

**TYPE OF CANCER:** Gastrointestinal Cancer  
**TYPE OF TRIAL:** Phase I/II  
**TRIAL SPONSOR:** Pfizer

**PRINCIPAL INVESTIGATOR:** Phillip Manno, M.D.  
**CONTACT PERSON:** Karen Welborne  
(702) 822-5367

### **STUDY SUMMARY**

A RANDOMIZED PHASE 2 STUDY OF THE ANTI-ANGIOGENESIS AGENT AG-013736 IN COMBINATIONS WITH CHEMOTHERAPY AND BEVACIZUMAB IN PATIENTS WITH METASTATIC COLORECTAL CANCER PRECEDED BY A PHASE 1 PORTION

### **TREATMENT OVERVIEW**

- Each cycle is 2 weeks long
- Patient should be seen by the physician at least every 2 weeks
- Patients may continue to participate in the study unless they experience unacceptable toxicity or disease progression.

### **PRETREATMENT ASSESMENT**

- Informed consent
- Inclusion/exclusion criteria
- Demographics/ Medical history
- Physical Examination
- Vital signs (temperature, BP, pulse, weight, ECOG)
- Tumor measurements
- 12 Lead EKG/ECG
- Hematology
- Serum Biochemistry
- Urine analysis (dipstick)
- Pregnancy test
- Concomitant medications
- Adverse Events

### **ENTRANCE CRITERIA FOR PARTICIPATION IN TRIAL**

#### **Inclusion Criteria**

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the trial:

1. Histologically or cytologically documented locally advanced or metastatic colorectal cancer, previously untreated with any systemic therapy. If, at the time of enrollment, there is an intent to resect all sites of metastatic disease in the future, this must be indicated.
2. Patients previously treated with adjuvant chemotherapy (with radiation therapy) will be eligible if the last dose of adjuvant therapy was >12 months prior to enrollment.
  - For phase I portion of the study only, patients with solid tumors who have had  $\leq$  1 prior chemotherapy for  $\leq$  3 months will qualify.
3. measurable disease by RECIST criteria
4. male or female, >18 years of age
5. life expectancy >12 weeks
6. ECOG performance status 0 or 1
7. Resolution of all acute toxic effects of prior therapy or surgical procedure to grade  $\leq$ 1 (except alopecia)
8. adequate bone marrow function as defined by the following criteria:
  - absolute neutrophil count (ANC)  $\geq$ 1500 cells/mm<sup>3</sup>
  - platelets  $\geq$ 100,000 cells/mm<sup>3</sup>
  - hemoglobin  $\geq$ 9.0 g/dL
9. adequate liver function as defined by the following criteria:
  - total serum bilirubin <1.5 times upper limit of normal (x ULN)
  - AST and ALT <2.5 x ULN, or AST and ALT <5 x ULN if liver function abnormalities are due to underlying malignancy
  - INR or prothrombine time (PT) <1.5 times upper limit of normal (x ULN)
10. adequate renal function as defined by the following criteria:
  - serum creatinine <1.5 x ULN
  - <500 mg urinary protein/24 hours or dipstick <2+
11. no evidence of preexisting uncontrolled hypertension as documented by 2 baseline blood pressure readings taken at least 1 hour apart (the baseline systolic blood pressure readings must be <140 mm Hg, and the baseline diastolic blood pressure readings must be <90 mm Hg. Patients whose hypertension is controlled by antihypertensive therapies are eligible)
12. negative serum or urine pregnancy test within the 3 days before treatment for women of child-bearing potential
13. Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all pertinent aspects of the trial before enrollment.
14. completed MDASI-D questionnaire
15. willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures
16. eligibility to receive FOLFOX (or FOLFIRI) and bevacizumab

### **Exclusion Criteria**

The presence of any of the following will exclude a patient from study enrollment:

1. prior systemic therapy for advanced colorectal cancer (Phase 2 portion only)
2. Prior treatment that target tumor angiogenesis, such as bevacizumab or VEGF receptor inhibitors.
3. Prior irradiation to  $\geq 25\%$  of the bone marrow (whole pelvis =25%; a patient with prior whole pelvis irradiation is ineligible. Standard adjuvant rectal cancer chemo-radiation will not exclude patient from eligibility)
4. Prior radiation therapy, major surgery, or investigational agent within 4 weeks before study entry except palliative radiotherapy to non-target, metastatic lesions. Patients must have completed any minor surgery  $\geq 2$  weeks prior to enrollment. Patients must have fully recovered from the procedure. (Insertion of a vascular access device is not considered major or minor surgery.)
5. pleural effusion or ascites that causes  $\geq$  grade 2 dyspnea.
6. Current use or anticipated need for food or drugs that are known CYP3A4 inhibitors (ie, grapefruit juice, verapamil, ketoconazole, miconazole, itraconazole, erythromycin, clarithromycin, ergot derivatives, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, and delavirdine) during the course of the study
7. current use or anticipated need for drugs that are known CYP3A4 or CYP1A2 inducers (ie, carbamazepine, dexamethasone, felbamate, omeprazole, phenobarbital, phenytoin, primidone, rifabutin, rifampin, and St John's wort) during the course of study (Note: the short-term use of dexamethasone as a premedication for chemotherapy is not an exclusion criterion)
8. History of significant bleeding episodes (e.g. hemoptysis, upper or lower GI bleeding) within 6 months unless the source of bleeding has been resected
9. patients with active seizure disorder or brain metastases
10. clinically significant gastrointestinal abnormalities including any of the following:
  - inability to take oral medication
  - requiring intravenous alimentation
  - malabsorption syndromes
  - requiring treatment of active ulcer disease in the past 6 months
  - prior gastric resection
  - GI perforation within prior 12 months
  - Active or known gastrointestinal bleeding, unrelated to cancer, as evidence by either hematemesis, hematochezia, or melena in the past 3 months
11. patients with proteinuria (Patients with  $>2+$  protein on urine dipstick at baseline should undergo a 24-hour urine collection. Results must demonstrate  $<500$  mg of protein in 24 hours to allow participation in the study)
12. history of any second malignancy except those patients treated with curative intent for skin cancer (other than melanoma) or in situ cervical cancer, or those treated with curative intent for any other cancer with no evidence of disease for 5 years
13. NCI CTCAE grade  $\geq 2$  sensory neuropathy from any cause.
14. known metastases in the central nervous system.
15. serious or non-healing wound ulcer or bone fracture

16. current congestive heart failure (New York Heart Association Class II, III or IV)
17. any arterial thrombotic events within 6 months before enrollment, including transient ischemic attack (TIA), cerebrovascular accident (CVA), unstable angina or angina requiring surgical or medical intervention, myocardial infarction (MI), clinically significant peripheral artery disease or any other arterial thrombotic event.
18. known homozygosity for UGT1A1\*28 allele for patients receiving FOLFIRI
19. known dihydropyridine dehydrogenase deficiency
20. History of hypersensitivity to oxaliplatin, 5-FU, leucovorin, bevacizumab, Chinese hamster ovary cell products or other recombinant human antibodies
21. known human immunodeficiency virus (HIV) seropositivity
22. serious active infection (viral, fungal, bacterial). Infection requiring parenteral antibiotics at time of enrollment will disqualify the patient.
23. women who are pregnant or breast feeding. Female patients must be surgically sterile or be postmenopausal, or must agree to use effective contraception during the period of therapy. All female patients with reproductive potential must have a negative pregnancy test (serum or urine) within the 3 days prior to treatment. Male patients must be surgically sterile or must agree to use effective contraception during the period of therapy. The definition of effective contraception will be based on the judgment of the principal investigator or a designated associate.
24. Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for entry into this study.