

**CTSU E5202: A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin vs. 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients with Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers**

**FAST FACTS**

**ELIGIBILITY CRITERIA**

**STEP 1: INITIAL REGISTRATION**

1. The distal extent of the tumor must be  $\geq 12$  cm from the anal verge on endoscopy. If the patient is not a candidate for endoscopy, the distal extent of the tumor must be  $\geq 12$  cm from the anal verge as determined by surgical examination.  
(If tumor is located beyond sigmoid colon and centimeter distance unavailable, include anatomic region of colon, e.g. right colon, transverse colon, hepatic flexure descending colon, cecum etc.)
2. Patients must have paraffin-embedded tumor specimen available for evaluation of microsatellite instability and loss of heterozygosity at 18q. to determine high risk vs. low risk.
  - a. High-risk patients will be randomized to treatment Arms A or B.
  - b. Low-risk patients will be registered to Arm C for observation.

**\*Every effort should be made to submit blocks to the PCO immediately. Blocks CANNOT be accepted after day 50 (post surgery) in order to allow for molecular assessment.**
3. Patients must not have had synchronous tumors.
4. Patients must not have appendiceal tumors.
5. Patients must not have a history of inflammatory bowel disease (IBD).
6. Patients with hereditary non-polyposis colorectal cancer (HNPCC) are eligible.
7. Patients must have no history of isolated, distant, or non-contiguous intra-abdominal metastases, **even if restricted.**
8. Patients must have histologically confirmed adenocarcinoma of the **colon** that meets criteria below:
  - Stage II carcinoma (T<sub>3,4</sub> N<sub>0</sub> M<sub>0</sub>): The tumor invades through the muscularis propria into the subserosa or into non-peritonealized pericolic or perirectal tissues (T<sub>3</sub>) or directly invades other organs or structures and/or perforates visceral peritoneum (T<sub>4</sub>).

Patients must have had a complete resection (R0 resection)
9. Patients must have  $\geq 8$  lymph nodes evaluated and reported.
10. Patients must NOT have presented with clinical complete obstruction or perforation of the bowel.
11. Patients must NOT have had any systemic or radiation therapy initiated for the malignancy.
12. Patients must not have had a previous or concurrent malignancy, with the exception of:
  - a. Nonmelanoma skin cancer, *in situ* cervical cancer, or breast cancer *in situ*
  - b. Treated non-pelvic cancer from which the patient has been continuously disease-free more than five years.

NOTE: Patients with a history of breast cancer (without evidence of disease) who remain on hormonal therapy > 5 years are eligible
13. Patients must be  $\geq 18$  years of age.
14. Patients must have ECOG performance status of 0-2.

**STEP 2: RANDOMIZATION (HIGH RISK PATIENTS – ARMS A & B ONLY)**

1. Within two weeks prior to randomization, patients must have the following laboratory values:
  - AGC  $\geq 1500/\text{mm}^3$  (or  $< 1500/\text{mm}^3$ , if in the opinion of the investigator, this represents an ethnic or racial variation of normal)
  - Platelets  $\geq 100,000/\text{mm}^3$
  - Bilirubin  $\leq$  ULN unless the patient has a chronic grade 1 bilirubin elevation due to Gilbert's disease or similar syndrome due to slow conjugation of bilirubin.
  - Alkaline phosphatase  $< 2.5 \times$  ULN
  - AST  $< 1.5 \times$  ULN
  - Serum creatinine  $\leq 1.5 \times$  ULN
  - UPC ratio of  $< 1.0$ . Patients with a UPC ratio  $\geq 1.0$  must undergo a 24-hour urine collection, which must be an adequate collection and must demonstrate  $< 1$  gm of protein in order to participate.
2. Patients with any significant bleeding that is not related to the primary colon tumor within 6 months prior to study entry are NOT eligible.
3. Patients with gastroduodenal ulcer(s) determined to be active by endoscopy are NOT eligible.

4. Patients with a history of hypertension must measure < 150/90 mmHg and be on a stable regimen of anti-hypertensive therapy.
5. Patients must NOT have a serious or non-healing wound, skin ulcers, or bone fracture.
6. Patients experiencing clinically significant peripheral neuropathy at the time of step 2 randomization, as grade 2 or greater neurosensory or neuromotor toxicity, are NOT eligible.
7. Patients must NOT have had invasive procedures, defined as follows:
  - Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to randomization.
  - Core biopsy or other minor procedure, excluding placement of a vascular access device, within 7 days prior to randomization or anticipate the need for major surgical procedure(s) during the course of the study.
8. Patients must begin adjuvant treatment no less than 28 days and no more than 60 days from surgery.
9. Eligible patients of reproductive potential (both sexes) must agree to use an accepted and effective Method of contraceptive during study therapy and for at least 3 months after the completion of bevacizumab.
10. Women must not be pregnant or breast-feeding because the study drugs administered may cause harm to an unborn child. All females of childbearing potential must have a serum pregnancy test to rule out pregnancy within 2 weeks prior to step 2 randomization.
11. Patients with PT (INR) > 1.5 are NOT eligible, unless the patient is on full-dose anticoagulants. If so, The following criteria must be met for enrollment:
  - Patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin or on a stable dose of low molecular weight heparin.
  - Patient must NOT have active bleeding or a pathological condition that is associated with a high risk of bleeding.
12. Patients with non-malignant systemic disease (cardiovascular, renal, hepatic, etc.) that would preclude any of the study therapy drugs are NOT eligible. Specifically excluded are the following conditions:
  - NYHA Class III or IV cardiac disease
  - Current symptomatic arrhythmia
  - Any non-malignant system disease
13. Patients with a history of transient ischemic attack (TIA) or cerebrovascular accident (CVA) are NOT eligible.
14. Patients with a history of the following within 12 months of study entry are NOT eligible:
  - Arterial thromboembolic events
  - Unstable angina
  - Myocardial infarction
15. Patients with symptomatic peripheral vascular disease are NOT eligible.
16. Patients with psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude them from meeting the study requirements are NOT eligible.
17. Patients must not have a known allergy to platinum compounds.

#### **STEP 2: REGISTRATION (Low-Risk Patients – Arm C)**

Note: Patients determined as low risk must be registered to Step 2.

1. Patients determined to be low risk are eligible.

#### **PRE-STUDY PARAMETERS (Arms A & B)**

1. H&P/Ht&Wt/ECOG Performance Status
2. CBC/Diff/Platelets;Serum Creatinine;SGOT(AST); Bilirubin; CEA
3. Alkaline phosphatase/Hepatitis B & C testing – Required at baseline only, unless clinically indicated.
4. Prothrombin time (PT) or INR, PTT (For patients on full-dose warfarin, the PT (INR) should be monitored throughout the study treatment period per the physician's usual practice.
5. Serum Pregnancy Test (premenopausal women)
6. Urine protein/creatinine (UPC) ratio
7. Blood pressure

**TREATMENT PLAN****ARM A**

AGENT	DOSE	ROUTE	NOTES
Oxaliplatin	85 mg/m <sup>2</sup>	IV infusion over 2 hours	Day 1
Leucovorin	400 mg/m <sup>2</sup>	IV infusion over 2 hours	Day 1
5-FU	400 mg/m <sup>2</sup>	IV bolus injection immediately following Leucovorin	Day 1
5-FU	2.4 gm/m <sup>2</sup>	IV continuous infusion over 46 hours immediately following bolus 5-FU	Days 1 and 2

*Repeated every 2 weeks for a total of 12 (2 week) cycles.*

**NOTE:** Oxaliplatin and Leucovorin can be administered simultaneously using Y-line tubing provided that the Leucovorin has been diluted with 5% dextrose in water and NOT 0.9% sodium chloride because of the incompatibility of oxaliplatin and saline. **See Section 8.2.7.**

**ARM B**

AGENT	DOSE	ROUTE	NOTES
Bevacizumab <sup>1</sup>	5 mg/kg	IV infusion over 90 minutes <sup>2</sup>	Day 1
Oxaliplatin	85 mg/m <sup>2</sup>	IV infusion over 2 hours	Day 1
Leucovorin	400 mg/m <sup>2</sup>	IV infusion over 2 hours	Day 1
5-FU	400 mg/m <sup>2</sup>	IV bolus injection immediately following Leucovorin	Day 1
5-FU	2.4 gm/m <sup>2</sup>	IV continuous infusion over 46 hours immediately following bolus 5-FU	Days 1 and 2

*Repeated every 2 weeks for a total of 12 (2 week) cycles.*

- 1. Bevacizumab will continue for 12 additional cycles following completion of chemotherapy. Patients will receive a total of 24 (2-week) cycles of bevacizumab.**
- 2. Initial dose should be administered over a minimum of 90 minutes. If no adverse reactions occur, the second dose should be administered over a minimum of 60 minutes. Again, if no adverse reactions occur, the third and subsequent doses should be administered over a minimum of 30 minutes. Infusions should be run in via a volumetric infusion device. If infusion-related adverse reactions occur, subsequent infusions should be administered over the shortest period that is well tolerated.**

**NOTE:** Oxaliplatin and Leucovorin can be administered simultaneously using Y-line tubing provided that the Leucovorin has been diluted with 5% dextrose in water and NOT 0.9% sodium chloride because of the incompatibility of oxaliplatin and saline. **See Section 8.2.7.**