THE JANUS RECTAL CANCER TRIAL: A RANDOMIZED PHASE II TRIAL TESTING THE EFFICACY OF TRIPLET VERSUS DOUBLET CHEMOTHERAPY TO ACHIEVE CLINICAL COMPLETE RESPONSE IN PATIENTS WITH LOCALLY ADVANCED RECTAL CANCER

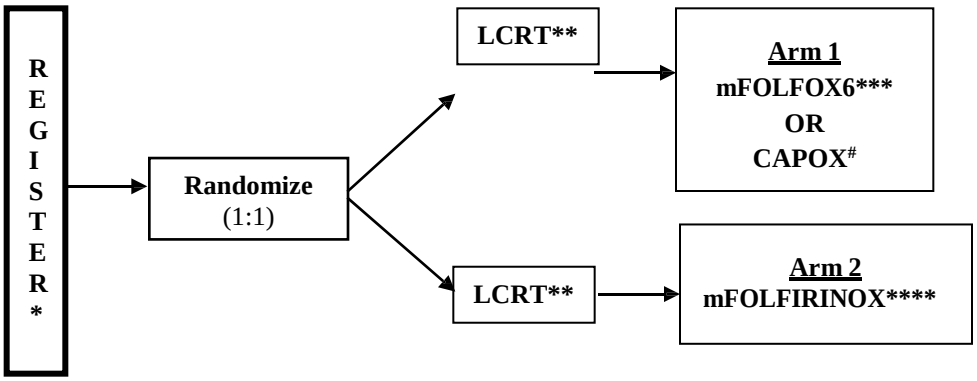
Eligibility Criteria (see Section 3.2)

- Clinical stage II or III rectal adenocarcinoma defined as T4N0, or any T with node positive disease (any T, N+); also T3N0 requiring APR or coloanal anastomosis
- No prior systemic chemotherapy, targeted therapy, or immunotherapy; or radiation therapy administered as treatment for colorectal cancer within the past 5 years
- Not pregnant and not nursing
- Age ≥ 18 years
- ECOG Performance Status 0-1
- No upper rectal tumors (distal margin of tumor > 12 cm from the anal verge)
- No recurrent rectal cancer; prior transanal excision, prior distal sigmoid cancer with a low anastomosis
- No known mismatch repair deficient rectal adenocarcinoma

Required Initial Laboratory Values

ANC	≥ 1500/mm^3
Platelet count:	≥ 100,000/mm^3
Creatinine:	≤ 1.5 x upper limit of normal (ULN) OR
Calc. creatinine clearance:	≥ 50 mL/min
Total bilirubin:	≤ 1.5 x ULN
AST/ALT:	≤ 3 x ULN

Schema



* Patients with locally advanced rectal cancer: <=12cm, T4N0 OR anyT, N1 OR T3N0 that would require APR or coloanal anastomosis

** LCRT = long-course chemoradiation (5 weeks)

***mFOLFOX6 = 8 cycles (1 cycle = 2 weeks)

****mFOLFIRINOX = 8 cycles (1 cycle = 2 weeks)

CAPOX = 5 cycles (1 cycle = 3 weeks)

Treatment is to continue for the full course of LCRT and Arm 1 or Arm 2 chemotherapy unless there is a clinical reason to stop. Following neoadjuvant chemotherapy, patients will either proceed to surgery (TME) or watch & wait (WW). Patients will be followed for 8 years or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

LCRT, chemotherapy (as noted in Arm 1 or Arm 2) and surgery will be conducted at the registering institution.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

2.1 OBJECTIVES

2.2 Primary objective

To evaluate and compare the cCR rates in patients with locally advanced rectal cancer treated with neoadjuvant LCRT followed by neoadjuvant mFOLFIRINOX versus neoadjuvant LCRT followed by neoadjuvant mFOLFOX6.

2.3 Secondary objective(s)

2.3.1 To evaluate and compare organ-preservation-time (OPT) between two treatment arms.

2.3.2 To evaluate and compare the disease-free survival (DFS) time between the two treatment arms

2.3.3 To evaluate and compare time to distant metastasis between two treatment arms

2.3.4 To evaluate and compare overall survival (OS) between two treatment arms

2.3.5 To evaluate and compare toxicity profiles of TNT between two treatment arms

2.4 Exploratory objective

2.4.1 Evaluation of ctDNA kinetics during neoadjuvant therapy & surveillance and to correlate with radiographic, pathologic, and clinical outcomes

3.1 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.2 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

- Physicians should consider whether any medical conditions would make this protocol unreasonably hazardous for the patient.
- Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational neoadjuvant regimen or primary endpoint are eligible for this trial.

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.3 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ **3.2.1 Documentation of Disease**

Histologic Documentation:

Stage: Clinical stage II or III rectal adenocarcinoma defined as T4N0 or any T with node positive disease (any T, N+); also T3N0 requiring APR or coloanal anastomosis

Tumor Site: Rectum; ≤ 12cm from the anal verge

___ **3.2.2 Prior Treatment**

No prior systemic chemotherapy, targeted therapy, or immunotherapy; or radiation therapy administered as treatment for colorectal cancer within the past 5 years is allowed.

___ **3.2.3 Not pregnant and not nursing,** because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects.

Therefore, for women of childbearing potential only, a negative pregnancy test (urine or serum according to institutional guidelines) done ≤ 14 days prior to registration is required. Female subjects agree to use highly effective contraception combined with an additional barrier method (eg, diaphragm, with a spermicide) while on study and for ≥ 9 months after last dose of study drug, and the same criteria are applicable to male subjects if they have a partner of childbirth potential. Male subject agrees to use a condom and not donate sperm while in this study and for ≥ 6 months after the last treatment.

___ **3.2.4 Age ≥ 18 years**

___ **3.2.5 ECOG Performance Status ≤ 2 (or Karnofsky ≥ 60%)**

___ **3.2.6 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Platelet Count	≥ 100,000/mm^3
Creatinine	≤ 1.5 x upper limit of normal (ULN) OR
Calc. Creatinine Clearance	≥ 50 mL/min
Total Bilirubin	≤ 1.5 x upper limit of normal (ULN)
AST / ALT	≤ 3 x upper limit of normal (ULN)

___ **3.2.7 Comorbid conditions**

- No upper rectal tumors (distal margin of tumor >12 cm from the anal verge)
- No recurrent rectal cancer; prior transanal excision, prior distal sigmoid cancer with a low anastomosis

- No known mismatch repair deficient rectal adenocarcinoma
- HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
- Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification1. To be eligible for this trial, patients should be class 2B or better.

3.2.8 Concomitant medications

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed on this study. Patients on strong CYP3A4 inhibitors must discontinue the drug for 14 days prior to registration on the study.

Chronic concomitant treatment with strong CYP3A4 inducers is not allowed. Patients must discontinue the drug 14 days prior to the start of study treatment.