

CALGB 80405: A Phase III Trial of Irinotecan/5-FU/Leucovorin or Oxaliplatin/5-FU/Leucovorin with Bevacizumab, or Cetuximab (C225), or with the Combination of Bevacizumab and Cetuximab For Patients with Untreated Metastatic Adenocarcinoma of the Colon or Rectum

FAST FACTS

ELIGIBILITY CRITERIA

1. Patients must have histologically or cytologically documented adenocarcinoma of the colon or rectum. Patients must have either locally advanced (unresectable) or metastatic disease. Patients with resected primary tumors who have documented metastases are eligible. Documentation of residual disease by CT scan or surgeon's notes is required for all patients and histologic confirmation of metastases is strongly encouraged. **Only patients with a wild type K-ras gene as determined by the laboratory at the SWOG Solid Tumor Repository are eligible.**
2. Patients with a history of colorectal cancer treated by surgical resection who develop radiological or clinical evidence of metastatic cancer do not require separate histological or cytological confirmation of metastatic disease unless:
 - Either an interval of greater than 5 years has elapsed between primary surgery and the development of metastatic disease OR
 - The primary cancer was stage I.
3. At the time of randomization, intent of this treatment must be indicated: palliative or neoadjuvant chemotherapy with the potential for resection of all sites of metastatic disease.
4. No prior systemic treatment for advanced or metastatic colorectal cancer is allowed. Prior regional chemotherapy (e.g., hepatic arterial infusion) is also not allowed.
 - Patients may have received prior adjuvant chemotherapy that included fluorouracil alone or in combination with fluorouracil and oxaliplatin or irinotecan (no more than 6 months); or radiation with radiosensitizing chemotherapy.
 - The last course of adjuvant chemotherapy must have concluded > 12 months prior to colorectal cancer recurrence.
 - Patients may have received neoadjuvant chemo-radiation with capecitabine or 5-fluorouracil.
 - Patients may not have received itraconazole or ketoconazole less than 4 weeks prior to randomization.
 - No prior exposure to any tyrosine kinase inhibitors or other agents (including protein products, monoclonal antibodies, antisense, etc) that target VEGF or EGF receptors is allowed.
 - No prior treatment with bevacizumab or cetuximab.
5. Patients may not have had any prior radiotherapy to greater than 25% of bone marrow. Radiation must have concluded ≥ 4 weeks prior to randomization.
6. Patients should have completed any major surgery ≥ 4 weeks from randomization. Patients should have completed any minor surgery ≥ 2 weeks prior to randomization.
7. No previous or concurrent malignancy is allowed except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the patient has been disease-free for five years.
8. For patients who are to receive FOLFIRI: No evidence of Gilbert's Syndrome or of homozygosity for the UGT1A1*28 allele.
 - Patients with Gilbert's Syndrome may have a greater risk of irinotecan toxicity due to the abnormal glucuronidation of SN-38. Evidence of Gilbert's Syndrome would include a prior finding of an isolated elevation of indirect bilirubin.
 - UGT1A1 genotyping is not required on this study. However, patients known to be homozygous for the UFT1A1*28 allele are not to receive FOLFIRI for this study.
 - Patients with Gilbert's Syndrome or who are found to be homozygous for the UGT1A1 allele who will receive FOLFOX are eligible.
9. No sensory peripheral neuropathy of \geq grade 2 at baseline for patients who are to receive FOLFOX.
10. No known central nervous system metastases or carcinomatous meningitis.
11. No interstitial pneumonia or extensive and symptomatic interstitial fibrosis of the lung.
12. No pleural effusion or ascites that causes \geq grade 2 dyspnea.

13. No predisposing colonic or small bowel disorders in which the symptoms are uncontrolled as indicated by baseline pattern of > 3 watery or soft stools daily in patients without a colostomy or ileostomy. Patients with a colostomy or ileostomy may be entered at investigator discretion.
14. Patients must not have an uncontrolled seizure disorder, or active neurological disease.
15. No current congestive heart failure.
16. Patients with a history of hypertension must be well controlled (< 160/90) on a regimen of anti-hypertensive therapy.
17. Patients on full-dose anticoagulation (e.g., warfarin) are eligible provided that both of the following criteria are met:
 - Patient has an in-range INR (usually between 2 and 3) on a stable dose of oral anticoagulant or be on a stable dose of low molecular weight heparin.
 - Patient has no active bleeding or pathological condition that carries a high risk of bleeding (e.g. tumor involving major vessels or known varices).
 - Patients receiving anti-platelet agents are eligible. In addition, patients who are on daily prophylactic aspirin or anticoagulation for atrial fibrillation are eligible.
18. No significant history of bleeding events or GI perforation.
 - Patients with significant bleeding episodes within 6 months of randomization are not eligible unless the source of bleeding has been resected
 - Patients with a history of GI perforation within 12 months of randomization are not eligible.
19. No arterial thrombotic events within 6 months before registration.
20. No serious or non-healing wound, ulcer or bone fracture.
21. Patients with known hypersensitivity to Chinese hamster ovary cell products or to recombinant human or murine antibodies are not eligible.
22. Women of child bearing potential must have a negative serum or urine pregnancy test within 72 hours prior to registration.
23. Patients must have a ECOG performance status of 0 – 1.
24. Patients must be ≥ 18 years of age.
25. Patients must have the following laboratory values:
 - Granulocytes $\geq 1500 /\mu\text{L}$
 - Hemoglobin ≥ 9.0 grams/dL (patient may be transfused to meet this criterion)
 - Platelet count $\geq 100,000/\mu\text{L}$
 - Creatinine ≤ 1.5 x ULN
 - Bilirubin ≤ 1.5 mg/dL
 - Albumin ≥ 2.5 g/dL
 - Urinalysis $\leq 1 +$ protein*

*Patients discovered to have $\geq 2 +$ proteinuria at baseline must undergo a 24-hour urine collection that must demonstrate < 1 g of protein/24 hr. or have a UPC < 1.0 to allow participation in the study.

PRE-STUDY PARAMETERS

1. H & P; Ht/Wt; Pulse/Blood Pressure; Performance Status.
2. CBC/Diff/Platelets; Serum creatinine, BUN; Electrolytes (na,K,Cl, bicarb); AST/ALT/Alkaline Phosphatase; Bilirubin; C-reactive protein, LDH, Albumin, CEA, Magnesium; PT/INR; Urinalysis/ Pregnancy test (for women of child-bearing potential; test must be performed within 72 hours prior to registration and within 72 hours prior to the initiation of protocol treatment).
3. Chest x-ray, PA, & Lateral – If CT or MIR scan of the chest is performed, chest x-ray is not required.
4. CAT Scan **or** MRI of abd/pelvis
5. Evaluation for resectability.

TREATMENT PLAN

Treatment is to begin within 7 days of randomization. One cycle will be defined as 8 weeks of treatment.

ARM A:

| Order Of Infusion: | WEEK | | | | | | | |
|-----------------------|------|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| Bevacizumab | X | | X | | X | | X | |
| FOLFOX/FOLFIRI | X | | X | | X | | X | |

ARM B:

| Order Of Infusion: | WEEK | | | | | | | |
|-----------------------|------|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| Cetuximab | X | X | X | X | X | X | X | X |
| FOLFOX/FOLFIRI | X | | X | | X | | X | |

- Patients should receive a minimum of two cycles of therapy. Treatment will be continued until disease progression, unacceptable toxicity, or surgery with curative intent as planned.
- See Section 7.0 for further instructions.

See Section 8.0 for dose modifications and toxicities.