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Neoadjuvant FOLFOX therapy with Short Course Radiation and active surveillance in locally advanced Rectal Cancer: A Phase II Study

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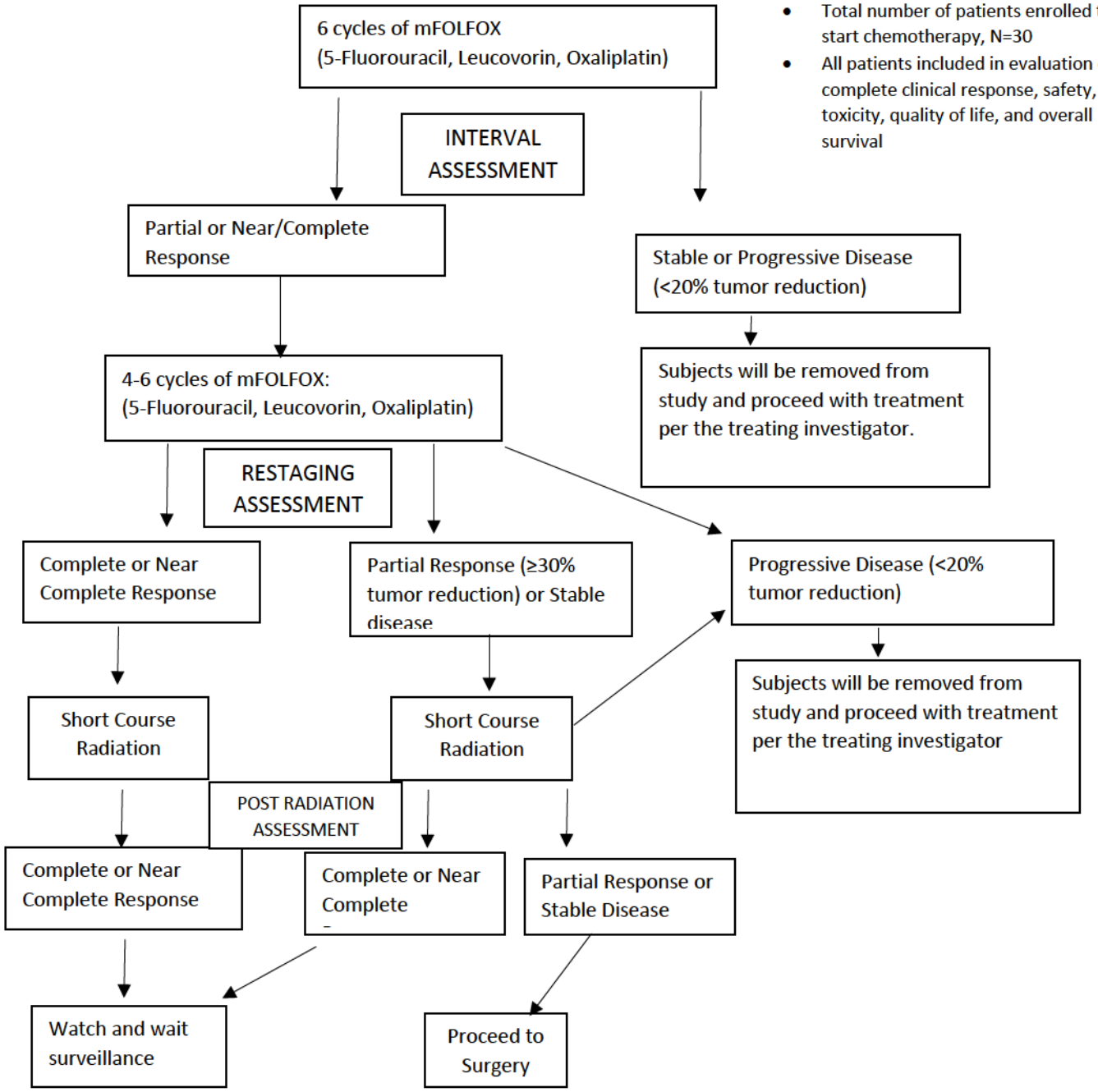
Figure 1. Schema



- Total number of patients enrolled to start chemotherapy, N=30
- All patients included in evaluation of complete clinical response, safety, toxicity, quality of life, and overall survival

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1.0 Purpose of Study and Rationale

1.1 Purpose of Study

The purpose of this study is to evaluate the treatment of patients with locally advanced rectal cancer for complete response to neoadjuvant chemotherapy followed by short course radiation. without surgery. These patients will be evaluated for complete clinical response (cCR) after completing up to 12 cycles of modified FOLFOX (mFOLFOX) (fluorouracil, leucovorin, oxaliplatin) chemotherapy, plus the use of short course radiation. Patients who have stable or progressive disease will be removed from study and treated per discretion of the treating physician. Those determined to have a near complete or complete response will complete full neoadjuvant treatment (chemotherapy and short course radiation) and undergo close surveillance with watchful waiting for local recurrence without immediate surgery. The primary endpoint of this study will be the rate of cCR, which is to include complete and near complete clinical response with induction chemotherapy and short course radiation, with secondary endpoints of disease-free survival (DFS), overall survival (OS), quality of life (QOL), as well as evaluation of safety and toxicity.

1.2 Rationale

Colorectal cancer has been well studied as it is the second leading cause of cancer death in the United States, with over 39,000 estimated newly diagnosed cases of rectal cancer each year. Due to ongoing improvements in treatment, there has been a decline in the overall incidence and mortality in the past two decades though annual deaths still total approximately 49,000 from combined colorectal cancer[1]. The current standard of care for locally advanced rectal adenocarcinoma is chemoradiation therapy (CRT) before or following surgical intervention, which has yielded a significant decrease in local recurrence at the expense of acute or extended toxicity from treatment. Disease free survival for neoadjuvant or adjuvant treatment for locally advanced rectal cancer has been shown to be 68% and 65% at five years, respectively[2].

However, this multi-modality treatment of CRT followed by surgery is associated with a high potential for creating substantial morbidity including diarrhea, hematologic toxicity, dermatologic toxicity, sexual dysfunction, bowel and bladder dysfunction, small bowel obstruction, and strictures at the site of anastomosis[2-4]. Additionally, patients undergoing surgery have higher rates of wound dehiscence following CRT[4]. Though sphincter-sparing surgery is preferable for improved quality of life, it is not always possible to obtain negative margins. When sphincter-sparing surgery is not an option, such patients require an abdominoperineal resection (APR), resulting in a permanent colostomy.

In review of earlier studies employing CRT, much of the current evidence supporting neoadjuvant therapy is derived from the randomized controlled trial by the German Rectal Cancer Study Group in 2004 comparing preoperative CRT with postoperative treatment. Though rates in overall survival remained unchanged, local recurrence rates were decreased, and more patients completed preoperative treatment. We note that 8% of those patients in the preoperative CRT arm were found to have a complete pathologic response (pCR) based on histopathology at the time of surgery[2].

Due to treatment related morbidity, and a growing trend of rectal cancer in patients younger than 50 years old, it has come in to question if rectal cancer has been over-treated in select

individuals[1]. At our own institution, following patient enrollment evaluating total neoadjuvant therapy (TNT) with 6 cycles of FOLFOX therapy followed by surgery in a collaborative study, it was noted that several individuals had a clinical complete or near complete response, or complete pathologic response. We now seek to evaluate if total neoadjuvant therapy with chemotherapy alone may produce such a response in some individuals, utilizing chemotherapy with short course radiation therapy. Those with a complete or near complete response may be spared surgical intervention.

Neoadjuvant therapy with watch and wait surveillance

In a 2014 study, 90 of 183 (49%) patients in a single institution study achieved a complete clinical response (cCR) after receiving CRT for 8 weeks alone. Following a close surveillance schedule of visits, 28 (31%) of initial responders experienced local recurrence, with 17 of these patients within the first year. Salvage therapy with surgery was feasible in 26 (93%) of these patients, and R0 resection in 25 (89%). The results of this study suggest that there is a population of patients not requiring CRT with surgery for their locally advanced disease. With a median follow up of 60 months, 62 (34%) of the 183 patients remained disease free and could safely avoid surgery. The 5-year overall survival for all patients was 91% and disease-free survival 68%. This study included tumors cT2-T4 and node-positive disease[4].

Evaluation of pathologic complete response rate after chemotherapy, chemoradiation

Several more recently published studies evaluated tumor response to neoadjuvant chemotherapy alone followed by surgery. Schrag et al. in 2014 conducted a phase II, single institution study of 32 patients with T2N+, T3N0, or T3N+ rectal tumors, excluding T4 staged disease. Patients underwent six cycles of FOLFOX plus bevacizumab, followed by total mesorectal excision (TME). Following completion of neoadjuvant therapy, 8 patients (25%) were found to have pCR at surgery. Four-year DFS and OS were 84% and 91%, respectively[5]. One may hypothesize the increased rates of DFS and OS may be improved from earlier trials with the exclusion of T4 tumors as part of the study. In a similar pilot study of 45 patients who had undergone six cycles of neoadjuvant FOLFOX without bevacizumab, only 2 patients (4.4%) were found to have cCR, with 29 (64.4%) in partial response, however, pCR following TME was observed in 8 (17.8%) patients. This study had included T4a disease (T2-T4a, N0-N2) and three-year DFS 67.9% and OS 80.8% [3].

Initial results of the Chinese FOWARC study, a multicenter trial of 495 patients comparing neoadjuvant fluorouracil-radiotherapy, FOLFOX-radiotherapy, and FOLFOX alone, achieved pCR in 14.0%, 27.5%, and 6.6% of patients, respectively. However, study protocol allowed for a minimum of only four cycles of FOLFOX therapy preoperatively, and inclusion criteria allowed for stage II (T3-4, N0) or stage III (T1-4, N1-2)[6]. The above study found lower rates of pCR with chemotherapy alone, especially when cycles became increasingly limited.

Complete response rates following neoadjuvant therapy with combined chemotherapy and chemoradiation.

There are a number of studies that has specifically evaluated pathologic or clinical complete response following the combination of CRT followed by further consolidative chemotherapy. Habr-Gama et al. evaluated 34 patients with CRT followed by 3 additional cycles of 5-FU and leucovorin, no oxaliplatin, followed by surveillance if there was complete response. CCR was maintained for at least 12 months in 48% of patients, with 5 additional patients demonstrating pCR after surgery, with portal combined complete response rate of 65%. This study did evaluate for long-term durability of results. A multicenter phase II study by Garcia-Aguilar et al. involving 292 patients compared pCR in patients receiving standard neoadjuvant CRT, or followed by 2, 4, or 6 cycles of FOLFOX. The study included patients with stage II-III locally advanced rectal cancer. The standard neoadjuvant group obtained a pCR rate of 18%, with pCR rates of 25%, 30%, and 30% with increasing cycles of FOLFOX therapy, respectively.

Recently, a retrospective cohort has been published by Memorial Sloan Kettering Cancer Center evaluating 628 patients with locally advanced T3-4, or N1-2 rectal cancer evaluating patients who had either received TNT or chemoradiation followed by adjuvant therapy after surgery. Participants in TNT cohort received 8 cycles of FOLFOX or 5 cycles CAPOX, followed by chemoradiation with 5-FU or capecitabine plus long course radiotherapy. The possibility of pCR was explained to patients who were found to have cCR at completion of TNT and given the choice if to proceed to surgery or undergo watchful waiting. CCR was recorded only at the 12-month mark, as most local recurrences occurred within that period. Of 308 patients with stage II or III disease, 18.3% of patients had a sustained cCR, and 21.8% with pCR with those who had proceeded immediately to surgery. A total of 36% of patients had either pCR or cCR with TNT at one year, compared to 21% of patients with pCR who received neoadjuvant CRT followed by adjuvant therapy. [7]

Short Course radiation in treatment of rectal cancer

In the above studies, we see that total neoadjuvant therapy has not been studied with chemotherapy and radiation and watch and wait surveillance, and with chemotherapy alone preceding surgery. The addition of radiation to locally advanced rectal tumors may provide additional local control and downstaging tumors prior to surgery. As there is growing evidence of it's not inferiorly to long course radiation in reducing patient time of treatment, our trial will add short course radiation to neoadjuvant chemotherapy.

Short course radiation therapy (RT) 5 to a radiation therapy inferior fractions, typically within one week compared to 5-6 weeks with long course RT. Short course RT has been studied in phase II and subsequently phase III trials by Bujko et al. in which it was compared with long course RT. Results of a phase III study demonstrated T3 and T4 tumor undergoing short course RT have significantly lower overall toxicity (p=0.006), overall survival of 73% versus 65% at 3 years (0.046) and trended towards improved pathologic response (0.07). The Stockholm III that he compared long course RT with a delay prior to surgery, short course RT with delay, and short course RT without delay. Short course RT with delay demonstrated similar outcomes for recurrence free survival and multivitamin analysis compared to the 2 other cohort, but demonstrated significantly lower postoperative complications and short course RT without delay.

Since completion of these studies, short course RT has been included in TNT trials. In a recently published abstract of a retrospective cohort study, 388 patients received either a long course RT (n=236) or short course RT (n=152) as part of TNT prior to surgery. Though the short course cohort had a higher number participants with more advanced stage disease, pCR and recurrence rates were found to be not severely different from the long course cohort, further support that short course RT is not inferior to long course therapy. Prospective trials are currently underway; the RAPIDO trial, early active but no longer enrolling patients, is evaluating the use of short course RT with chemotherapy prior to surgery (TNT) compared to conventional long course chemoradiation followed by adjuvant therapy postoperatively.

To our knowledge, there are no studies currently evaluating a complete response to full, upfront neoadjuvant chemotherapy with mFOLFOX plus short course CT in locally advanced rectal adenocarcinoma followed by surveillance. From review of available literature, we conclude that there is the potential for an identifiable population of patients that may benefit from treatment with systemic therapy and short course RT with a complete or near complete response, while sparing these patients the toxicity of a total mesorectal excision. Earlier phase II studies demonstrate a range of complete response from 25% to 65% for total neoadjuvant therapy, but we conclude from these studies that the complete response rate is likely in the range of 30-40%.

In conclusion, we hypothesize that some patients with locally advanced rectal cancer with stage I (T2N)-IIIB disease (excluding clinical T4 or N2b staging) will benefit from our proposed protocol of total neoadjuvant therapy, with proposed reduction in surgical related toxicities.

2.0 Study Objectives

2.1 Primary Objective

The primary objective of this study will be to assess the rate of clinical complete or near complete response to total neoadjuvant therapy with up to 12 cycles of mFOLFOX and short course radiation.

2.2 Secondary Objectives

The secondary objectives of this study will be to evaluate rate of clinical complete response to induction chemotherapy, 1-year disease free survival, 5-year disease free survival, overall survival, quality of life assessment, as well as safety and toxicity of treatment. Patients proceeding to surgery after stable or progressive disease during total neoadjuvant treatment and patients with recurrence within 5 years will be evaluated for rate of R0 resection.

3.0 Study Design

This is a multi-center, phase II study investigating the efficacy of total neoadjuvant therapy with mFOLFOX and short course radiation and selective non-operative management in patients with locally advanced rectal cancer.

Participants with Stage IIA, IIIA, IIIB rectal adenocarcinomas, except for any T4 or N2b disease, who would otherwise undergo long course concurrent chemotherapy and radiation therapy followed by TME may be enrolled for treatment with mFOLFOX therapy. Participants with lower sphincter rectal cancer deemed not eligible for sphincter sparing surgery are not eligible for participation. Participants would be treated with up to 12 cycles of mFOLFOX therapy. (One cycle of mFOLFOX= 14 days) and short course radiation.

All patients will be evaluated once following six cycles of chemotherapy via endoscopy and CT plus MRI.

Patients with a partial, near or complete response will receive an additional 4-6 cycles of chemotherapy followed by reassessment.

Patients with stable or progressive disease defined as less than 20% reduction will be removed from study.

Following completion of all chemotherapy (10-12 cycles) patients will be re-assessed via endoscopy and CT plus MRI. Patients will then receive short course radiation followed by repeat assessment with endoscopy and CT/MRI. Those patients with evidence of complete or near complete clinical response following completion of all chemotherapy and radiation will be treated non-operatively and undergo close surveillance.

Patients with a partial response or stable disease will undergoTME.

Those with <20% response will be removed from study and undergo treatment per the treating investigator. These patients will be followed for survival at six month intervals for up to 5 years.

All patients will be followed for 5 years following last date of treatment:

- For patients in the study not requiring surgery following chemotherapy, the last day of treatment will be considered the last day of mFOLFOX therapy.
- For patients who receive short course radiation, the last day of treatment will be considered the last day of radiation.
- For patients in the TME group, the last day of treatment will be considered the day of surgery.

4.0 Selection Criteria

4.1 Inclusion Criteria

1. Participants must be ≥18 years old at time of diagnosis

2. Histologically confirmed adenocarcinoma of the rectum from biopsy, excluding lower rectal cancer, (defined as patients requiring an abdominoperineal resection)
3. Clinical staging including T2N0, T3N0 tumors, or T1-3 with N1-2a disease
4. Rectal tumors must be determined as likely requiring total mesorectal excision (TME)
5. Participant must be treatment naïve for rectal cancer, with no prior radiation chemotherapy, radiation, or surgery specific for rectal cancer
6. No history of prior pelvic radiation
7. No active infections requiring intravenous antibiotics within 14 days of initiating treatment
8. Baseline lab work must meet the following parameters:
    a. Absolute neutrophil count (ANC) ≥1500/mm3
    b. Platelet count ≥100,000/mm3
    c. Hemoglobin ≥8.0 g/dL
    d. Total bilirubin ≤ 1.5x upper limit of normal (ULN)
    e. Total creatinine ≤ 1.5x upper limit of normal (ULN)
    f. AST and ALT ≤ 2.5 x ULN
9. Women of childbearing potential (WCBP) will be defined as those biologically capable of becoming pregnant. WCBP must be negative for pregnancy testing (urine or blood) and agree to use effective contraception starting after negative pregnancy testing and extending to one year after end of treatment as defined in Section 3.0. Viable contraception should be used after trial screening, before initiation of chemotherapy, and throughout the duration of active treatment in the study.
10. Participants must be explained the purposes of the study and sign a statement of informed consent prior to participation. Those who do not read or understand English are eligible and may be consented according to institutional and federal regulations.

4.2 Exclusion Criteria

1. Recurrent or refractory rectal adenocarcinoma
2. T1N0, T4a, T4b, or N2b tumors
3. Patients with lower rectal cancer requiring abdominoperioneal resection are excluded
4. Any evidence of metastatic disease
5. Primary unresectable rectal cancer. A tumor will be considered unresectable when invading adjacent organs such that an en bloc resection cannot achieve negative margins
6. Patients unable to undergo MRI imaging
7. Patient with a history of any arterial thrombotic event within the past 6 months. This includes angina, myocardial infarction, transient ischemic attack, or cerebral vascular accident.

8. Patients with history of venous thrombotic episodes such as deep vein thrombosis, pulmonary embolus occurring more than 6 months prior to enrollment may be considered for protocol participation, provided they are on stable doses of anticoagulant therapy. Patients who are anticoagulated for atrial fibrillation or other conditions may participate only if on stable doses of anticoagulant therapy.
9. Patients with cardiovascular, hepatic, or renal systemic diseases that would preclude use of chemotherapy per the treating investigator.
10. Peripheral neuropathy >grade 1 by Common Terminology Criteria for Adverse Events, or CTCAE
11. The patient must not be on any clinical trials involving other experimental therapies before or during study treatment
12. Women who are currently pregnant or breast-feeding
13. Men and women who are actively trying to father/conceive children
14. Patients with any other concurrent medical or psychiatric condition which were deemed inappropriate for entry into the study per the investigator.
15. History of other invasive malignancy within the past 3 years, except for adequately treated non-melanoma skin cancer, ductal carcinoma in situ of the breast, bladder carcinoma in situ or carcinoma in situ of the cervix.

[a]CTCAE version 5.0 from Department of Health and Human Services

5.0 Treatment Plan

5.1 Subject Recruitment and Consent

Patients will be recruited by GI oncology treatment teams, the research team, and by the principal and sub-investigators in the study. Potential patients will have their medical records screened to identify them as eligible for study. Eligible patients will be counseled on the rationale of the study, potential benefits and risks, and presented with a consent. Consent may be obtained by an investigator of the study.

5.2 Pre-treatment Evaluation

Patients eligible for treatment and have been consented will be registered in RED CAP by the Study Coordinator. Those patients who have been consented and become participants in the trial must complete pretreatment evaluation within 45 days (+/- 15 days) days of starting neoadjuvant therapy administration (Cycle 1, Day 1).

All patients will undergo pre-treatment staging via physical examination, labs, proctoscopy/sigmoidoscopy, baseline imaging, and pathologic assessment of the tumor within 45 days from the start of treatment (+/-15 days). Colorectal surgery must document if the participant has a lower rectal adenocarcinoma, generally tumors in the lower third of the rectum, not eligible for sphincter sparing surgery.

Pelvic MRI will also be performed to obtain baseline evaluation of the tumor. Endorectal ultrasound may be used if MRI is not conclusive in lymph node evaluation. Each patient will be evaluated by the treating physician to determine their eligibility for mFOLFOX therapy. If a patient is unable to obtain a CT due to contrast allergy or other contraindication, MRI imaging will be acceptable for evaluation.

Patients will complete an evaluation prior to treatment regarding their quality of life (QOL). This will also be completed during the interval assessment, restaging assessment, post radiation assessment, 6 months follow up, and annually for 5 years. Validated QOL forms EORTC QLQ-30, and EORTC QLQ-CR29 will be used for assessment[8, 9]. These two surveys can be completed on the phone or at clinic visits, and consist of four pages of questions pertaining to daily activities, symptoms, and overall health before, during, and after treatment. These would take an estimated 10 minutes to complete.

Rescreening may be allowed one time within 30 days of a screen failure. The patient will retain the same screening number.

Optional blood work will also be collected for correlative biomarkers at baseline, at cycle 6 day 1 and at the time of the post radiation assessment.

5.3 Administration Schedule

Patients treated on protocol will be treated with modified FOLFOX. Patients will receive up to 12 cycles of mFOLFOX, administered every other week. mFOLFOX will be given on day 1 of each 14 day cycle.

Patients will receive oxaliplatin 85 mg/m² IV over 120 minutes, leucovorin 400 mg/m² IV over 120 minutes, 5-FU 400 mg/m² IVP followed by 5-FU 2400 mg/m² infuse over 46 hours.

In an attempt to prevent adverse events, all patients will be treated with anti-emetics and supportive care agents per institutional guidelines. It is recommended that all patients receive dexamethasone, prochlorperazine maleate, and palonosetron. The use of growth factor support will be determined by the treating investigator.

Prior to radiation patients will undergo CT simulation (with IV and/or oral contrast if needed). The radiation prescription will be 20 Gy in 5 fractions to lymph node regions including mesorectum, internal iliac, and pre-sacral with simultaneous boost to 25 Gy in 5 fractions to the grossly involved rectal tumor plus adjacent mesorectum and grossly involved adenopathy. Treatment will be delivered over 5 days.

Table 1. Treatment Dosing

Treatment Agent	Dose	Administration	Day in Cycle
Oxaliplatin	85 mg/m^2	IV infusion over 120 minutes	1
Leucovorin	400 mg/m^2	IV infusion over 120 minutes	1
5-Fluorouracil (bolus)	400 mg/m^2	IV bolus infusion after oxaliplatin and leucovorin	1
5-Fluorouracil (infusion)	2400 mg/m^2	IV infusion over 46 hours following 5-FU bolus	1

5.4 Disease Progression

Patients with stable disease (<20% response) or disease progression at the interval assessment will be removed from study and follow treatment per the treating investigator.

Progression after completion of total neoadjuvant therapy or while on observation will also be at the discretion of the primary oncology provider.

5.5 Post-treatment Evaluation

All patients will be subject to surveillance for 5 years to monitor for progression of disease. Patients on watch and wait surveillance will undergo history and physical examination, imaging, laboratory testing, and surgical oncology evaluation as outlined in Table 4. Those patients who received surgery after partial response will be followed per NCCN guidelines regarding history and physical exam, CEA, imaging, and evaluation by colonoscopy.

5.6 Discontinuation of Study

Participants may be discontinued from treatment for any of the following reasons:

1. The participant wishes to no longer participate in treatment
2. The provider in charge of the patient's treatment withdraws the participant

3. The participant is determined to have unacceptable or intolerable toxicity
4. A participant becomes pregnant
5. A participant is diagnosed with another malignancy requiring treatment
6. The participant is lost to follow up
7. If treatment is held for greater than 28 days

All participants who are discharged from treatment and the study will continue to be followed for severe adverse events, disease free and overall survival whenever possible.

6.0 Schedule of Events

Table 2. Study Initiation to Interval Assessment

	Prior To Treatment	mFOLFOX (1 cycle =14 days)						Interval Assessment[e]
Study Day	**Within 30 days of C1D1 (+/- 15 days)**	**C1D1 (+/-3days)**	**C2D1 (+/-3days)**	**C3D1 (+/-3days)**	**C4D1 (+/-3days)**	**C5D1 (+/-3days)**	**C6D1 (+/-3days)**	**Within 14 days of C6D1 (+/-7days)**
History/Physical Exam								
H&P	X		X		X		X	
Height[a] and Weight	X	X	X	X	X	X	X	X
Performance Status	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X
Colorectal Surgical Oncologist Evaluation	X							X
EKG	X							
QOL	X							X
Review medications & adverse events	X	X	X	X	X	X	X	X
Imaging								
MRI pelvis	X							X
CT chest/abdomen/pelvis	X							X
Procedural								
Proctoscopy or Sigmoidoscopy, and DRE	X							X
Laboratory[b,f]								
CBC	X	X	X	X	X	X	X	X
CMP	X	X	X	X	X	X	X	X
CEA	X		X		X		X	
BHCG in WCBP[c]	X							
Correlative Biomarker[d]	X						X	

[a]Height needs to be obtained only at time of screening

[b]Laboratory work can be obtained up to 48 hours prior to any treatment or assessment

[c]Women of child-bearing potential (urine or blood testing)

[d]1 vial of extra blood will be collected and stored for biomarker research. Correlative biomarker for screening can also be collected at C1D1 prior to treatment

[e]Patients who have stable disease or progression will be removed from study and followed for survival.

F Pre-study labs can be used for C1D1 if performed within 7 days

Table 3. Partial or Complete Response after Interval Assessment to Restaging Assessment

	mFOLFOX						Restaging Assessment	Short course Radiation	Post Radiation Asssesment
Study Day	**C7D1 (+/-3 days)**	**C8D1 (+/-3 days)**	**C9D1 (+/-3 days)**	**C10D1 (+/-3 days)**	**C11D1 (+/-3 days if applicable)**	**C12D1 (+/-3 days if applicable)**	**Within 4-12 weeks of last chemo (+/-7 days)**	**Days 1-5 (if applicable)**	**Within 6-12 weeks following RT**
History/Physical Exam									
H&P	X		X		X		X		X
Weight	X	X	X	X	X	X	X	X	X
Performance Status	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X
Colorectal Surgical Evaluation							X		
QOL[a]							X		X
Review medications & adverse events	X	X	X	X	X	X	X	X	X
Imaging									
MRI pelvis							X		X
CT chest/abdomen/pelvis							X		
Procedural									
Proctoscopy or Sigmoidoscopy, and DRE							X		X
Laboratory[b]									
CBC	X	X	X	X	X	X	X	X	X
CMP	X	X	X	X	X	X	X	X	X
CEA	X		X				X		X
Correlative Biomarker									X

[a]QOL will be assessed on all patients, including those that did not continue mFOLFOX after cycle 6 due to stable or progressive disease

[b]Laboratory work can be obtained up to 48 hours prior to any treatment or assessment

Table 4. Surveillance following completion of total neoadjuvant therapy without surgery

	Year 1		Year 2		Year 3		Year 4		Year 5	
Months from completion of study	**3-6**	**9-12**	**15-18**	**21-24**	**30**	**36**	**42**	**48**	**54**	**60**
History/Physical Exam										
H&P	X	X	X	X	X	X	X	X	X	X
Performance Status	X	X	X	X	X	X	X	X	X	X
QOL[a]	X	X	X	X	X		X	X		X
Imaging										
MRI pelvis	X	X		X		X		X		X
CT chest/abdomen/pelvis	X	X		X		X		X		X
Procedural										
Proctoscopy or Sigmoidoscopy, and DRE	X	X	X	X	X	X	X	X	X	X
Laboratory										
CBC	X	X	X	X	X	X	X	X	X	X
CMP	X	X	X	X	X	X	X	X	X	X
CEA	X	X	X	X	X	X	X	X	X	X

[a]QOL will be assess on all patients, including those that did not continue watch and wait surveillance as the proceeded to surgery

7.0 Treatment Dose Modifications

Treatment dose may be modified or held by the primary treating oncologist at their discretion. Treatment may be held a total of 4 weeks to account for toxicity. We recommend the following dose modifications in the event of ≥Grade 2 toxicity. If treatment has been held for greater than 4 weeks the patient will be discontinued from study. If dose modifications require more than 2 dose level reductions, the patient will be discontinued from the study.

Patients with grade 2 or greater neuropathy attributed to Oxaliplatin can discontinue oxaliplatin provided that they have received at least 6 cycles and be treated with single agent 5-Fluorouracil.

Growth factor support, such as pegfilgrastim, may be used at provider discretion.

Table 5. Dose Modifications Guide

Treatment	Dose Level 0	Dose Level -1	Dose Level -2
Oxaliplatin	**85 mg/m^2**	**65 mg/m^2**	**50 mg/m^2**
Leucovorin	**400 mg/m^2**	**320 mg/m^2**	**260 mg/m^2**
5-Fluorouracil (bolus)	**400 mg/m^2**	**320 mg/m^2**	**260 mg/m^2**
5-Fluorouracil (infusion)	**2400 mg/m^2**	**1920 mg/m^2**	**1540 mg/m^2**

8.0 Study Treatment Toxicities

8.1 Oxaliplatin

Common Toxicities:

- Peripheral neuropathy (may be dose limiting)
- Nausea
- Vomiting
- Diarrhea
- Fatigue
- Abdominal pain
- Constipation
- Increased liver transaminases AST and ALT
- Anemia
- Thrombocytopenia

Less Common Toxicities:

- Leukopenia
- Anorexia
- Cough

- Back or myalgias (muscle aches)
- Arthralgias (joint aches)
- Edema
- Flushing
- Skin Rash
- Alopecia
- Dyspepsia
- Dysgeusia
- Hypersensitivity
- Local site reaction with redness or swelling
- Increase serum creatinine

Rare but serious:

- Anaphylaxis
- Chest pain
- Shortness of breath
- Palmar-plantar erythrodysesthesia (hand-foot syndrome, with redness and/or pain)
- Sepsis
- Death

8.2 Leucovorin

Toxicities:

- Thrombocytopenia
- Pruritus
- Hypersensitivity
- Urticaria
- Wheezing
- Skin rash
- Erythema (redness)
- Toxicities of 5-fluorouracil are enhanced

Rare but Serious:

- Anaphylaxis
- Seizures
- Death

8.3 5-Fluorouracil

Common Toxicities:

- Anemia
- Thrombocytopenia

- Leukopenia
- Nausea
- Vomiting
- Anorexia
- Diarrhea
- Nail changes, brittle nails

Less Common Toxicities

- Chest pain
- Alopecia
- Headache
- Palmar-plantar erythrodysesthesia (hand-foot syndrome, with redness, pain)
- Venous hyperpigmentation
- Dermatitis

Rare but Serious:

- Vasospasm
- Myocardial Infarction
- Death

8.4 Short Course Radiation

Common Toxicities:

- Fatigue
- Diarrhea
- Rectal pain/pressure
- Perineal Skin irritation
- Dysuria

Less Common Toxicities

- Change in bowel habit
- Vomiting
- Abdominal Pain

Rare but Serious:

- Bowel Obstruction
- Fecal Incontinence
- Secondary Malignancy

9.0 Adverse Events Monitoring and Reporting

9.1 Definition of Adverse Event (AE)

Adverse events (AE) will be defined as any sign, symptom, illness, abnormal or adverse laboratory value, or experience that was not present at the start of treatment and occurs or worsens during the course of the therapy proposed regardless if related to that therapy.

9.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) will be those signs, symptoms, illnesses, abnormal or adverse laboratory values, or experiences that were not present at the start of treatment and occurs, or worsens during the course of therapy and has one of the following outcomes:

- Death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Requires medical or surgical intervention to prevent permanent impairment or damage

9.3 Reporting of Adverse Events

With each visit, the patient provider will assess the patient for AE since prior visits. Providers will directly ask about adverse events and record their occurrence, as well as those that are offered voluntarily by the participant.

Events will be documented to include:

- The participant's identification, disease and stage, cycle and day of treatment when AE occurred (if applicable)
- Time of onset
- Duration
- Severity by grade (per CTCAE Version 5.0),
- A brief description of the event
- Drug, device, or intervention suspected of causing the event
- Contributing factors, if applicable
- Action taken to intervene
- Time of resolution, or
- If the AE is ongoing at the conclusion of participation in the study
- Laboratory values will be included as adverse events if clinically significant and included in reporting.

9.4 Severity of Adverse Events

Numerical grading of adverse events will follow the Common Terminology for Criteria for Adverse Events version 5.0 from the U.S. Department of Health and Human Services:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic implications only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

Grade 4: Life-threatening consequences with urgent intervention indicated.

Grade 5: Death from AE.

10.0 Objectives and Data Analysis

10.1 Primary Endpoint

The primary outcome will be the rate of a complete clinical response. Response rates will be determined by the following:

- **A complete response** will consist of a digital rectal exam with normal appearing mucosa and sigmoidoscopy/proctoscopy with scarring but no nodularity or ulcerations.

- **A near complete response** will consist of digital rectal exam with smooth or minor mucosal abnormalities, and sigmoidoscopy/proctoscopy with small mucosal abnormalities, or superficial ulceration or erythematous scarring. No palpable lymph nodes but some induration/mucosal abnormalities

- **Partial response**, in our study, will be those tumors read with a ≥20% decrease in size without obtaining near or complete response, or remaining palpable lymph nodes with partial response

- **Stable disease**, in our study, will be those tumors read with a <20% decrease in size without obtaining near or complete response, or palpable lymph nodes, no change in size on proctoscopy/sigmoidoscopy

- **Progressive disease** will be those tumors with >20% increase in size, new lesions or palpable lymph nodes.

10.2 Secondary Endpoints

Secondary outcomes of our study will include the analysis of safety and toxicity, disease free survival, and overall survival from data included up to five years after enrollment in the study. Date will be stored in the RedCap database.

10.3 Data Analysis

We aim to accrue 40 participants over approximately a 5-year period. Though we hypothesize that this study will be of clinical benefit to those who may avoid surgical intervention, we have no knowledge that a similar study has been conducted. Thus, we aim to gain a preliminary estimate of the rate of locally advanced rectal cancer patients that can be spared surgical intervention through the use of neoadjuvant chemotherapy plus short course radiation. We anticipate a 30% rate of complete or near complete clinical response to neoadjuvant chemotherapy plus short course radiation at the post-radiation assessment. This rate will include subjects discontinuing mFOLFOX due to stable or progressive disease at the interval assessment or re-staging assessment in the denominator.

With an anticipated response rate of 30%, a sample size of 40 subjects produces a one-sided 95% lower-limit exact binomial confidence interval with a width of 13.4% (lower limit of 16.6%). The maximum width of a one-sided 95% lower-limit confidence interval with 40 subjects would be 16.1% when the response rate is 50%. We target the lower limit of the confidence interval to determine if this regimen demonstrates sufficient evidence of efficacy to be considered worthy of future study.

The complete or near complete response rate and associated 95% one-sided exact binomial confidence interval will be presented. Disease-free and overall survival will be described using the Kaplan-Meier method. Types and grades of adverse events will be tabulated. Changes in QOL (from baseline) will be described using means and standard deviations at each time point assessed. We will calculate these summary measures separately in those who obtain a complete or near complete response to up to 12 cycles of mFOLFOX and short course radiation and are entering watch and wait surveillance, and those who required surgery with or without radiation therapy prior to completion of mFOLFOX therapy. QOL will be measured using validated

QOL forms EORTC QLQ-30, and EORTC QLQ-CR29 as mentioned in Section 5.2, with paper-based surveys and scored according to the EORTC scoring manual [10].

11.0 Data and Safety Monitoring

11.1 Assessments and documentation of adverse events:

Adverse events and grade will be recorded at each follow-up visit. Serious adverse events will be collected and reported from the time patient signs informed consent until the first surveillance safety follow-up visit. Non-serious adverse events will be collected from the time of first study drug dosing until the first surveillance safety follow-up visit.

11.2 Reporting of serious adverse events:

The definition of serious adverse events (SAEs) is given in Section 9.2.

Each serious adverse event must be followed up until resolution or stabilization, by submission of updated reports to the designated person. An isolated laboratory abnormality that is assigned grade 4, according to CTC definition, is not reportable as an SAE; unless the investigator assesses that the event meets standard ICH criteria for an SAE. CTC grade 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as an SAE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria.

When required, and according to local law and regulations, serious adverse events must be reported to the Ethics Committee and Regulatory Authorities.

Study Investigators will conduct continuous review of data and patient safety. The Investigator will submit twice yearly progress reports of these data to the Data Safety Monitoring Committee for review. The review will include: the number of patients enrolled, withdrawals, significant toxicities as described in the protocol, serious adverse events both expected and unexpected, dose adjustments, and responses observed. The PI maintains a database of all adverse events with toxicity grade and information regarding treatment required, complications, or sequelae. The Investigator will submit a copy of the AE spreadsheet along with a Progress Report to the Data Safety Monitoring Committee (DSMC) for review. Actual review dates will be assigned when the 1st patient is accrued.

The DSMC at the Wilmot Cancer Institute, University of Rochester provides oversight of study progress and safety by review of accrual and adverse events at twice yearly meetings or more often if concerns arise. Any adverse event requiting expedited review per protocol, including those occurring at participating sites, will be submitted to the Safety Coordinator of the DSMC at the University of Rochester for

determination as to whether further action is required. When patient safety is of concern, an interim meeting may be called

- Any serious adverse event that is serious, related AND unexpected must be reported within 10 calendar days to both the DSMC Safety Coordinator and the RSRB (see RSRB guidelines). The DSMC Chair will determine whether further action is required, and when patient safety is of concern, an interim meeting may be called.
- Serious adverse events that are related AND expected or unrelated AND unexpected will be reported to the DSMC for review at the quarterly meeting. SAE reports are expected to include sufficient detail so that the DSMC can determine the severity, toxicity grade, expectedness, treatment required, and a follow up report documenting resolution or if there are sequelae. Serious adverse events that require detailed reports (but not necessarily expedited) are expected, related, non-hematologic toxicities of grades 3, 4 or 5.

The Safety Coordinator administratively coordinates reports and data collection and prepares documents for the DSMC Chair and committee review. The Safety Coordinator will administratively monitor adverse event rates utilizing the report from the study database. If any study has had two or more of the same SAE's reported in a month or more than six of the same SAE's in six months, the DSMC will review the summary of SAEs, discuss events with Study Chair, and conduct a more detailed review with the Study Chair. The Data Safety Monitoring Chair will determine if further action is required.

12.0 Data Confidentiality and Storage

During participation in the study, subject data including laboratory results, imaging, exams, treatments, and outcomes will be part of the patient's chart. Data extracted from the chart for the purpose of the study will be stored in the RedCap database.

Subjects will each have their own unique code in place of name, date of birth or other identifier that may be used in charting. The key will not be derived from patient data and will be available to the principle and/or sub-investigators. To avoid unauthorized disclosure of subject data with consent, the following safeguards will be in place:

- Not storing identifying information in the research database except unique subject code that will be used for subject identification
- Subject codes will be randomly assigned, and codes will be protected and treated as confidential as they link subject to data
- Security measures for physical and electronic data i.e.) locking up research files/logging out of electronic systems while they are unsupervised
- Using screensavers

- Shredding excess copies of paper documents

13.0 Data and Specimen Banking for Future Research Use

Upon consenting for study enrollment, participants will be given the option also to consent for banking of their rectal tissue specimen(s) for future use related to the study. The purpose of banking is to have the option to evaluate for genetic, histologic, or molecular information retrospectively following the initial study. This may be used to continue further research or clinical questions that may arise from our proposed study.

Consideration for access to these specimens will be determined by the principal investigator. Raw data from the study will be stored in the RedCap database, and participant specimens will be stored with pathology for 5 years. Both data and specimen(s) will be identified by a unique assigned subject code not derived from patient data as to protect confidentiality, with the key remaining with the principle investigator and/or sub-investigators.

Subjects will not be re-consented for use of their specimens if used in part of this study by the current principle and sub-investigators. The subject may request for their data or specimen(s) to be removed from the study or storage at any at the initiation of study or thereafter.

Optional Correlative Biomarker:

Patients will have the option to consent for additional correlative biomarker blood samples for future research use. Two 10.0 mL EDTA lavender tubes (total of 20.0 mL) will be collected at each time point – baseline, Cycle 6 Day 1 and time of post radiation assessment (if applicable). Both plasma and buffy coat samples will be collected. Within 1 hour of collection, centrifuge collection tubes for 10 minutes at 1600 x g. Transfer the supernatant into a conical tube. Remove the buffy coat (~1.0 mL) from the collection tubes and place in 1.5 mL cryotube. Centrifuge supernatant for an additional 10 minutes at 1600 x g. Divide the plasma into three cryotubes – two 3.0 mL tubes and one 1.5 mL tube. Freeze plasma and buffy coat samples in -80°C freezer. All samples should be labeled with subject ID number, study time point, collection date and sample type.

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