

**NSABP R-04: A Clinical Trial Comparing Preoperative Radiation Therapy and Capecitabine with or without Oxaliplatin with Preoperative Radiation Therapy and Continuous Intravenous Infusion of 5-Fluorouracil with or without Oxaliplatin in the Treatment of Patients with Operable Carcinoma of the Rectum**

***FAST FACTS***

**ELIGIBILITY CRITERIA**

1. Patients must have a diagnosis of adenocarcinoma of the rectum obtained by a biopsy technique which leaves the major portion of the tumor intact.
2. The interval between the initial diagnosis of rectal adenocarcinoma and randomization must be no more than 42 days.
3. Prior to randomization, the investigator must specify the intent for sphincter saving or non-sphincter saving surgery.
4. Patients must be  $\geq 18$  years of age.
5. Patients must have a life expectancy of 5 years, excluding their diagnosis of cancer (as determined by the investigator) and must have an ECOG (Zubrod) performance status of 0 or 1 (see Appendix B).
6. The tumor must be either palpable by digital rectal exam or be accessible via a proctoscope or sigmoidoscope, and its distal border must be located  $< 12$ cm from the anal verge. The tumor must be considered by the surgeon to be amenable to curative resection. (Note that curative resection can include pelvic exenteration)
7. The tumor must be clinically Stage II ( $T_{3-4}N_0$  with  $N_0$  being defined as all imaged lymph nodes are  $< 1.0$  cm) or Stage III ( $T_{1-4}N_{1-2}$  with the definition of a clinically positive node being any node  $\geq 1.0$  cm). Stage of primary tumor may be determined by ultrasound or MRI. CT scan is acceptable provided there is evidence of  $T_4$  and/or  $N_{1-2}$  disease (see section 6.0).
8. Patients with prior malignancies, including invasive colon cancer, are eligible if they have been disease-free for  $\geq 5$  years and are deemed by their physician to be at low risk for recurrence. Patients with squamous or basal cell carcinoma of the skin, melanoma in situ, carcinoma in situ of the cervix, or carcinoma in situ of the colon or rectum that have been effectively treated are eligible, even if these conditions were diagnosed within 5 years prior to randomization.
9. Patients must have the following laboratory values:
  - $ANC \geq 1,200/mm^3$
  - Platelet count  $\geq 100,000/mm^3$   
Total Bilirubin must be  $\leq 1.5$  x ULN
  - Alkaline Phosphatase  $\leq 2.5$  x ULN
  - $AST \leq 2.5$  x ULN  
*If AST is  $> ULN$ , serologic testing for Hepatitis B and C must be performed and results must be negative.*
  - Calculated creatinine clearance must be  $> 50$  mL/min.

**INELIGIBILITY CRITERIA**

1. Findings of metastatic disease.
2. On imaging, clear indication of involvement of the pelvic side wall(s).
3. Rectal cancers other than adenocarcinoma, i.e., sarcoma, lymphoma, carcinoid, squamous cell carcinoma, cloacogenic carcinoma, etc.
4. History of *invasive* rectal malignancy, regardless of disease-free interval.
5. Pregnancy or lactation at the time of proposed randomization. Eligible patients of reproductive potential (both sexes) must agree to use adequate contraceptive methods.

6. Any therapy for this cancer prior to randomization.
  7. Synchronous colon cancer.
  8. History of viral hepatitis or other chronic liver disease.
  9. Patients with nonmalignant systemic disease (cardiovascular, renal, hepatic, etc.) that would preclude the patient receiving either chemotherapy treatment option or would prevent required follow-up are NOT eligible. Specifically excluded are patients with active ischemic heart disease (class III\* or class
10. IV\*\* myocardial disease as described by the New York Heart Association), a recent history (within 6 months) of myocardial infarction, or symptomatic arrhythmia at the time of randomization.

\*Class III: Patients with cardiac disease resulting in marked limitation of physical activity. Such patients are comfortable at rest. Less-than-ordinary physical activity that causes fatigue, palpitation, dyspnea, or anginal pain.

\*\*Class IV: Patients with cardiac disease resulting in inability to perform any physical activity without discomfort. Symptoms of cardiac insufficiency or anginal syndrome may be present even at rest.

11. Patients who currently have active inflammatory bowel disease (requiring medical intervention or who are symptomatic) are NOT eligible.
12. Patients with uncontrolled hypertension are NOT eligible.
13. Patients with prior pelvic radiation therapy for any reason are NOT eligible.
14. Patients with known hypersensitivity to 5-fluorouracil, capecitabine, or oxaliplatin are NOT eligible.
15. Patients with clinically significant peripheral neuropathy at the time of randomization are NOT eligible.
16. Patients with existing uncontrolled coagulopathy are NOT eligible.
17. Patients with an inability to take oral medications are NOT eligible.
18. Patients may NOT have participated in any investigational drug study within 4 weeks prior to randomization.
19. Patients with psychiatric or addictive disorders or other conditions that would preclude obtaining informed consent are NOT eligible.
20. Patients must be informed of the investigational nature of this study and give written informed consent according to institutional and federal guidelines.

#### **PRE-STUDY PARAMETERS**

1. H&P; Ht/Wt; Performance status
2. CBC/Diff/Platelets;Hgb; Serum Creatinine; Calculated Creatinine Clearance; Bilirubin/ Alkaline Phosphatase; AST
3. If technically feasible, a complete colonoscopic exam; if not feasible, proctoscopy or sigmoidoscopy exam.
4. Clinical staging of the tumor
5. CT or MRI of the abdomen and pelvis (combined PET/CT may be substituted), and a chest x-ray (PA and lateral) or CT scan of the chest to exclude patients with metastatic disease (see appendix A)
6. QOL questionnaire, after consent prior to randomization (For all patients who complete the baseline questionnaire (See Section 8.0), until recurrence or second primary cancer. If study therapy is discontinued for other reasons, QOL assessments continue to be required.)

**See section 6.0 for complete Pre-study requirements**

**TREATMENT PLAN**

**Group 1: 5-FU with Radiation Therapy**

*All patients randomized to this group will need central venous access.*

| DRUG | DOSE/ADMINISTRATION           | DOSING SCHEDULE  |
|------|-------------------------------|--|
| 5-FU | 225 mg/m <sup>2</sup> /day IV | Continuous infusion beginning on the first day of RT, continuing 5 days/week on days of planned RT (including the boost), and ending on the last day of RT |

**Group 2: 5-FU and Oxaliplatin with RT**

*All patients randomized to this group will need central venous access.*

| Drug        | Dose/Administration   | Dosing Schedule  |
|-------------|---|--|
| Oxaliplatin | 50 mg/m <sup>2</sup> administered IV in 250 mL D5W over 1 hour* | Weekly x 5 beginning on the first day of RT  |
| 5-FU        | 225 mg/m <sup>2</sup> /day IV                                   | Continuous infusion beginning on the first day of RT, continuing 5 days/week on days of planned RT (including the boost), and ending on the last day of RT |

**\*Note that Oxaliplatin is not compatible with normal saline solution.**

**Group 3: Capecitabine with RT**

| DRUG         | DOSE/ADMINISTRATION  | DOSING SCHEDULE  |
|--------------|--|--|
| Capecitabine | 825 mg/m <sup>2</sup> po BID<br>(See Appendix F for dosing instructions) | Daily, for 5 days per week on days of planned RT (including the boost), beginning on the morning of the first day of RT and ending on the evening of the last RT treatment |

**Group 4: Capecitabine and oxaliplatin with RT**

| Drug         | Dose/Administration  | Dosing Schedule  |
|--------------|--|--|
| Oxaliplatin  | 50 mg/m <sup>2</sup> administered IV in 250 mL D5W over 1 hour*          | Weekly x 5 beginning on the first day of RT  |
| Capecitabine | 825 mg/m <sup>2</sup> po BID<br>(See Appendix F for dosing instructions) | Daily, for 5 days per week on days of planned RT (including the boost), beginning on the morning of the first day of RT and ending on the evening of the last RT treatment |

**\*Note that Oxaliplatin is not compatible with normal saline solution.**

**SEE SECTION 11.0 FOR DOSE MODIFICATIONS AND DELAYS**