set forth below are to foster consistency of interpretation across sites.

1. Estimated radiographic tumor stage: T1, T2, T3, T4 Tumor length should be measured using calipers on the sagittal T2W image showing the greatest tumor extent craniocaudad. This may consist of several connecting vectors to follow the curvature of the rectum. Tumor width will be measured on sagittal T2W images as the greatest wall thickness (1-wall); a bi-dimensional product will be calculated.

2. Estimated radiographic nodal stage will be derived from preoperative imaging procedures using the AJCC 7th edition staging criteria. It is essential to note that this categorical system (e.g., N0, N1, N2) (AJCC 7th edition) is designed to record pathologic staging at the time of surgical resection. Its application and use in clinical rectal cancer staging is necessarily imprecise and numerous studies have documented the fact that large nodes may be tumor free and small nodes may contain tumor.

3. The total number of nodes to determine stage (N1 = 1-3, N2 = 4 or more) will include mesorectal and superior rectal stations.

4. Final analysis criteria will be short axis measurement with nodes positive at any size N1=1-3, N2=4 or more. Changes in short axis must be applied only to evaluable nodes (5mm or greater) and include 3mm or more (5-10mm baseline), 4mm (11-19mm baseline) or 25% (20mm or more). These changes will constitute PD (modification of RECIST 1.1 as defined for this protocol). Diminutive nodes (<5mm) are not considered.

5. Internal iliac nodes are uncommonly affected and more closely follow size changes and minimum size requirements as for other nodes outside of the mesorectal and superior rectal regions. Therefore, for evaluation of change after treatment, a node must have been 1.0 cm in short axis and increase by the rules above for PD.

6. Nodal stations considered suspicious for metastatic disease (M1) (AJCC 7th edition) are for rectal cancer: common iliac, external iliac nodes and inguinal nodes. Also bone metastases and peritoneal tumor implants.

7. Distance of the tumor from the mesorectal fascia reflection (AKA radial margin, AKA CRM or circumferential resection margin). A distance of 1 mm or less will be considered to have close/threatened radial margins and are ineligible.

8. Radiographic N2 status is estimated as: 4 or more nodes that measure 10mm or more in short-axis. Radiographic N1 status is estimated as: fewer than 4 lymph nodes that measure 10 mm or greater in short axis but 1 or more lymph nodes that measure 5 mm or greater.

APPENDIX XVII: SWISS SPECIFIC APPENDIX

Swiss Specific Appendix: Information only applicable to SAKK site participants that are full members of the Alliance.

SAKK - SWISS GROUP FOR CLINICAL CANCER RESEARCH

SWISS SPECIFIC APPENDIX

Version 1.2 – 02.12.2016

N1048 (PROSPECT**) A Phase II/III Trial of Neoadjuvant FOLFOX with Selective Use of Combined Modality Chemoradiation versus Preoperative Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision

** Pre-operative Radiation or Selective Preoperative Radiation and Evaluation before Chemotherapy and TME

Protocol Version Date: February 3, 2016

The purpose of this appendix is to specify information applicable for sites within the SAKK participating in this trial.

Coordinating Investigator for SAKK sites	[redacted]	[redacted]
CRA	[redacted]	[redacted]
Internet-based registration:	Alliance	[redacted]
Website:	[redacted]	
Internet-based SAE Reporting and Information:	Alliance	[redacted] via CTEP-AERS system via:

[redacted]

1 ABBREVIATIONS

5-FU	5-Fluorouracil
BioMS	Biospecimen Management System
CRA	Clinical Research Associate
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
CTEP	Cancer Therapy Evaluation Program
CTEP-AERS	CTEP Adverse Event Reporting System
CTSU	Cancer Trials Support Unit
CV	Curriculum vitae
EC	Ethics committee*
FOLFOX	5FU + Leucovorin + Oxaliplatin
GCP	Good Clinical Practice
HMO	Head of Monitoring
Swiss HRA	Swiss Human Research Act
ICH	International Conference on Harmonization
ID	Identification
IMP	Investigational Medicinal Product
NCI	National Cancer Institute
OPEN	Oncology Patient Enrollment Network
OSU	Alliance Biorepository at Ohio State University
PI	Principal Investigator
SAE	Serious Adverse Event
SAKK	Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung and
SAKK	Coordinating Center (SAKK CC)
SDV	Source data verification
SM	Swissmedic
SPC	Summary of Product Characteristics
SUVA	Swiss National Accident Insurance Fund /
Schweizerische	Unfallversicherungsanstalt
TME	Total Mesorectal Excision

*EC is known as Institutional review board (IRB) in the US.

TABLE OF CONTENTS

2 RANDOMIZATION AND PATIENT INCLUSION

2.1 Randomization procedure

Patient registration and randomization procedures are explained in detail in the protocol section 6.3.

3 DRUG SUPPLY AND HANDLING

3.1 Drugs / Radiotherapy / surgery in protocol

For this trial Fluorouracil, Leucovorin, Oxaliplatin and Capecitabine are the IMPs.

Fluorouracil (5-FU) is licensed in Switzerland for the use in malignant tumors of the rectum, colon, stomach, pancreas, liver, breast, uterus, cervix, ovary and the bladder.

Leucovorin is licensed in Switzerland for the treatment of advanced colorectal cancer in combination with 5-FU.

Oxaliplatin is licensed in Switzerland for the use in both curatively resected advanced ("adjuvant" setting) and metastatic colorectal cancer in combination with Leucovorin and 5-Fluorouracil. This combination builds up the FOLFOX treatment regimen, which is now a standard in the treatment of colorectal cancers, showing high response rates [1].

In daily clinical practice FOLFOX is used to treat patients with metastatic rectal cancer and to bridge the time between first patient visit and start date of radiotherapy, as the latter is frequently delayed due to planning and scheduling issues. Small series [2], [3], [4] have reported response of the primary tumor before surgery, thus confirming clinical experience

Capecitabine is licensed in Switzerland for the treatment of colorectal, esophageal, gastric and breast cancer. Capecitabine and 5-Fluorouracil are equally effective in the treatment of colorectal cancer.

Especially in Europe, Capecitabine concomitant to radiotherapy is a treating standard [5], [1]. Recent trials in rectal cancer, a German [6] and an American study [7], confirm the effectiveness and safety of chemoradiotherapy with Capecitabine.

For more details (e.g. regarding the treatment and dose levels with the IMPs) refer to the protocol section 7.0.

Surgical considerations

Photo documentation of every TME specimen is required and will be reviewed by the Surgical Quality Committee. These photos should be sent electronically to [redacted] within 2 weeks. For more details please refer to the Appendix VII of the protocol.

3.2 Drug safety and handling

Handling and safety

Leucovorin and Fluorouracil are applied within its approved indication and Capecitabine and Oxaliplatin according to standard of care. Therefore drugs will be prescribed by the investigator. For handling refer to the product information. SUVA guidelines on handling on cytostatics [8] and radiopharmaceuticals [9] have to be followed.

Oxaliplatin, Leucovorin and 5FU are administered intravenously. Capecitabine will be taken orally.

Labeling, dispensing and accountability of Oxaliplatin, Leucovorin and 5FU

For Oxaliplatin, Leucovorin and 5FU, which will be administered intravenously at the hospital, the SAKK will provide labels. It is the responsibility of the local pharmacist or designee to label each package of trial drug with the additional trial-specific label before dispensing Oxaliplatin, Leucovorin and 5FU. Each package will be labeled in English, stating the trial reference code, patient study ID, the contact details of the sponsor representative SAKK as well as the remark “for clinical trial use only”. The patient study ID has to be written on the label of the package before the study drug is dispensed to the patient.

The principle investigator or designee has to ensure the use of the drug inventory log for Oxaliplatin, Leucovorin and 5FU, which must be kept up-to-date and identify the receipt and dispensing of the drug (including date, amount, batch number, patient study ID). If sites already have their own accounting system, it may be used instead of the SAKK drug inventory log only after inspection and approval by the CRA.

Drug inventory logs are available from the SAKK website under the section useful tools

Labeling, dispensing and accountability of Capecitabine

For the medication Capecitabine, which is taken at home by the patient, the SAKK will provide labels. It is the responsibility of the local pharmacist or designee to label each package of trial drug with the additional trail-specific label before dispensing Capecitabine to the patient.

Each package will be labeled depending on the local language in German, French and Italian, stating the trial reference code, patient study ID, the contact details of the sponsor representative SAKK, as well as the remark “for clinical trial use only”. The study drug must be dispensed in the original package with the label clearly visible. The patient study ID has to be written on the label of the package before the study drug is dispensed to the patient.

Patients will be instructed to note the date of the drug intake in a diary (available on the SAKK website) and to return empty packages or unused medication (see also 5.3.).

The principle investigator or designee has to ensure the use of the drug inventory log for Capecitabine, which must be kept up-to-date and identify the receipt and dispensing of the drug (including date, amount, batch number, patient study ID). If sites already have their own accounting system, it may be used instead of the SAKK drug inventory log only after inspection and approval by the CRA.

Drug inventory logs are available from the SAKK website under the section useful tools.

3.3 Precaution

In order to exclude a pregnancy before treatment start of women with child bearing potential, either and urine or a blood beta HCG test must be used.

Women with child-bearing potential who take part in this trial must use effective contraception during the trial and 12 months thereafter.

It can’t be excluded that the treatment damages the sperms. Therefore, to avoid procreation men should use effective contraception (condoms). In addition, the partner should use also an effective contraception method. The combination of barrier (e.g. condom) and hormonal (e.g. the pill) is recommended by most experts.

If the partner gets pregnant during the trial or 12 months thereafter, please invite also the partner to a trial visit for an information exchange and ask permission to request information about the development of the pregnancy and the health of the baby.

4 SAFETY REPORTING

(See protocol section 10.4 “Expedited Reporting Requirements”)

As the SAKK is the Swiss sponsor representative of the trial, an agreement with the overall

sponsor Alliance was reached in such that serious adverse events (SAEs) (single cases) and pregnancy events have to be reported directly to Alliance and will be evaluated by Alliance.

4.1 Definition of Serious Adverse Event (SAE)

In the trial protocol section 10.4 adverse events which will be considered as serious adverse events are explained in detail. Exceptions are described in the protocol section 10.4.1.

In contrast to the reporting timeframes given in the protocol under section 10.4, all Swiss sites have to report all SAEs within 24 h to Alliance, without any exceptions.

4.2 Reporting of SAEs via CTEP-AERS system

The evaluation of SAEs in this trial is to be based on CTCAE Version 4.0. SAE reporting will be done using the internet based CTEP-AERS system. Additionally all SAEs need to be reported on a Solicited Adverse Event Form. For further details please refer to the section 10.4 of the protocol.

All SAEs must be immediately reported to Alliance via CTEP-AERS (within 24 hours of awareness of the SAE).

Every Swiss SAE must be forwarded by email immediately (within 2 working days) by Alliance to the SAKK Coordinating Center for reporting to the Swiss authorities. The SAKK will forward all Swiss SAEs to the Swiss Coordinating Investigator.

SAKK Coordinating Center

Swiss Group for Clinical Cancer Research

[redacted]

4.2.1 Pregnancy

Pregnancy should be reported via CTEP-AERS. For further information refer to the trial protocol section 10.3.5.

- **NOTE: To be eligible for Prospect (N1048), the patient must not be pregnant or nursing at the time of enrollment and must be willing to employ adequate contraception during treatment (see protocol section 3.1)**

4.3 Definition of Serious Adverse Drug Reaction (SAR)

SARs are all SAEs considered to be related (possibly, probably, definitely) to the trial treatment.

4.4 Definition of Suspected Unexpected Serious Adverse Reactions (SUSARs)

SUSARs are serious adverse reactions to the trial treatment. Drug related SUSARs are assessed as unexpected on the basis of the summary of product characteristics (SPC).

4.5 Reporting of SAEs to the Swiss ethics committee and competent authorities.

The SAKK CC ensures that all reporting requirements according to applicable Swiss law are followed [10].

It is the responsibility of the SAKK CC to inform the local and Lead EC about fatal SAEs from Switzerland within 7 days.

Alliance will evaluate if the SAE of a Swiss patient qualifies as a Serious Unexpected Adverse Reaction (SUSAR) and if so forwards all relevant information to the SAKK CC. The SAKK CC reports any SUSAR which occurred on the trial at a Swiss site to the PIs, Lead and local EC as well as to Swissmedic. The timelines for reporting are specified in the Swiss HRA and its ordinances.

4.6 Periodic reporting on safety to principal investigators and ethics committees.

Alliance will make the annual study summary report available to SAKK CC. This annual study summary contains a listing of adverse events grade ≥ 3, which are at least possibly related to the treatment. This report will be available on the CTSU website. SAKK CC will provide this summary together with Swiss specific information to the investigators, to the local and lead EC and Swissmedic.

5 DOCUMENTATION

5.1 Case report forms

All participant sites will submit study data electronically using the iMedidata Rave® System [redacted]). A detailed submission table of data can be found in the protocol section 17.

5.2 Quality of Life (QOL)

QOL will not be assessed in the Swiss cohort. The protocol section 4.5 and the Appendix VI do therefore not apply to Swiss sites.

5.3 Capecitabine medication diary

Patients who receive Capecitabine have to complete the Capecitabine medication diary.

The diary will be completed during the entire period of radiation and capecitabine therapy. This lasts usually for 5.5 weeks but may be longer for any reason.

The diary is available on [redacted]_→ Members → Trials → Gastrointestinal Cancers→ Prospect → Patient Diary.

5.4 Patient screening, enrollment and identification list

Sites must use a patient screening and enrollment list and a patient identification list in order to allow identification of a patient (available from the SAKK website: [redacted] → Members → Trials → Gastrointestinal Cancers → Prospect → Useful tools).

Patients will be identified with a patient study ID and the date of birth. These lists must be kept up to date at the site in the Investigator's File (IF).

6 TRANSLATIONAL RESEARCH

The translational research part of the PROSPECT study attempts to understand the molecular events related to tumor treatment using genomic characterizations, immunologic studies and pharmacogenomics.

For this purpose, tumor material from baseline biopsy and from surgical resection, as well as whole blood samples are mandatory and will be sampled for both Group 1 and Group 2 patients.

6.1 Procedure (to be performed by the sites)

No tube or shipping material will be provided by the SAKK CC or by the Alliance. All sites should use their own material (for details see section 14 of the protocol).

6.1.1 Scheduling of sampling

The collection of tumor tissue samples and blood samples is a mandatory part of this trial. Scheduling as well as further information can be found in the protocol section 14.0.

6.1.2 Shipment

Shipment of blood and tissue samples will be done separately.

Blood samples

Guidelines and more information for blood samples of Swiss sites can be found on the SAKK website: [redacted] → Members → Trials → Gastrointestinal Cancers → Prospect → Useful tools. The blood samples at baseline should be withdrawn only on Monday and Tuesday before the treatment starts. It has to be shipped to USA on the same day in order to reach the Pathology Department at the latest on Friday.

Tumor block samples

Sites will register the collected biospecimen with the BioMS system and send the tumor specimens directly to OSU by TNT/Swiss Post mail using a padded envelope.

Costs

Costs for shipment of the blood and tissue samples will be covered by the SAKK CC.

6.1.3 Labeling and handling

All blood samples have to be clearly labeled according to the protocol section 14.4.

All tumor tissue samples have to be clearly labeled according to the protocol section 14.3.
The submission of paraffin blocks is described in detail in the section 14.5 of the protocol.

All the specimen need to be logged and shipped via Alliance Biospecimen Management System (BioMS), for details see the trial protocol section 14.2.

6.2 Sample banking

Sampling of blood and tumor blocks is a mandatory part of this trial. The banking of the rest of the samples at Alliance Biorepository at OSU, according to the Biobank regulations [11], for future research is an optional part for which the patient has to give an additional consent (IC for Translational Research).

The patient retains the right to have the sample material destroyed at any time by contacting the PI without giving any reasons. However, already obtained data from this material can be used for intended analysis. Alliance is responsible for the destruction of the sample(s) at the request of the research patient through the principal investigator or at the end of the storage period. The PI will provide the Alliance with the required trial and the patient's study ID, so that any remaining tissue sample and any other components from the cells can be located and destroyed.

Any new analysis on these samples not planned in the protocol Prospect has to be approved by the Alliance board and by the responsible Ethics committee according to local law.

7 ETHICAL CONSIDERATIONS

This trial is to be performed in accordance with the Declaration of Helsinki, the Guidelines of Good Clinical Practice issued by ICH, and Swiss regulatory authorities requirements [12-15].

Before planning to enter any patients into this trial, the investigator has to make sure that the trial has been approved by the EC and Swissmedic and that his/her site has officially been opened by the SAKK CC (see chapter 8.5).

7.1 Patient information and informed consent

There are two Informed consents for this trial: One for the main trial and an additional for the sample banking of blood and tissue material (Biobank).

7.2 Data confidentiality

The personal information and the medical records of the patients will be kept private. The data will be anonymized with a code. The code(s) shall be kept secret and confidential by the principal investigator. Only anonymized data will be accessible to experts for scientific evaluation. During inspections professionals selected and designated by the sponsor and members of Swiss authorities may examine patient's medical history.

Identifiable personal details won't be published in study reports and publications. The sponsor is responsible for compliance of the data protection with the national and international guidelines.

7.3 Trial categorization

The trial is classified as a Category B in accordance with the new legal ordinance on clinical trials with investigational medicinal product (IMP) [13].

8 ADMINISTRATIVE CONSIDERATIONS

8.1 Insurance

The SAKK will indemnify patients included from Swiss centers for damages they have suffered as participants in the trial. For this purpose SAKK has taken out a special insurance for clinical trials with CHUBB, Insurance Company of Europe, UK.

8.2 Monitoring and auditing

Source data must be accessible for monitoring and auditing.

8.2.1 Monitoring / auditing strategy

This trial will be monitored / audited by SAKK CC. SAKK will perform auditing as requested by Alliance. Alliance will perform the first audit of one Swiss site (probably the highest recruiting site) and will during this audit train SAKK CRAs who will perform thereafter audits according to Alliance guidelines for further Swiss sites. In addition to participating sites, Alliance has also the option to audit the SAKK CC.

A trial initiation will be performed on site, before the enrollment of the first patient. At least two monitoring visits per site are planned, if patients are accrued at the site into the trial. The frequency of the visit will be adjusted according to the site recruitment, the monitoring tasks and the findings at a site. Extent of source data verification, topics to be audited as well as all the duties of the CRA during the visit are described in the monitoring plan. No monitoring is foreseen during the follow-up phase.

The CRA must provide all monitoring reports for review to the Head of Monitoring (HMO) within 2 weeks of the visit. After the review by HMO, the CRA forwards the reports to Alliance and keeps the original reports accessible for other involved persons.

8.2.2 Auditing / Inspections

Authorities have the right to perform inspections and SAKK CC as well as Alliance has the right to perform audits.

8.3 Trial activation procedure

The activation of a site covers the fulfillment of different steps. The sites have to obtain an NCI ID / CTEP ID, must register all investigators, get access to OPEN, RAVE and CTEP- AERS systems.

Further information is available in the Appendix XV of the protocol. A guideline to all of the above mentioned points is available on the SAKK website: [redacted] → Members → Trials → Gastrointestinal Cancers → Prospect → Useful tools.

8.4 Protocol specific requirements (to be performed by the site)

Patients may not be registered to this trial, until the protocol specific requirements have been submitted to the CTSU Registration Office as described in the protocol section 6.2.

- **Note: PRO-CTCAE assessments will not be done in Swiss cohort of patients: the protocol specific requirement as described in the protocol section 4.4 is thus void for Swiss study sites.**

8.5 Activation requirements by SAKK CC (to be performed by sites)

To become activated, sites have to fulfill both the activation requirements of Alliance and those of SAKK.

Prior to activation, investigators have to submit the following documents to the SAKK CC:

- The signed and dated Principal Investigator's Agreement, indicating that they will fully comply with the protocol, including an estimation of their annual accrual and additional items
- Signed and dated sign-off page of the protocol by the principal investigator

- Signed and dated CV of the principal investigator (not older than 2 years), including proof of GCP training
- The signed and dated radiation oncologist's agreement and the signed and dated CV of the radiation oncologist (not older than 2 years)
- The signed and dated surgeon's agreement and the signed and dated CV of the surgeon (not older than 2 years)
- Staff list
- Infrastructure statement

After both Alliance and SAKK activation steps were taken and after the successful initiation visit and having received EC and Swissmedic authorization, the site will receive an opening e-mail from the SAKK.

Please note, that only thereafter the site can include the first patient to the study.

8.6 Local trial records

8.6.1 Investigator's file

All trial-related documentation and correspondence should be filed in the investigator's file. A suggested table of contents (according to ICH E6, chapter 8) is provided on the website ([redacted] → Members → Trials → Gastrointestinal Cancers → Prospect → Useful tools).

8.6.2 Useful tools

Useful tools can be downloaded from our website ([redacted] → Members → Trials → Gastrointestinal Cancers → Prospect → Useful tools).

8.6.3 Record retention

The site will retain all essential documents according to ICH GCP. This includes copies of the patient trial records, which are considered as source data, CRFs, patient informed consent statement, laboratory data and printouts and all other information collected during the trial as well as all necessary documentation requested by Alliance and SAKK for the site activation. These documents will be stored for at least 10 years after the termination of the trial. The end of this retention period will be communicated to the sites by the SAKK CC.

For the patient trial records, which are entered into the EDC system, the sponsor guarantees the access and availability of the data at any time at least 15 years after the termination of the trial.

In the event that the investigator retires or changes employment, custody of the records may be transferred to another competent person who will accept responsibility for those records. Written notice of such transfer will be given to the SAKK CC. The SAKK CC will notify the relevant EC and the foreign group.

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