

SCRI GI 154 - A Phase II Trial of Single Agent Axitinib as Maintenance Therapy for Patients with First Line Metastatic Colorectal Cancer (mCRC)

Fast Facts

CTCAE v.4

Axitinib provided

Inclusion Criteria

1. Histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum.
2. Patients must have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1
3. No previous systemic therapy for metastatic colorectal cancer. Previous radiosensitizing chemotherapy is allowed, if completed at least 4 weeks prior to Cycle 1 Day 1 of study treatment, and previous neoadjuvant and/or adjuvant chemotherapy is allowed, if completed at least 6 months prior to diagnosis of metastatic disease.
4. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 to 1
5. Male or female patients \geq 18 years-of-age.
6. Life expectancy \geq 12 weeks.
7. Adequate hematologic function defined as:
 - Absolute neutrophil count (ANC) \geq 1500/uL
 - Hemoglobin (Hgb) \geq 9 g/dL (5.6 mmol/L)
 - Platelets \geq 100,000/uL
8. Adequate liver function defined as:
 - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $<$ 2.5 x the institutional upper limit of normal (ULN) or \leq 5.0 x the institutional ULN in patients with liver metastases.
 - Total bilirubin within normal limits (WNL) (or \leq 1.5 x the institutional ULN in patients with liver metastases; or total bilirubin \leq 3.0 x ULN with direct bilirubin within normal limits in patients with well documented Gilbert Syndrome).
9. Adequate renal function defined as:
 - Serum creatinine \leq 1.5 mg/dL OR calculated 24-hour creatinine clearance \geq 60 mL/min.
10. Patients who are on coumadin should have an INR value within the therapeutic range (i.e., 2 to 3 x ULN). Patients who are on stable, chronic doses of coumadin are eligible.
11. Male patients willing to use adequate contraceptive measures (see Appendix D). Female patients who are not of child-bearing potential (see Appendix D), and female patients of child-bearing potential who agree to use adequate contraceptive measures (see Appendix D), who are not breastfeeding, and who have a negative serum or urine pregnancy test performed within 48 hours prior to start of treatment.
12. Willingness and ability to comply with the trial and follow-up procedures.
13. Ability to understand the investigative nature of this trial and give written informed consent.

Exclusion Criteria

1. History or known presence of central nervous system (CNS) metastases.
2. Patients who have had a major surgical procedure (not including mediastinoscopy or significant traumatic injury \leq 4 weeks prior to beginning treatment.
3. Women who are pregnant or lactating. All females of child-bearing potential must have negative serum or urine pregnancy tests within 7 days prior to study treatment (see Appendix D)
4. History of hypersensitivity to active or inactive excipients of any component of treatment (5 fluorouracil, bevacizumab, oxaliplatin, or axitinib), or known dipyrimidine dehydrogenase deficiency.
5. Patients with proteinuria at screening as demonstrated by:
 - urine dipstick for proteinuria \geq 2+ (patients discovered to have \geq 2+ proteinuria on dipstick urinalysis at baseline should undergo a 24 hour urine collection, and must demonstrate \leq 1 g of protein/24 hours to be eligible)
6. Patients with a serious non healing wound, active ulcer, or untreated bone fracture.
7. Patients with evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation).
8. Patients with history of hematemesis or hemoptysis (defined as having bright red blood of $\frac{1}{2}$ teaspoon or more per episode) \leq 1 month prior to study enrollment.
9. Patients requiring concomitant treatment with potent CYP3A4 or CYP1A2 inducers and CYP3A4 inhibitors (see Appendix E).
10. History of myocardial infarction or unstable angina \leq 6 months prior to beginning treatment.
11. Inadequately controlled hypertension (defined as systolic blood pressure [BP] $>$ 150 mmHg and/or diastolic BP $>$ 100 mmHg while on antihypertensive medications). Initiation of antihypertensive agents is permitted provided adequate control is documented at least 1 week prior to Day 1 of study treatment.
12. New York Heart Association Grade II or greater congestive heart failure (see Appendix B)

13. Serious cardiac arrhythmia requiring medication. Patients with chronic, rate-controlled atrial fibrillation are eligible.
14. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair, or recent peripheral arterial thrombosis) ≤ 6 months prior to Day 1 of treatment.
15. History of stroke or transient ischemic attack ≤ 6 months prior to beginning treatment.
16. Any prior history of hypertensive crisis or hypertensive encephalopathy.
17. History of abdominal fistula or gastrointestinal perforation ≤ 6 months prior to Day 1 of beginning treatment.
18. Concurrent severe, intercurrent illness including, but not limited to, ongoing or active infection, or psychiatric illness/social situations that would limit compliance with study requirements.
19. Any known positive test for human immunodeficiency virus, hepatitis C virus or acute or chronic hepatitis B infection.
20. Mental condition that would prevent patient comprehension of the nature of, and risk associated with, the study.
21. Use of any non-approved or investigational agent ≤ 28 days prior to administration of the first dose of study drug. Patients may not receive any other investigational or anticancer treatments while participating in this study.
22. Past or current history of neoplasm other than the entry diagnosis with the exception of treated non-melanoma skin cancer or carcinoma in situ of the cervix, or other cancers cured by local therapy alone and a disease free survival ≥ 5 years.
23. Infection requiring IV antibiotics.
24. Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter drug absorption (e.g. active inflammatory bowel disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or significant small bowel resection).
25. Inability to swallow whole tablets.
26. Patients with $>$ Grade 2 peripheral neuropathy.

Pre-study Parameters

1. History and physical including vital signs, height, weight, performance status, baseline signs and symptoms, concomitant medication review
2. Labs including CBC with differential, CMP, thyroid function tests (T4, TSH), PT/INR for patients on anticoagulants, CEA, urine dipstick for protein, serum or urine B-HCG
3. CT of chest, abdomen, pelvis

Treatment

The following treatments will be administered as 1st-line therapy for 4 cycles (or 6 cycles with approval of the Medical Monitor). A cycle is 28 days:

1. Bevacizumab 5 mg/kg IV Days 1 and 15
2. 5-FU IV 400 mg/m² Days 1 and 15
3. 5-FU CIV 2400 mg/m² over 46-48 hours Days 1 and 15
4. Leucovorin 400 mg/m² IV Days 1 and 15
5. Oxaliplatin 85 mg/m² IV Days 1 and 15

Maintenance after 4 cycles (or 6 cycles with approval of the Medical Monitor):

1. Axitinib PO 5 mg twice a day Days 1 through 28

Axitinib provided

See section 5 for complete details.