Non-Operative Management and Early Response Assessment in Rectal Cancer (NOM-ERA)

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Protocol Revision History

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Principal Investigator Signature Page

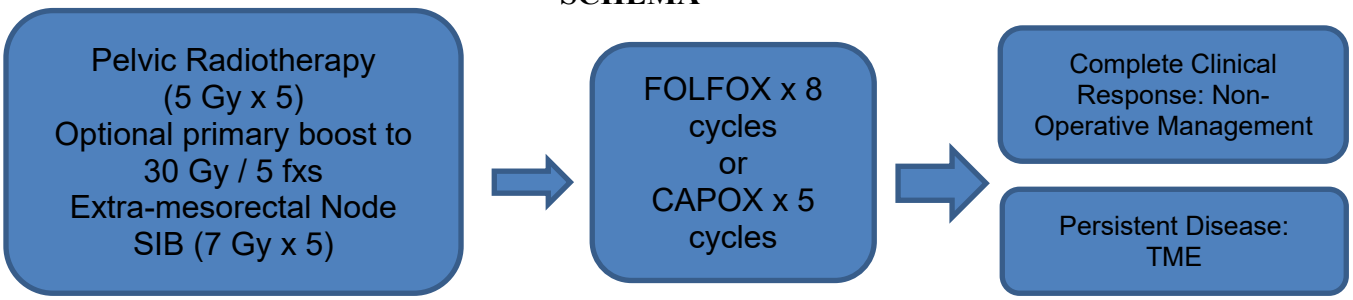
Principal Investigator (printed):

Name of Institution:

PI Signature *Date*

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

SCHEMA



Primary Objective
To determine the clinical complete response (cCR) rate of patients with Stage I-IIIB (cT1-3, N0-2a, M0) rectal cancer being treated with sequential short course radiotherapy followed by multi-drug chemotherapy.

Secondary Objectives:

1. To determine the 2 year progression free survival (PFS)
2. To determine the incidence of any grade ≥ 3 toxicity during treatment
3. To determine the incidence of post chemoradiotherapy grade ≥ 3 toxicity at 1 year
4. To determine quality of anorectal function at 1 year using the FACT-C questionnaire
5. To determine the 1 and 2 year organ preservation rate

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1 BACKGROUND

1.1 Stage I-III Rectal Cancer

With the exception of a small group of favorable risk stage I disease, the standard of care for stage I-III rectal cancer usually includes a total mesorectal excision (TME). TME in the form of an abdominoperineal resection (APR) results in a permanent stoma, which may significantly impact the patient's self-image and quality of life (QOL). TME in the form of a low anterior resection (LAR) obviates the need of an ostomy but is associated with poorer rectal function.

There are increasing data supporting the use of chemotherapy and radiation therapy for non-operative management of rectal cancer[1–4]. Habr-Gama et al. treated 183 distal rectal cancer (T2-4 N0-2) patients with 50.4-54 Gy in 30 fractions and concurrent 5-fluorouracil (5FU)/leucovorin and demonstrated an initial complete clinical response (cCR) of 49% patients 69% demonstrating a sustained cCR at 5 years[1]. Appelt et al. treated 55 patients (T2-3 N0-1) with 60 Gy in 30 fractions with a 5 Gy brachytherapy boost plus oral tegafur-uracil[2]. They reported 78% cCR with 16% local recurrence at 1 year with all local recurrences occurring within 2 years at the time of study publication[2]. Maas et al. found that patients with cCR after neoadjuvant chemoradiation therapy have similar oncologic outcomes to those with pathologic complete response (pCR)[4]. The radiation in these trials was delivered over 5-6 weeks of daily treatment.

1.2 Short Course Radiation Therapy

Short course radiation therapy delivered as 25 Gy in 5 fractions is routinely used as preoperative therapy in Europe and Australia[5–7]. The first Polish rectal study demonstrated that patients with T3-4 resectable rectal cancer treated with 25 Gy in 5 fractions followed by surgery versus 50.4 Gy in 28 fractions with concurrent 5FU followed by surgery had similar local recurrence (9% vs 14%), disease free survival (58% vs 56%) and overall survival (67% vs 66%)[6]. There was no difference in severe late toxicity (10% vs 7%). The second Polish rectal trial demonstrated that there was no difference in R0 resection and pCR rates in patients with T3-4 rectal cancer treated with 25 Gy in 5 fractions followed by FOLFOX then surgery compared to 50.4 in 28 fractions with FOLFOX followed by surgery[7]. There was even a 3 year overall survival advantage for short course radiation (73% versus 65%), but the reason for this survival advantage in light of a non-significant difference in disease free survival is unclear. Important to note is that the dose prescribed with pre-operative short course radiation (5 Gy x 5 fractions) has a biologic effective dose (BED) of 37.5 Gy ($\alpha/\beta=10$) in contrast to the BED of 63.7 Gy when 54 Gy is given in 30 daily fractions. Increasing the radiation dose to the tumor may further increase the clinical complete response (cCR) rate and allow for non-operative management.

1.3 Addition of Chemotherapy

There are increasing data to support increasing the interval from radiation to surgery. The

pCR rate of standard short course radiation followed by surgery 1 week later is approximately 1%[5,6]. Increasing the interval to surgery from 2 to 6-8 weeks may increase the pCR rate without compromising oncologic outcomes[8–10]. The Lyon R90-01 trial demonstrated that patients with T2 rectal adenocarcinoma treated with 39 Gy in 13 fractions had increased pCR if surgery is delayed to 6-8 weeks post-radiation versus 2 weeks post-radiation (26% vs 10%)[8]. In the non-inferiority Stockholm III, which evaluated short course radiation followed by surgery at 1 versus 4-8 weeks versus long course radiation therapy, there were no differences in long term cancer outcomes between the three treatment groups[11]. The GRECCAR-6 trial showed that increasing the interval from chemoradiation to surgery from 7 to 11 weeks did not improve pCR. However, chemotherapy was not used during the interval between treatments[12]. The Timing study provides evidence that extending the time from radiation to surgery with 3 months of chemotherapy increased pCR rates compared to observation and 1-2 months[13]. Thus increasing the interval from radiation completion to surgery, especially with chemotherapy, may improve treatment outcomes.

In a phase II trial for patients with cT3-4, any N, any M rectal cancer recently completed at Washington University evaluating short-course radiotherapy followed by 4 cycles of FOLFOX chemotherapy (5FU, oxaliplatin, and leucovorin), a pCR was seen in 25% of patients. Mean prospective Functional Assessment of Cancer Therapy-Colorectal (FACT-C) scores for all five categories were not significantly different for pre-treatment (20.6 ± 5.6), pre-surgery (20.2 ± 5.4), or post-surgery time points (20.0 ± 5.4). Improved patient-reported functional outcomes were observed for patients undergoing sphincter sparing surgery, compared to those requiring an abdominoperineal resection with ostomy, In patients with an ostomy, FACT-C scores for functional well-being 1-year post-surgery were significantly reduced (lower QOL) compared to patients without ostomy (13.2 vs 19.2)[14]. Thus despite the side effect profile associated with radiation and chemotherapy, it may provide improved QOL over the sequelae associated with an ostomy and permanent stoma.

1.4 Rationale

Our phase I trial of short course radiation therapy followed by chemotherapy showed 74% cCR. Given the promising response rate, we are evaluating short course radiation therapy (SCRT) followed by chemotherapy in a multi-institution phase II trial to validate the cCR rate of this treatment paradigm. SCRT has not been prospectively evaluated in non-operative management for patients with non-metastatic rectal adenocarcinoma.

1.5 Correlative Background

In contrast to the parallel technologies that guide the management of breast[15,16] or prostate cancer[17,18], there are no clinically implemented biomarkers that predict or prognosticate outcomes for rectal cancer. Colorectal cancer metastatic potential and aggressive proliferative phenotype have been linked to its tumor microenvironment. Cancer-associated fibroblasts (CAFs) deposit extra-cellular matrix (ECM) proteins resulting in a dense fibrotic stroma[19] that may confer resistance to chemotherapy, potentiate aggressive

phenotype[20] and limit infiltration and function of anti-tumor immune cells. FAK expression is associated with poorer survival in colorectal cancer patients after chemoradiation[21,22] and is also associated with fibrosis and poor patient outcomes in pancreas adenocarcinoma[23].

Cell-free DNA is emerging as a powerful method for quantitating tumor disease burden noninvasively[24,25]. Recently, the Vogelstein group at Johns Hopkins University measured circulating tumor DNA (ctDNA), the tumor component of cell-free DNA, in colorectal cancer patients treated with surgery and chemotherapy and demonstrated robust ability to measure molecular residual disease which was highly prognostic[26,27]. Similar data are now available in breast cancer[28], lung cancer[29], cervical cancer[30], and pancreatic cancer[31]. While the majority of this data is in the setting of surgery, Chaudhuri et al. demonstrated that ctDNA can also be measured before and after radiotherapy +/- chemotherapy for lung cancer, with post-treatment molecular residual disease (MRD) detection correlating significantly with eventual disease progression[29]. In preliminary data, Chaudhuri et al. further showed that mid-treatment ctDNA quantitation during chemoradiation may be prognostic for lung cancer patients[32]. Given these data, our goal is to measure circulating tumor DNA pre-, during and post-treatment as part of rectal cancer nonoperative management and correlate our findings with clinical and radiographic outcomes.

2 OBJECTIVES

Objectives	**Endpoints**	**Justification for Endpoints**
Primary		
To determine the clinical complete response (cCR) rate of patients with stage I-IIIB (cT1-3, N0-2a, M0) rectal cancer being treated with sequential short course radiotherapy followed by multi-drug chemotherapy.	cCR at completion of short course radiation therapy and chemotherapy	Nonoperative management treatment paradigms must be effective at eliciting a clinical complete response.
Secondary		
1. To determine the 2 year progression free survival (PFS) 2. To determine the incidence of any grade ≥ 3 toxicity during treatment. 3. To determine the incidence of post chemoradiotherapy grade ≥ 3 toxicity at 1 year 4. To determine quality of anorectal function at 1 year	1. PFS at 2 years 2. Incidence of any grade ≥ 3 toxicity during treatment 3. Incidence of post chemoradiotherapy grade ≥ 3 toxicity 4. Quality of anorectal function as measured by the FACT-C questionnaire at 1 year	1. Important to assess disease recurrence, metastasis and death when implementing new treatment paradigm. 2. Important to assess acute toxicity as there is concern that short course radiation is associated with significantly more acute toxicity.

using the FACT-C questionnaire. 5. To determine the 1 and 2 year organ preservation rate	5. Organ preservation rate at 1 and 2 years	3. Important to assess toxicity with new treatment paradigm, especially if rectum is not resected for nonoperative patients. 4. Treatment cannot be so toxic that even with preserved rectum patient QOL is poor. 5. Patients with cCR may still have regrowth of primary resulting in surgery. Need to assess how many patients can keep their rectum.
Tertiary/Exploratory		
1. To associate tumor microenvironment (including FAK expression) with cCR and other clinical outcomes. 2. To associate ctDNA levels with cCR and other clinical outcomes.		

3 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

1. Diagnosis of biopsy proven stage I-IIIB (cT1-3, N0-2a, M0) adenocarcinoma of the rectum; staging must also be based on multidisciplinary evaluation including MRI
2. Tumor ≤ 12 cm from anal verge as determined by MRI or endoscopy
3. Clinically detectable (MR, endoscopy, or DRE) tumor present
4. ECOG performance status 0-2
5. At least 18 years of age
6. Adequate bone marrow function defined as:
    a. ANC > 1,500 cells/mm^3
    b. Hgb > 8 g/dl
    c. platelets >100,000 cells/mm^3
7. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

8. Able to understand and willing to sign an IRB-approved written informed consent document.

3.2 Exclusion Criteria

1. Prior radiation therapy, chemotherapy or extirpative surgery for rectal cancer.
2. Prior oxaliplatin or capecitabine use for any malignancy.
3. Prior radiation therapy to the pelvis.
4. A history of other malignancy (except non-melanomatous skin cancers) with the exception of malignancies for which all treatment was completed at least 2 years before registration and the patient has no evidence of disease.
5. Currently receiving any investigational agents.
6. A history of allergic reaction attributed to compounds of similar chemical or biologic composition to capecitabine, 5FU, oxaliplatin, or leucovorin.
7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.
8. Pregnant and/or breastfeeding. Women of childbearing potential must have a negative serum pregnancy test within 14 days of study entry.
9. Patients with known history of HIV are eligible unless their CD4+ T-cell counts are < 350 cells/mcL or they have a history of AIDS-defining opportunistic infection within the 12 months prior to registration. Concurrent treatment with effective ART according to DHHS treatment guidelines is recommended. HIV testing for patients without a history of HIV is not a protocol requirement.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4 PATIENT REGISTRATION

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility by Washington University
2. Registration of patient in the Siteman Cancer Center OnCore database
3. Assignment of unique patient number (UPN)

Once the patient has been entered in the Siteman Cancer Center OnCore database, the WUSM coordinator will forward verification of enrollment and the UPN via email.

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the research coordinator listed in the *Siteman Cancer Center Clinical Trials Core Protocol Procedures for Secondary Sites* packet at least one business day prior to registering patient:

1. Your name and contact information (telephone number, fax number, and email address)
2. Your site PI's name, the registering MD's name, and your institution name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and a dash) for the patient's initials
5. Currently approved protocol version date
6. Copy of signed consent form (patient name may be blacked out)
7. Planned date of enrollment
8. Completed eligibility checklist, signed and dated by a member of the study team
9. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

Registrations may be submitted Monday through Friday between 8am and 5pm CT. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the Washington University research coordinator. Registration will be confirmed by the research coordinator or his/her delegate by email within one business day. Verification of eligibility and registration should be kept in the patient chart.

All patients at all sites must be registered through the Siteman Cancer Center OnCore database at Washington University.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

5 EVALUATION STUDIES

5.1 Pre-treatment

Within 12 weeks of day of simulation for RT but no later than the first radiation treatment:

- Examination by treating surgeon, medical oncologist, and radiation oncologist
- CBC with diff, CMP, CEA
- Staging study to evaluate extent of disease in the chest, abdomen and pelvis: CT w/ contrast is preferred to rule out metastatic disease

- Rectal protocol MRI pelvis to assess the local extent of the primary tumor, including T and N stage.
- Pregnancy test (for women of childbearing potential) – within 14 days of first treatment
- Colonoscopy (within 6 months is acceptable)
  - If feasible it is strongly recommended that the following physical findings should be scored:
    - Tumor location (distance in cm from the anal verge to the distal tumor margin)
    - Circumferential lesion Y/N
- Research biopsy (see Section 11.1)
- Blood for ctDNA (see Section 11.2)
- FACT-C quality of life questionnaire

5.2 During Radiotherapy and Chemotherapy

Routine standard of care examinations and blood work will be done.

- CMP and CBC with differential prior to each cycle of chemotherapy
- On treatment assessment by radiation oncologist during the week of radiation therapy
- Assessment by medical oncology physician or nurse with each cycle of chemotherapy.
- Please see Section 6 for radiation therapy guidelines and Section 7 for chemotherapy guidelines.
- Rectal protocol MRI pelvis 8 weeks after completion of radiation (preferably after at least 3 cycles of chemotherapy completed) – OPTIONAL.

5.3 Completion of Chemotherapy/Post-Treatment Evaluation

Three to eight weeks after completion of chemotherapy, patients will have the following assessments:

- CEA
- FACT-C questionnaire.
- Surgical assessment w/ endoscopy (sigmoidoscopy preferred, rigid proctoscopy acceptable) to evaluate the extent of residual tumor
- Rectal protocol MRI pelvis to evaluate ycT and ycN stage
- Digital rectal exam (DRE) to evaluate ycT stage

For patients with a cCR, non-operative management will be pursued. For patients with residual disease who do not meet criteria for cCR by 3-8 weeks after completion of the last cycle of FOLFOX or CAPOX, further therapy is recommended and at the discretion of the treating physicians. At investigator discretion, patients who achieve a near clinical complete response[33] with equivocal findings concerning for residual disease may be followed closely with short interval observation (i.e. 6-8 week MR/endoscopic follow-up),

with non-operative management pursued if a subsequent cCR is achieved. Patients whose disease is amenable to transanal endoscopic microexcision (TEM) or local excision (LE) may undergo TEM/LE to evaluate degree of residual disease. For those with ypT1 disease without LVSI present, non-operative management may continue with evaluation noted above. For those with residual ypT2-3 disease or ypT1 with LVSI, extirpative surgery including TME is recommended with treatment at investigators discretion proceeding off-study.

Post-treatment lymph nodes are to be evaluated by imaging and reviewed in muldisciplinary tumor board with a radiologist and classified as progressive, persistent disease, indeterminate or benign. Patients with progressive or persistent lymph node disease will not be eligible for non-operative management and will undergo additional therapy. Patients with indeterminate or benign lymph nodes AND cCR of primary will undergo non-operative management.

5.4 Follow-up

The FACT-C questionnaire and follow-up visit will be done 10-14 months from treatment (radiotherapy) start date.

Patients undergoing nonoperative management will be assessed for sustained cCR by rectal protocol MRI pelvis, endoscopy (sigmoidoscopy preferred, rigid proctoscopy accepted) and DRE every three months (not necessarily on the same day / appointment) for 1 year then every 3-4 months for the second year. If patient is unable to receive an MR pelvis every 3 months, every 6 months is acceptable as long as endoscopic exam is performed as per protocol schedule. CT chest and abdomen with contrast is to be obtained every 6 months for the first 2 years. Each of the follow-up studies and visits have a permitted variation of ±2 weeks. After 2 years of follow-up on study, we recommend off-protocol follow-up with the same studies every 4-6 months per treating physician discretion.

Once a patient undergoes surgical resection they will undergo imaging and surgical follow-up as per institutional standard of care. These patients will continue to be followed for data collection for during study follow-up.

6 RADIATION THERAPY GUIDELINES

6.1 Dose, Fractionation and Constraints

When feasible it is strongly recommended that radiotherapy begin on a Monday. It is accepted that occasional logistical delays may occur during radiotherapy treatment due to machine downtime or other issues. Radiotherapy as administered during this study may take up to 10 business days without being considered a protocol deviation.

Radiotherapy will consist of five fractions, delivered once daily, to a total dose of 25 Gy at 5 Gy per fraction (PTV2500). An optional simultaneous integrated boost of 30 Gy in 5

fractions to the primary tumor is permitted. Monday through Friday treatment is strongly recommended. Daily imaging to verify accurate setup is mandatory. It is required that at least 95% of the PTV_2500 receive at least 95% of the prescription dose and that the maximum dose be ≤ 115% of the prescription dose. Every effort should be made for 100% of the PTV_2500 to be covered by 95% of the prescription dose. For treatment plans to 25 Gy, this is most reproducibly accomplished via a 3D plan with four fields and optional field-in-field technique. The maximum allowed dose to small bowel is 25 Gy (with an acceptable deviation of up to 25.5 Gy). A boost dose of 30 Gy in 5 fractions to the primary is strongly recommended for T3 tumors, tumors >4 cm and tumors involving the circumferential resection margin.

It is recommended that pelvic lymph nodes outside of the mesorectum determined to be clinically suspicious by an experienced radiologist be boosted to 35 Gy in 5 fractions. The maximum allowed small bowel dose is 25 Gy (with an acceptable deviation of up to 25.5 Gy) when a primary or LN boost is given as well. There is no coverage requirement for boost doses. SIB plans may be delivered with IMRT (recommended) or multiple field 3D planning as long as dose constraints are met.

The following constraints are recommended (IMRT optimization) when boosting lymph node(s):
Bladder V20Gy < 15 cc. Dmax < 38 Gy.
Penile bulb V30Gy < 3 cc.
Femoral heads V30Gy < 10 cc.
Skin V36.5Gy < 10 cc. Dmax < 38.5 Gy.

6.2 Treatment Planning Procedures

Image-based treatment planning and IMRT are permitted. Proton therapy is not permitted. Dose volume histogram (DVH) information for the target volumes, small bowel, and uninvolved colon (defined to be large bowel outside the clinical target volumes) is mandatory. This is to assist in interpreting outcome, including morbidity. Daily cone beam CT to assess for rectal and bladder filling is recommended.

6.3 Simulation Procedures/Patient Positioning

The prone position with a bowel displacement device incorporated into the immobilization cast is generally recommended as the best way to exclude small bowel from the pelvis. The exceptions would be patients unable to lay prone or morbidly obese patients whose diagnostic supine CT scans demonstrate little or no small bowel in the pelvis. Those patients with good bladder control should be treated with a full bladder per institutional practice to further exclude small bowel. All patients should be simulated with oral small bowel contrast.

6.4 Clinical Target Volume (CTV) and Planning Target Volume (PTV) Definitions and Radiation Treatment Planning

Contouring should be as per the RTOG anorectal contouring atlas. CTV_2500 should include rectum and associated mesentery extending caudad at least to two cm below the distal edge of palpable disease. Superiorly it should include the rectum and its mesentery to the level of the rectosigmoid or two cm proximal to macroscopic disease, whichever is more cephalad. In addition, the internal iliac, internal obturator, and pre-sacral lymph node regions should be included (superiorly to approximately the level of L5/S1, including the inferior mesenteric vessels). PTV_2500 is generated by a uniform 0.5-0.7 cm expansion about CTV_2500. CTV_3000 for boost is 0.5 cm expansion off of the GTV. PTV_3000 is a 0.5-0.7 expansion off of CTV_3000. If a SIB for extra-mesorectal pelvic lymph nodes is used, CTV_3500 should be a 0.5 cm expansion from the gross lymph node. PTV_3500 is a 0.5-0.7 cm expansion from CTV_3500.

It is required that a physician review daily setup images (either pre or post-treatment) for each of the five fractions.

Ideally the 95% dose should not extend more than 3-6 mm below or above the PTV contour.

6.5 Normal Tissue Contours

Individual loops of small bowel should be contoured tightly. Bowel bag is not permitted. The CTV is NOT to be extracted from small bowel. If small bowel lies within a CTV, that WILL contribute to the small bowel dose. Since absolute rather than relative bowel volumes are to be tracked, it is not necessary to contour the entire small bowel, only those loops caudal to 2 cm above the most cephalad extent of PTV_2500.

7 CHEMOTHERAPY GUIDELINES

7.1 Chemotherapy Schedule and Doses

Chemotherapy should begin 2 to 4 weeks after completion of radiotherapy and will consist of FOLFOX (5FU/leucovorin/oxaliplatin) every other week for 8 courses (16 weeks). Leucovorin may be substituted with levoleucovorin (200 mg/m^2) if leucovorin is not available. Alternatively, CAPOX (capecitabine/oxaliplatin) may be given for 5 cycles over 15 weeks. A maximum (total) delay of treatment of 4 weeks is allowed per protocol due to factors or adverse events (AEs) listed in this section. Cumulative delays in excess of 4 weeks will need to be discussed with the Principal Investigator. Such cases will need to be individualized depending on the clinical scenario. Patients receiving CAPOX will be given a pill diary (Appendix B) to assess compliance for capecitabine.

7.2 Agent Administration

FOLFOX			
Agent	**Dose**	**Route**	**Schedule**
Oxaliplatin*	85 mg/m^2	IV over 2 hours	On Day 1, Q 14 days

Leucovorin*	400 mg/m^2	IV over 2 hours	On Day 1, Q 14 days
5-FU Bolus*	400 mg/m^2	IV push	On Day 1, Q 14 days
5-FU Infusion*	2400 mg/m^2	IV CIIV	On Day 1, Q 14 days over 46 hours

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

CAPOX			
Agent	**Dose**	**Route**	**Schedule**
Capecitabine	1000 mg/m^2	PO	BID Days 1-14, Q21 days
Oxaliplatin	130 mg/m^2	IV over 2 hours	On Day 1, Q 21 days

Dose calculations for both regimens should be based on actual weight and not corrected for obesity.

7.3 Supportive Care Recommendations

Veno-occlusive disease is a very rare AE associated with the administration of the combination of 5-FU and oxaliplatin. VOD disease is characterized by hepatomegaly, ascites, and jaundice. These signs and symptoms should prompt consideration of VOD. A Doppler ultrasound showing reversal of portal blood flow or other evidence of portal hypertension is suggestive of this diagnosis. In addition, standard clinical practice for evaluation of VOD should include observation of liver and spleen size, history of or gastrointestinal bleeding, development of esophageal varices, ascites, bleeding, or jaundice. All patients on and off therapy who develop signs and symptoms suggestive of VOD should be thoroughly evaluated and closely monitored and supported as clinically dictated.

Grade 3/4 hypersensitivity, including anaphylactic/anaphylactoid reactions, has been observed with oxaliplatin. These allergic reactions, which can be fatal, can occur within minutes of administration, and can occur during any cycle. There were similar in nature and severity to those reported with other platinum-containing compounds, such as rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. These reactions are usually managed with standard epinephrine, corticosteroid, and antihistamine therapy, and require discontinuation of therapy.

Ice should be avoided during the infusion of oxaliplatin because cold temperatures can exacerbate acute neurological symptoms.

8 DOSE DELAYS/DOSE MODIFICATIONS

8.1 Radiotherapy Dosing

Radiotherapy for this trial may take place over a maximum of 10 business days before it is considered a protocol deviation. There are no dose adjustments (reductions, omissions) associated with radiotherapy.

8.2 Chemotherapy Dosing

FOLFOX				
Chemotherapy	**Starting Dose**	**Dose Level -1**	**Dose Level -2**	**Dose Level -3**
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2	40 mg/m^2
Bolus 5-FU	400 mg/m^2	300 mg/m^2	200 mg/m^2	100 mg/m^2
Infusion 5-FU	2400 mg/m^2	1920 mg/m^2	1600 mg/m^2	1360 mg/m^2
Leucovorin	400 mg/m^2	400 mg/m^2	400 mg/m^2	400 mg/m^2

CAPOX				
Chemotherapy	**Starting Dose**	**Dose Level -1**	**Dose Level -2**	**Dose Level -3**
Oxaliplatin	130 mg/m^2	100 mg/m^2	80 mg/m^2	50 mg/m^2
Capecitabine	1000 mg/m^2 BID	800 mg/m^2 BID	650 mg/m^2 BID	500 mg/m^2 BID

Dose modifications of the chemotherapy agents may be made independently of each other. Patients unable to tolerate one of more drugs due to toxicity may remain on study with the other drugs. All toxicities should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Dose modifications are based upon dose level administered at last treatment day. If the dose level has been reduced due to toxicity, re-escalation is permitted at the discretion of the primary treating physician.

8.3 Dose Modifications for Toxicity Related to FOLFOX-6

Dose modifications during FOLFOX chemotherapy are at the discretion of the primary treating provider. The use of 5-FU bolus is at the discretion of the treating physician. Modifications should be reported to research coordinator. Refer to the tables below for guidance regarding suggested dose reductions and treatment delays, consistent with best oncologic practices.

Toxicity NCI Grade (Value)	Worst interval toxicity	Day of treatment
Neutropenia (ANC)		
Grade 1 (ANC < LLN – 1500/mm^3)	Maintain dose level	If ANC < 1000 on day of treatment, hold and check weekly until $\geq$ 1000 mm^3. Then treat based on interval toxicity. If ANC < 1000 after 4 weeks, discontinue therapy.
Grade 2 (ANC <1499 – 1000/mm^3)		
Grade 3 (ANC <999 – 500/mm^3)	Reduce 1 dose level	
Grade 4 (ANC < 500/mm^3)		
Thrombocytopenia		
Grade 1 (PLT < LLN – 75,000/mm^3)	Maintain dose level	If PLT < 75,000 on day of treatment, hold and check weekly until $\geq$ 75,000 mm^3. Then treat based on interval toxicity. If PLT < 75,000 after 4 weeks, discontinue therapy.
Grade 2 (PLT 74,999 – 50,000/mm^3)		
Grade 3 (PLT 49,999 – 25,000/mm^3)	Reduce 1 dose level	

Grade 4 (PLT< 25,000/mm^3)		
Diarrhea		
Grade 1	Maintain dose level	Hold chemotherapy if any grade of diarrhea above grade 1 is present with the patient not taking antidiarrheal agents within 24 hours of treatment. Reduce 5-FU and oxaliplatin 1 dose level upon resolution of diarrhea. If diarrhea has not resolved within 4 weeks of scheduled treatment day, discontinue therapy.
Grade 2	Reduce 5-FU and oxaliplatin 1 dose level	
Grade 3		
Grade 4		
Other nonhematologic toxicities (except neurologic, alopecia, anorexia, nausea/vomiting if can be controlled by antiemetics)		
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
Grade 3	Reduce 1 dose level	Hold until resolved to grade ≤1. Reduce 5-FU and oxaliplatin 1 dose level
Grade 4		

8.4 Dose Modifications for Neurologic Toxicity (Paresthesia or Dysesthesia) Related to Oxaliplatin

Grade	**Duration of Toxicity**		
	1 – 7 Days	> 7 Days	Persistent Between Doses
Grade 1 Short duration that resolves and does not interfere with function	No change	No change	No change
Grade 2 Interfering with function, but not activities of daily living (ADL)	No change	No change	Reduce oxaliplatin 1 dose level
Grade 3 With pain or with functional impairment that also interferes with ADL	1st time: reduce oxaliplatin 1 dose level 2nd time: reduce oxaliplatin another dose level	1st time: reduce oxaliplatin 1 dose level 2nd time: reduce oxaliplatin another dose level	Discontinue oxaliplatin
Grade 4 Persistent symptoms that are disabling or life-threatening	Discontinue oxaliplatin	Discontinue oxaliplatin	Discontinue oxaliplatin

8.5 Dose Modifications for Toxicity Related to CAPOX

Dose modifications may be made as per standard of care following the package inserts or standard practice. Based on recent report by Cercek et al., in Lancet Oncology 2018 (PMID29566109), dose modification of 5-FU or oxaliplatin is quite common, up to 54% with oxaliplatin and 25% with 5-FU. However, about 85% were able to complete >75% of

planned doses. Therefore, we believe up to 70% of patients requiring dose modification would be acceptable.

Specifically, for diarrhea, the following table is recommended for dose modification of capecitabine. Standard antidiarrheal agents will be recommended.

Recommended Dose Modification and Toxicity Management Guidelines for Diarrhea Attributable to Capecitabine

Toxicity Grades	**During a Course of Therapy**	**Dose Adjustment for Next Treatment (% of starting dose)**
Grade 1	*Maintain dose level*	*Maintain dose level*
Grade 2		
-1st appearance	Interrupt until resolved to grade 0-1	100%
-2nd appearance		75%
-3rd appearance		50%
-4th appearance	Discontinue treatment permanently	-
Grade 3		
-1st appearance	Interrupt until resolved to grade 0-1	75%
-2nd appearance		50%
-3rd appearance	Discontinue treatment permanently	-
Grade 4		
-1st appearance	Discontinue permanently OR If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%

9 MR IMAGING GUIDELINES

9.1 Requirements

- **Imaging must be performed with at least 1.5 T (3 T also acceptable).**
- External phased array coils must be used
- Endorectal coils must not be used
- 2D fast T2-weighted sequences in the sagittal, axial and coronal planes must be obtained.
- Axial sequence angled perpendicular to the tumor and a coronal sequence angled parallel to the tumor for accurate staging
- DWI sequences should be obtained
- Contrast agents may be used (should contrast agents be used, imaging without contrast must also be obtained)

10 ADVERSE EVENT REPORTING

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix C for definitions and Appendix D for a grid of reporting

timelines.

Adverse events will be tracked from start of treatment through one year after the start of radiation therapy. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF
- Grade 1 or grade 2 events, which will not be captured or reported

Refer to the data submission schedule in Section 14 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 10.1. Reporting requirements for secondary site study teams participating in Washington University-coordinated research may be found in Section 10.2.

Please note that toxicities will be collected using version 4.0 of the CTCAE for comparison to a previous study in this population, HRPO# 201512140.

10.1 WU PI Reporting Requirements

10.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

10.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The Washington University PI (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

For events that occur at secondary sites, the Washington University PI (or designee) is required to notify the QASMC within 10 days of Washington University notification via email to qasmc@wustl.edu. Submission to QASMC must include either the myIRB form and supporting documentation or (if not submitted to

myIRB) the date of occurrence, description of the event, whether the event is described in the currently IRB approved materials, the event outcome, determination of relatedness, whether currently enrolled participants will be notified, and whether the informed consent document and/or any study procedures will be modified as a result of this event.

10.1.3 Reporting to Secondary Sites

The Washington University PI (or designee) will notify the research team at each secondary site of all unanticipated problems involving risks to participants or others that have occurred at other sites within **10 working days** of the occurrence of the event or notification of the PI (or designee) of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable. Refer to Section 19.0 (Multicenter Management) for more information.

10.2 Secondary Site Reporting Requirements

The research team at each secondary site is required to promptly notify the Washington University PI and designee of all serious adverse events (refer to Appendix C, Section D) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report (using FDA Form 3500A (MedWatch) and Washington University's cover sheet (Appendix E)). A formal written report must be sent to the Washington University PI and designee within **4 calendar days** (for fatal or life-threatening suspected adverse reactions) or **11 calendar days** (for serious unexpected adverse reactions) of the occurrence of the event or notification of the secondary site's PI of the event.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines.

Washington University pre-approval of all protocol exceptions must be obtained prior to implementing the change. Local IRB approval must be obtained as per local guidelines. Washington University IRB approval is not required for protocol exceptions occurring at secondary sites.

10.3 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 10.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

11 CORRELATIVE STUDIES

11.1 Research Tissue

Biopsy samples of the rectal tumor will be taken from the patient tumor prior to treatment initiation for tumor microenvironment and FAK expression assessment. Two samples by alligator forceps are recommended. These biopsies can be obtained at the time of initial biopsy or any time prior to initiating treatment. For patients at Washington University who co-enrolled in HRPO# 201107221 (Tissue and Blood Acquisition for Genomic Analysis and Collection of Health Information for Patients with Gastrointestinal Cancers) pre-treatment specimens may be requested from the bank and used in lieu of the fresh biopsy performed under this protocol. For patients at affiliate sites who do not have enough tissue from the diagnostic biopsy, a repeat pre-treatment biopsy is optional.

Biopsy tissue 1A:
One biopsy should be split in half with the first half being placed in a cryo vial and snap frozen in liquid nitrogen. This will be stored at -80°C until shipment. Shipment should be overnight with dry ice.

Biopsy tissue 1B:
The other half will be placed in formalin with the following processing steps:

1. Formalin for 24 hours.
2. Drain the formalin (pour it out of the container), then add 30% ethanol and set on shaker for 10-15 minutes.
3. Repeat with 50% ethanol for 10 minutes.
4. Repeat with 70% ethanol for 10 minutes.
5. Store in 70% ethanol at 4 degrees until shipped (within 2 weeks). Please ship overnight using wet ice/ice pack.

Blocks will be processed and immunohistochemical analysis performed in the lab of Dr. DeNardo.

Alternatively, tissue can be prepared as paraffin embedded blocks per institutional standards and stored at room temperature until shipment.

External institutions should ship samples to:

425 S. Euclid Ave, St. Louis MO 63110
BJC Institute of Health, Room 7207
Phone: 314-362-9534 (ask for Savannah or Brett)

Biopsy tissue 2:
The second biopsy tissue will be processed per institutional standard. Biopsy tissue block (or 6-10, 10-micron slides) is required for Signatera analysis (below).

11.2 Blood for ctDNA

Approximately 20 mL of blood will be collected into STRECK tubes (26 mL for first draw) at the following time points:

- Prior to the start of treatment (purple top and 2 STRECK tubes)
- Post-RT labs (with SOC CBC/CMP prior to start of Cycle 1 of chemotherapy)
- Day 1 of Cycle 3 (FOLFOX) or Day 1 of Cycle 2 (CAPOX) (with SOC CBC/CMP)
- Completion of chemotherapy (3-8 weeks after the end of chemotherapy)
- 10-14 months after RT (if this visit aligns with a follow-up time point described below, one draw can be used to satisfy both time points)
- Follow-up months (months 3, 6, 9, 12, 16, 20, 24) until salvage surgery or 2 years from the completion of chemotherapy, whichever is first

Blood will be collected at the hospital lab collection via Natera specimen acquisition form and will be shipped to Natera for processing by the blood collection lab.

Natera, Inc
201 Industrial Road, Suite 410
San Carlos, CA 94070
650-489-9050

12 PHARMACEUTICAL INFORMATION

FOLFOX and CAPOX are standard of care, FDA-approved regimen for the treatment of rectal cancer, and treatment will be provided and administered according to standard of care guidelines. More detailed information can be found in the products' package inserts.

12.1 Leucovorin

12.1.1 Mechanism of action

Leucovorin is a tetrahydrofolate acid derivative that acts as a biochemical cofactor for carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolate reductase for conversion to tetrahydrofolic acid. Leucovorin potentiates the effects of fluorinated pyrimidines like 5-FU. Leucovorin increases the folate pool, increasing the biding of folate cofactor and active metabolites of 5-FU.

12.1.2 Pharmacodynamics

Leucovorin is well absorbed after oral administration and is readily converted to 5-methyltetrahydrofolate after administration. Peak serum concentrations occur 1.7 to 2.5 hours after an oral dose. Leucovorin is excreted in the urine as metabolites and has a half-life of approximately 2-6 hours.

12.1.3 Availability

Leucovorin calcium is commercially available in: 50 mg, 100 mg, 350 mg vials for reconstitution.

12.1.4 Supplier(s)

Leucovorin is commercially available and will not be provided by this study.

12.1.5 Storage and Stability

Intact vials should be stored at room temperature and protected from light. Solutions reconstituted with Bacteriostatic Water for Injection (BWI) are stable for at least 7 days at room temperature.

12.1.6 Administration

Leucovorin may be reconstituted with BWI or with sterile water. Solutions should be further diluted in D5W, 0.9% NaCl or Ringers solution for infusion over two hours.

Leucovorin will be administered as a 400 mg/m^2 IV infusion over 2 hours. It may be given either concurrent with (via a separate infusion line) or following oxaliplatin and immediately before fluorouracil.

12.2 5-Fluorouracil (5-FU)

12.2.1 Mechanism of Action

Fluorouracil, $C_4H_3FN_2O_2$, a pyrimidine antagonist, is an antimetabolite antineoplastic agent. Although the precise mechanisms of action of fluorouracil have not been fully elucidated, the main mechanism is thought to be the binding of the deoxyribonucleotide of the drug (FdUMP) and the folate cofactor, N5-10-methylenetetrahydrofolate, to thymidylate synthase (TS) to form a covalently bound ternary complex, which inhibits the formation of thymidylate from uracil, thereby interfering with DNA synthesis. In addition, FUTP can be incorporated into RNA in place of uridine triphosphate (UTP), producing a fraudulent RNA and interfering with RNA processing and protein synthesis.

12.2.2 Pharmacodynamics/kinetics

Absorption: Following IV administration of fluorouracil, no intact drug is detected in plasma after 3 hours.

Distribution: Fluorouracil is distributed into tumors, intestinal mucosa, bone marrow, liver, and other tissues. Despite its limited lipid solubility, the drug readily

crosses the blood-brain barrier and distributes into CSF and brain tissue. Distribution studies in humans and animals have usually shown a higher concentration of the drug or its metabolites in the tumor than in surrounding tissue or in corresponding normal tissue. It has also been shown that there is a longer persistence of fluorouracil in some tumors than in the normal tissues of the host, perhaps due to impaired uracil catabolism. From these data, it has been suggested that the drug may possibly have some specificity against certain tumors in comparison with normal tissues.

Elimination: Following IV administration, the plasma elimination half-life averages about 16 minutes (range: 8-20 minutes) and is dose dependent. A small portion of fluorouracil is anabolized in the tissues to 5-fluoro-2-deoxyuridine and then to 5-fluoro-2-deoxyuridine-5-monophosphate, the active metabolite of the drug. The major portion of the drug is degraded in the liver. The metabolites are excreted as respiratory carbon dioxide and as urea, α-fluoro-β-alanine, α-fluoro-β-guanidopropionic acid, and α-fluoro- β-ureidopropionic acid in urine. Following a single IV dose of fluorouracil, approximately 15% of the dose is excreted in urine as intact drug within 6 hours; over 90% of this is excreted in the first hour.

12.2.3 Availability

Fluorouracil is commercially available as a 50 mg/mL solution for injection in 10 mL, 20 mL, 50 mL and 100 mL vials.

12.2.4 Supplier

5-FU is commercially available and will not be provided by this study.

12.2.5 Solution Preparation

Inspect for precipitate; if found, agitate or gently heat in water bath. Bolus injections are prepared using undiluted drug. Continuous infusions of fluorouracil should be prepared for administration via ambulatory infusion pump according to the individual institution’s standards. These solutions may be prepared in D5W or 0.9% NaCl.

12.2.6 Storage and Stability

Intact vials should be stored at room temperature and protected from light. Slight yellow discoloration does not usually indicate decomposition. 5-FU is stable in syringes for up to 72 hours. Stability in ambulatory pumps varies according to the pump, manufacturer of drug, concentration and dilution. Please refer to appropriate reference sources for additional information.

12.2.7 Administration

Fluorouracil will be given as a 400 mg/m^2 IV bolus injection followed by 2400 mg/m^2 continuous IV infusion over 46 hours.

12.3 Oxaliplatin

12.3.1 Mechanism of action

Oxaliplatin is a new platinum derivative with an oxalo ligand group. Although the exact mechanism of oxaliplatin's action remains unclear, the cytotoxicity of platinum compounds is thought to result from inhibition of DNA synthesis. Intrastrand platinum DNA adducts, the main cytotoxic lesions, are formed by cross-linking activated platinum species and specific base sequences, notably 2 adjacent guanine residues or 2 adjacent guanine-adenine bases.

12.3.2 Pharmacodynamics/kinetics

Time to peak concentration with a single 2-hour infusion of oxaliplatin 85 milligrams/square meter yielded a peak plasma concentration (Cmax) of 0.814 micrograms/milliliter. The area under the curve for total plasma platinum was 207-290 mg/L x hr; ultrafilterable plasma platinum was 11.9-13.6 mg/L x hr. Oxaliplatin has 70 to 95% platinum-protein binding while 37% represents total platinum taken up by red blood cells (addition of oxaliplatin to whole blood). The volume of distribution is 440 liters after a single 2-hour infusion of 85 milligrams/square meter oxaliplatin. Oxaliplatin undergoes rapid and extensive (30%) nonenzymatic biotransformation. In vitro studies indicate no cytochrome P450-mediated metabolism. Oxaliplatin metabolites include approximately 17 different platinum containing derivatives with some being cytotoxic (monochloro DACH platinum, dichloro DACH platinum, and monoaquo and diaquo DACH platinum). Breast milk – It is not known whether oxaliplatin is excreted into breast milk. Renal clearance is 9.3-17 liters/hour. Elimination half life: intravenous, total plasma platinum, alpha half-life (0.2-0.43 hours), beta half-life (15-16.8 hours), gamma half-life (252-391 hours). The decline of ultrafilterable platinum levels is triexponential with a relatively short alpha and beta half-life (0.43 hours and 16.8 hours) and a long terminal gamma half-life (391 hours).

12.3.3 Formulation

Molecular formula: $C_8H_{14}N_2O_4Pt$ with the chemical name of cis-[(1R, 2R)-1,2 cyclohexanediamine-N, N'][oxaloto (2-)-o, o'] platinum. Molecular weight is 397.3.

12.3.4 Availability

Oxaliplatin is formulated as a white freeze-dried powder in amber glass vials containing 50 mg and 100 mg of oxaliplatin in lactose monohydrate. Each vial is sealed with a stopper with a crimped aluminum cap. Drug will be ordered from

commercial supply.

12.3.5 Supplier

Oxaliplatin is commercially available and will not be provided by this study.

12.3.6 Solution Preparation

The freeze-dried powder is reconstituted by adding 10 to 20 ml (for the 50-mg vial) or 20 to 40 ml (for the 100-mg vials) of sterile water for Injection or 5% dextrose solution and then by diluting in an infusion solution of 250 ml or 500 ml of 5% dextrose solution. Avoid performing these manipulations with aluminum needles. The reconstitution or final dilution must never be performed with a sodium chloride solution.

12.3.7 Storage and Stability

Oxaliplatin freeze-dried powder may be stored at room temperature protected from light. Do not combine with alkaline medications or media, which cause oxaliplatin to degrade. Do not use needles or intravenous infusion sets containing aluminum items (risk of degradation of oxaliplatin upon contact with aluminum) for the preparation or administration of oxaliplatin. Do not mix oxaliplatin with sodium chloride or other chloride containing solutions. Freeze-dried powder: The compound may be stored for 3 years at room temperature protected from light. Reconstituted solution: In 5% dextrose solution or sterile Water for Injection in the original vial, the solution may be stored for 24 to 48 hours at 2-80° C. Infusion solution: after dilution in 5% dextrose solution, the shelf-life is 24 hours at room temperature.

12.3.8 Administration

Antiemetic premedication (5-HT3 blocker with or without dexamethasone) is recommended. Cold temperatures can precipitate/exacerbate neurological symptoms-avoid during the infusion of oxaliplatin. Never reconstitute/dilute with a chloride-containing solution; avoid aluminum parts when preparing/mixing oxaliplatin. Incompatible with alkaline media (i.e., solutions of 5-fluorouracil). Prepare oxaliplatin in 250-500 mL D5W.

12.4 Capecitabine

12.4.1 Mechanism of action

Enzymes convert capecitabine to 5-fluorouracil (5-FU) in vivo. Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor, N5-10-

methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from 2'-deoxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis.

12.4.2 Pharmacodynamics/kinetics

Following oral administration of 1255 mg/m2 BID to cancer patients, capecitabine reached peak blood levels in about 1.5 hours (Tmax) with peak 5-FU levels occurring slightly later, at 2 hours. Food reduced both the rate and extent of absorption of capecitabine with mean C_{max} and $AUC_{0-\infty}$ decreased by 60% and 35%, respectively. The C_{max} and $AUC_{0-\infty}$ of 5-FU were also reduced by food by 43% and 21%, respectively. Food delayed Tmax of both parent and 5-FU by 1.5 hours.

The pharmacokinetics of XELODA and its metabolites have been evaluated in about 200 cancer patients over a dosage range of 500 to 3500 mg/m^2/day. Over this range, the pharmacokinetics of XELODA and its metabolite, 5'-DFCR were dose proportional and did not change over time. The increases in the AUCs of 5'-DFUR and 5-FU, however, were greater than proportional to the increase in dose and the AUC of 5-FU was 34% higher on day 14 than on day 1. The interpatient variability in the C_{max} and AUC of 5-FU was greater than 85%.

Capecitabine is extensively metabolized enzymatically to 5-FU.

Capecitabine and its metabolites are predominantly excreted in urine.

12.4.3 Formulation

Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity. The chemical name for capecitabine is 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine and has a molecular weight of 359.35. It's supplied as biconvex oblong film-coated tablets for oral administration.

12.4.4 Availability

Capecitabine is available in 150 mg and 500 mg tablets.

12.4.5 Supplier

Capecitabine is commercially available and will not be provided for this study.

12.4.6 Storage and Stability

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

12.4.7 Administration

Patients will be instructed to take capecitabine with water 30 minutes after a meal as described in Section 7.2.

13 STUDY CALENDAR

	Screening[4]	During RT	Day 1 of Each Cycle of Chemo[8]	Completion of Chemo[10]	10 to 14 Months after RT[17]	Follow-up[9]
Informed consent	X					
H&P	X	X (once)	X	X	X	
CBC diff, plts	X		X			
CMP	X		X			
CEA	X		X			
Pregnancy test[5]	X[6]					
Colonoscopy or barium enema or Hypaque enema	X[11]					
Surgical assessment with proctoscopy or sigmoidoscopy				X		X[15]
Digital rectal exam	X			X		X
Staging study to evaluate disease in abdomen and pelvis[1]	X					X
Staging study to evaluate disease in lungs[2]	X					X
Imaging study to assess local extent of primary tumor[3]	X		X[12]	X		X[14]
Radiotherapy		X[7]				
FOLFOX / CAPOX			X			
Biopsy for research (refer to Section 11)	X					
Blood for ctDNA[16]	X		X[13]	X	X[16]	X[16]
FACT-C	X			X	X	
AE assessment	AEs should be collected through 1 year following the start of RT					
Progression and survival						X

1. CT with contrast or MRI or PET/CT or PET/MRI; obtain every 6 months during the 2 years of follow-up. Once patients undergo surgical resection they will undergo imaging and surgical follow-up as per institutional standard of care.
2. CT of the chest or PET/CT; obtain every 6 months during the 2 years of follow-up. Once patients undergo surgical resection they will undergo imaging and surgical follow-up as per institutional standard of care.
3. Rectal protocol (pelvic) MRI (preferred), MRI, CT scan
4. Within 12 weeks of day of simulation for RT but no later than the first radiation treatment
5. Women of childbearing potential only
6. No more than 14 days prior to the first day of treatment
7. 5 fractions delivered over the course of no more than 10 business days (preferably starting on a Monday).
8. Chemotherapy should start 2 to 4 weeks after the end of RT. FOLFOX cycles are 14 days and a total of 8 cycles will be given; CAPOX cycles are 21 days and a total of 5 cycles will be given. Labs with each chemotherapy may occur up to 3 days prior to Day 1 of the cycle.
9. For patients undergoing nonoperative management, follow-up visits will occur every 3 months for the first year and every 3-4 months for the second year (± 2 weeks). After 2 years of follow-up we will recommend the same studies every 4-6 months per treating physician discretion. Once patients undergo surgical resection they will undergo imaging and surgical follow-up as per institutional standard of care.
10. 3-8 weeks after the end of chemotherapy
11. Within 6 months of day of simulation for RT but no later than the first radiation treatment
12. OPTIONAL; within 8 weeks of completion of RT
13. Prior to Cycle 1 Day 1 (for FOLFOX and CAPOX) and on Day 1 of Cycle 3 (FOLFOX) and Day 1 of Cycle 2 (CAPOX)

14. Rectal protocol MRI pelvis. If patient is unable to receive an MR pelvis every 3 months, every 6 months is acceptable as long as endoscopic exam is performed on schedule.
15. Sigmoidoscopy preferred, rigid proctoscopy accepted
16. Blood for ctDNA will be collected every 3 months after chemotherapy completion until salvage surgery or 2 years from the completion of chemotherapy, whichever is first.
17. If the 10-14 month after RT visit aligns with a follow-up time point, one visit can be used to satisfy both time points

14 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Form	Completion Schedule
On-Study Form Medical History Form	Time of registration
Radiation Therapy Form	Completion of RT
Chemotherapy Form	At the end of each cycle of chemotherapy
Disease Assessment Form	Baseline 8 weeks post-RT (OPTIONAL) 3-8 weeks post-chemoradiation
Follow-Up Form	Months 3, 6, 9, 12, 16, 20, and 24 (for subjects who have not undergone surgery only)
FACT-C	Baseline Completion of chemoradiation 10-14 months after chemoradiation
Research Tissue Form	Time of biopsy
Research Blood Form	Prior to the start of treatment Post-RT (with SOC CBC/CMP) Day 1 of Cycle 3 (FOLFOX) or Day 1 of Cycle 2 (CAPOX)Completion of chemotherapy (3-8 weeks after the end of chemotherapy) 10-14 months after RT Follow-up (Months 3, 6, 9, 12, 16, 20, 24) until salvage surgery or 2 years from the completion of chemotherapy, whichever is first
Adverse Events Form	Ongoing
Progression Form	Time of disease progression
Death Form	Time of death

Any queries generated by Washington University must be responded to within 28 days of receipt by the participating site. The Washington University research team will conduct a regular review of data status at all secondary sites, with appropriate corrective action to be requested as needed.

14.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 10.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the

Death Form.

15 MEASUREMENT OF EFFECT

Criteria for clinical complete response:

- No residual gross tumor at procto/sigmoidoscopy; or only erythematous scar or ulcer
- No palpable tumor on DRE
- No radiographic evidence of tumor on MRI
- No suspicious mesorectal lymph nodes on MRI
- Negative biopsy from scar, ulcer, or former tumor site (if necessary according to surgeon's judgment)

Criteria for not clinical complete response (also known as clinical partial response):

- Does not meet criteria for cCR or progressive disease
    - Residual disease by DRE, endoscopy or MR.

Criteria for progressive disease:

- Increase in size of primary tumor by RECIST criteria (increase of at least 20% from nadir in the sum of the target lesion, with an absolute increase of at least 5 mm)
- New metastatic disease

16 DATA AND SAFETY MONITORING PLAN

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Siteman Cancer Center independent standing Data and Safety Monitoring Board (DSMB) will be specifically convened for this trial to review toxicity data. This DSMB will consists of clinical investigators with expertise in multiple modalities and at least one biostatistician. Members of this DSMB are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMB will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMB must also be disclosed.

Until such a time as the first secondary site enrolls its first patient, a semi-annual DSM report to be prepared by the study team will be submitted to the Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after study activation at Washington University (if at least one patient has been enrolled) or one year after study activation (if no patients have been enrolled at the six-month mark).

The DSM report for the DSMB will be prepared by the study team with assistance from the study statistician, will be reviewed by the DSMB, and will be submitted to the QASMC. The DSMB must meet at least every six months beginning six months after enrollment of the first patient at a secondary site, no more than one month prior to the due date of the DSM report to QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date, accrual by site
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities at all participating sites
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Further DSMB responsibilities are described in the charter.

The study principal investigator and coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines (please refer to Section 10.0).

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMB. This is located on the QASMC website at https://siteman.wustl.edu/research/clinical-research-resources/protocol-office-prmcqasmc/

17 AUDITING

As coordinating center of this trial, Washington University (via the Quality Assurance and Safety Monitoring Committee (QASMC) will monitor each participating site to ensure that all protocol requirements are being met; that applicable federal regulations are being followed; and that best practices for patient safety and data collection are being followed per protocol. Participating sites will be asked to send copies of all audit materials, including source documentation. The audit notification will be sent to the Washington University Research Patient Coordinator, who will obtain the audit materials from the participating institution.

Notification of an upcoming audit will be sent to the research team one month ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review (up to 10 for each site) will be sent to the research team. However, if during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Items to be evaluated include:

- Subject screening and enrollment
- Reporting of adverse events
- Maintenance of HIPAA compliance
- Completeness of regulatory documentation
- Completeness of participant documentation
- Acquisition of informed consent
- IRB documentation
- Issues of protocol adherence

Additional details regarding the auditing policies and procedures can be found at https://siteman.wustl.edu/research/clinical-research-resources/protocol-office-prmcqasmc/.

18 STATISTICAL CONSIDERATIONS

18.1 Study Objectives and Endpoints

The primary objective is to determine the cCR response rate of patients with stage I-IIIB (cT1-3, N0-2a, M0) rectal cancer being treated with sequential short course radiotherapy followed by multi-drug chemotherapy (either 8 cycles of FOLFOX or 5 cycles of CAPOX). The endpoint is cCR at the completion of short course radiation therapy and chemotherapy. Secondary endpoints include PFS at 2 years, incidence of any grade ≥ 3 toxicity during treatment, incidence of post chemoradiotherapy grade ≥ 3 toxicity, quality of anorectal function as measured by the FACT-C questionnaire at 1 year, and 1 and 2 year organ preservation rate. Exploratory objectives are to associate tumor microenvironment (including FAK expression) and ctDNA levels with cCR and other clinical outcomes.

18.2 Study Design and Sample Size Justification

The purpose of this phase II study is to determine if the cCR of short course radiation therapy followed by multiple agent chemotherapy in rectal adenocarcinoma is at least 50% in a multi-institution setting. Given that less than one-third of patients with cCR is deemed as an ineffective therapy clinically, our null hypothesis is that cCR rate is 30%. Our phase 1 data indicated a 74% cCR rate but our retrospective study showed 50%, which is more representative of advanced stage and all patients. Therefore, a cCR rate of 50% was considered in the alternative hypothesis. A Simon two-stage design[1] with a 90% power at one-sided 5% type I error will be used to test the null hypothesis. At the first stage, we will enroll 24 patients. If the study continues, 39 additional patients will be needed. Study is not powered for secondary endpoints.

18.3 Interim Analyses and Stopping Rules

An interim analysis will be performed on the primary endpoint once 24 subjects have been enrolled and have completed the evaluation after chemotherapy. If ≤ 8 patients have cCR in these 24 patients, the study will be stopped for futility. Otherwise, the additional 39 patients will be enrolled. The null hypothesis will be rejected if ≥25 patients with cCR are observed in 63 patients.

18.4 Definition of Evaluability

Endpoint	**In order to be evaluable for this endpoint, a patient must…**
Primary	
cCR at completion of short course radiation therapy and chemotherapy	Have completed the evaluation after completion of radiation therapy and chemotherapy.
Secondary	
Progression-free survival at 2 years	Have received at least one fraction of radiation therapy and one dose of chemotherapy.
Incidence of any grade ≥ 3 toxicity during treatment	
Incidence of post chemoradiotherapy grade ≥ 3 toxicity	
Anorectal function per FACT-C at 1 year	Have completed a FACT-C at baseline and at least one post-treatment time point.
1 and 2 year organ preservation rate	Have received at least one fraction of radiation therapy and one dose of chemotherapy.
Exploratory	
Associate tumor microenvironment with cCR and other clinical outcomes	Have tissue collected at baseline, received at least one fraction of radiation therapy and one dose of chemotherapy, and completed evaluation of their disease.
Associate ctDNA levels with cCR and other clinical outcomes	Have blood collected at baseline and at least one post-dose time point, received at least one fraction of radiation therapy and one dose of chemotherapy, and completed evaluation of their disease.

All eligible enrolled patients that receive any treatment will be included in the intention to treat analysis. Patients that complete protocol therapy (both radiation therapy and chemotherapy) as prescribed will be included in a per protocol analysis.

18.5 Data Analysis

Demographic and clinical characteristics of the sample will be summarized using descriptive statistics. Primary endpoint of the cCR rate will be reported as a proportion with 95% confidence interval (CI), and a one-sided asymptotic Wald test will be performed

to compare the study cohort cCR rate to the null value of 30%. PFS is defined as the time from date of treatment to death or progression, which occurs first. The alive patients without progression are censored as the last date follow-up. Kaplan-Meier method will be used to calculate PFS at 2-year. Proportions of any grade ≥ 3 toxicity during treatment, of post chemoradiotherapy grade ≥ 3 toxicity and organ preservation rates at 1 and 2 year will be calculated. Their corresponding 95% CIs will also be provided. The quality of anorectal function as measured by the FACT-C questionnaire is collected at screening, completion of chemo, and 1 year after RT. The generalized estimating equation (GEE) model with appropriate link function will be used to analyze this longitudinal data, in which the correlation among the repeated measures from the same patient need be considered. The autoregressive of first order as working correlation structure will be used and the patients with missing values at any time points will be excluded from GEE analysis. Least square means for quality of anorectal function at 1 year after RT will be estimated and 95% CI calculated within the use of GEE sandwich method when accounting for within-patient correlation.

18.6 FAK Expression and Tumor Microenvironment Analysis

Rectal cancer biopsies will be assessed for total and phosphorylated FAK1 (Tyr-397, p-FAK1) and PYK2 (FAK2) by immunohistochemistry (IHC) as previously described[23]. Rectal cancer samples will be stratified by high or low epithelial (tumor cell) p-FAK1 levels using IHC intensity and assessed for tumor-infiltrating CD3+, CD8+ cytotoxic T lymphocytes, neutrophil elastase and CD15+ granulocytes. Tumor fibrosis will be assessed by total collagen staining by Sirius Red and collagen I, III and IV deposition by IHC. Flow cytometry and IHC will be performed as previously reported[23,34]. To investigate the relationship between tumor microenvironment (including FAK expression) or ctDNA levels with the outcomes of cCR, incidence of any grade ≥ 3 toxicity during treatment, incidence of post chemoradiotherapy grade ≥ 3 toxicity, and organ preservation rates, the logistic regression model will be considered. To investigate the relationship between tumor microenvironment (including FAK expression) or ctDNA levels with PFS, the Cox regression model will be considered. To investigate the relationship between tumor microenvironment (including FAK expression) or ctDNA levels with the outcomes of quality of anorectal function, the linear regression model will be considered.

18.7 Accrual

The overall accrual will be 63 patients. The rate of accrual for the study is expected to be about 20 patients per year. It is expected that the accrual period of the study will be completed in about 3 years.

19 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Regulatory Coordinator (or designee) prior to IRB/IEC submission.

Site activation is defined as when the secondary site has received official written documentation from the coordinating center that the site has been approved to begin enrollment. At a minimum, each participating institution must have the following documents on file at Washington University prior to study activation:

- Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution's IRB. This documentation must show which version of the protocol was approved by the IRB.
- Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.
- Documentation of FWA, signed FDA Form 1572 (if applicable), and the CVs of all participating investigators.
- Protocol signature page signed and dated by the investigator at each participating site.

The coordinating center Principal Investigator (or designee) is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 4 weeks of obtaining Washington University IRB approval. Activated secondary sites are expected to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt unless otherwise noted. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

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Appendix A: FACT-C Questionnaire

Patient ID#: _____ Date of Completion: _____

FACT-C (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Patient ID#: _____ Date of Completion: _____

FACT-C (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Patient ID#: _____ Date of Completion: _____

FACT-C (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
Q2	Do you have an ostomy appliance? (Mark one box)	☐ No		or	☐ Yes	
	If yes, please answer the next two items:					
C8	I am embarrassed by my ostomy appliance	0	1	2	3	4
C9	Caring for my ostomy appliance is difficult	0	1	2	3	4

APPENDIX B: PATIENT'S MEDICATION DIARY

Today's Date: _____ Agent: Capecitabine

Cycle: _____ Study ID#: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month. Take _____mg (___pills) of capecitabine twice daily on Days 1 through 14 of each cycle, once in the morning and once in the evening. Take it with a glass of water and drink the glass of water in as little time as possible. Swallow the pills whole and do not chew them.
2. Record the date, the number of pills taken, and when you took them.
3. If you forget to take dose within 4 hours of the usual time, then do not take that dose. Restart taking it with the next dose.
4. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
5. Please return the forms to your physician or your study coordinator when you go to your next appointment. Please bring your unused study medications and/or empty bottles with you to each clinic visit so that a pill count can be done.

Day	Date	What time was dose taken?		# of tablets taken		Comments
		AM Dose	PM Dose	AM Dose	PM Dose	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
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21						

APPENDIX C: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX D: Reporting Timelines

Expedited Reporting Timelines		
Event	**HRPO**	**QASMC**
Serious AND unexpected suspected adverse reaction		
Unexpected fatal or life-threatening suspected adverse reaction		
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.	
Protocol exception	Approval must be obtained prior to implementing the change	
Clinically important increase in the rate of a serious suspected adverse reaction of that list in the protocol or IB		
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Breach of confidentiality	Within 10 working days.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

Routine Reporting Timelines		
Event	**HRPO**	**QASMC**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.
Minor deviation	Report summary information at the time of continuing review.	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

Expedited Reporting Timelines for Secondary Sites		
Event	**WU (Coordinating Center)**	**Local IRB**
Serious AND unexpected suspected adverse reaction	Report no later than 11 calendar days after it is determined that the information qualifies for reporting.	Report all applicable events to local IRB according to local institutional guidelines.
Unexpected fatal or life-threatening suspected adverse reaction	Report no later than 4 calendar days after initial receipt of the information.	
Unanticipated problem involving risk to participants or others	Report no later than 4 calendar days after initial receipt of the information.	
Adverse event or SAE that does not require expedited reporting	As per routine data entry expectations	
Protocol exception	Approval must be obtained prior to implementing the change.	

APPENDIX E: Washington University SAE Reporting Cover Sheet

SAE COVER SHEET- Secondary Site Assessment

Washington University HRPO#:	Sponsor-Investigator:
Subject Initials:	Subject ID:
Treating MD:	Treating Site:
EVENT TERM:	Event Start Date:
EVENT GRADE:	Date of site's first notification:

Treating MD Event Assessment:

Is this event **possibly, probably, or definitely** related study treatment?

☐ yes ☐ no

If yes, please list which drug (if more than one)_____

Explain _____

_____

_____ _____ _____

Physician's Name **Physician's Signature** **Date**

APPENDIX F: STUDY SPECIFIC DSM TABLES

Protocol Objectives and Subject Evaluability	
Objective	**# of patients evaluable for this endpoint to date**
Primary	
To determine the clinical complete response rate (cCR) rate of patients with stage I-IIIB (cT1-3, N0-2a, M0) rectal cancer being treated with sequential short course radiotherapy followed by multi-drug chemotherapy.	
Secondary	
To determine the 2 year progression free survival (PFS)	
To determine the incidence of any grade ≥ 3 toxicity during treatment.	
To determine the incidence of post chemoradiotherapy grade ≥ 3 toxicity at 1 year	
To determine quality of anorectal function at 1 year using the FACT-C questionnaire.	
To determine the 1 and 2 year organ preservation rate	
Exploratory	
To associate tumor microenvironment (including FAK expression) with cCR and other clinical outcomes.	
To associate ctDNA levels with cCR and other clinical outcomes.	

Interim Analysis and Early Stopping Rules
Does the study design include an interim toxicity analysis? No
Does the study design include an interim futility analysis? Yes
If yes, describe. An interim analysis will be performed on the primary endpoint once 24 subjects have been enrolled and have completed the evaluation after chemotherapy. If ≤ 8 patients have cCR in these 24 patients, the study will be stopped for futility. Otherwise, the additional 39 patients will be enrolled. The null hypothesis will be rejected if ≥25 patients with cCR are observed in 63 patients.
Has the interim futility analysis been conducted?
If yes, describe the results of the interim futility analysis.
Are there early stopping rules that outline circumstances under which the study must be suspended or closed? Yes
If yes, describe. If ≤ 8 patients have cCR in the first 24 patients, the study will be stopped for futility.

Provide data describing whether the stopping rules have been met.

Response Data					
UPN	**Subject Site**	**On tx date**	**# of cycles completed**	**Pt replaced?**	**Best response**

Aggregated Response Data								
Response	**Completion of Chemo**	**Non-operative patients only**						
		3 mon	**6 mon**	**9 mon**	**12 mon**	**16 mon**	**20 mon**	**24 mon**
cCR								
PR								
SD								
PD								
NE								

Treatment Discontinuation and Survival				
UPN	**Date off tx**	**Reason off tx**	**Vital status**	**If dead, cause**

Summary of Specimen Collections			
Type of specimen	**Time point**	**# of patients eligible for collection at this time point**	**% of patients who have reached this time point and had the specimen collected**
Tumor tissue	Screening		
Blood for ctDNA	Screening		
Blood for ctDNA	Post-RT/prior to C1 chemo		
Blood for ctDNA	C2D1 chemo		
Blood for ctDNA	Completion of chemo		
Blood for ctDNA	10-14 mon after completion of RT		
Blood for ctDNA	3 mon		
Blood for ctDNA	6 mon		
Blood for ctDNA	9 mon		

Blood for ctDNA	12 mon		
Blood for ctDNA	16 mon		
Blood for ctDNA	20 mon		
Blood for ctDNA	24 mon		