FAST FACTS

CTSU E7208: A Randomized Phase II Study of Irinotecan and Cetuximab with or without the Anti-Angiogenic Antibody, Ramucirumab (IMC-1121B), in Advanced, K-ras Wild-type Colorectal Cancer Following Progression on Bevacizumab-Containing Chemotherapy

Commercial Drugs: Irinotecan and Cetuximab
Provided Drug: Ramucirumab (supplied by ImClone)

PATIENT ELIGIBILITY
1. Age ≥ 18 years.
2. Women must not be pregnant or breast-feeding due to potential danger to the fetus, by therapy including Ramucirumab. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy.
3. Women of childbearing potential and sexually active males must use an accepted and effective method of contraception or agree to abstain from sexual intercourse during their participation in the study and for 3 months following completion of their participation.
4. Patients must have measurable disease as defined in Section 6.1.2.
5. Histologically documented adenocarcinoma (including the histologic variants of adenocarcinoma) of the colon or rectum.
6. Patients K-ras status must be wild type (not mutated). K-ras status determination may be based on either primary or metastatic tumor.
   NOTE: The assay must be performed by a Clinical Laboratory Improvement Amendments (CLIA) approved laboratory.
7. Patients must have had prior first-line therapy with oxaliplatin-based fluoropyrimidine-containing chemotherapy and bevacizumab for metastatic colorectal cancer.
8. Registration within 42 days of evidence of disease progression.
9. Was Oxaliplatin discontinued before date of progression? Yes or No (stratification factor)
11. Adequate Organ Function ≤ 4 weeks prior to registration.
   - Hematologic: Absolute neutrophil count (ANC) ≥ 1500/µL, hemoglobin ≥ 9 g/dL, and platelets ≥ 75,000/µL.
   - Renal: Serum creatinine ≤ 1.5 x the ULN, or creatinine clearance (measured via 24-hour urine collection) ≥ 40 mL/minute.
   - Proteinuria: Urinary protein/creatinine (UPC) ratio < 0.5 or urine protein ≤ 1+ on dipstick or routine urinalysis (UA); if UPC > 0.5 or urine dipstick or routine analysis is ≥ 2+, a 24-hour urine collection for protein must demonstrate < 1000 mg of protein in 24 hours to allow participation in the study.
   - Hepatic: Total bilirubin ≤ 2.0 mg/dL, and aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 x the institutional upper limit of normal (ULN) [or 5.0 x the ULN in the setting of liver metastases]. Albumin within institutional normal range.
   - Coagulation: International Normalized Ratio (INR) ≤ 1.6 (unless receiving anticoagulation therapy). Patients on full-dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin. If receiving warfarin, the patient must have an INR ≤ 3.0 and no active bleeding (i.e., no bleeding within 14 days prior to first dose of study therapy).
12. No prior therapy with drugs other than oxaliplatin and a fluoropyrimidine plus bevacizumab for this disease. Chemotherapy drugs and bevacizumab may be stopped and started as long as no prior disease progression requiring change in chemotherapy agents occurred.
13. No clinically significant (equivalent to NCI CTCAE grade 3-4) bleeding episodes within the prior 3 months.
14. No active infection, symptomatic congestive heart failure, unstable angina pectoris, symptomatic or poorly controlled cardiac arrhythmia, uncontrolled thrombotic or hemorrhagic disorder.
15. No uncontrolled or poorly-controlled hypertension despite standard medical management (e.g. consistently SBP > 160 and DBP > 90 mmHg).
16. No major surgery within 28 days prior to randomization, or subcutaneous venous access device placement within 7 days prior to randomization.
17. No history of acute arterial thrombotic events within 6 months (including CVA, TIA, MI or unstable angina).
18. No brain or CNS metastases.
19. No other cancer requiring therapy within last three years (except *in situ* carcinoma or non-melanoma skin cancer).
20. Patients must not have an acute or subacute intestinal obstruction. No history of bowel obstruction, GI perforation, major abdominal surgery with bowel resection, or peri-rectal/peri-anal abscess within 6 months prior to randomization.
21. Patient must not have a history of inflammatory bowel disease requiring pharmacological and/or surgical intervention within the 12 months prior to randomization.
22. Patient must not have a known allergy to any of the treatment components

**TREATMENT**

**ARM A – (IC)**
- Cetuximab 500 mg/m2 IV q 14 days
- Irinotecan 180 mg/m2 IV over 60-90 minutes q 14 days

*Repeat cycles every 14 days until progression.*

**ARM B – (ICR)**
CLOSED to accrual
- An analysis of the accrued patients at the time of the suspension found that those patients treated at reduced doses tolerated the ICR regimen, were treated longer, and had fewer disease progression events than those treated at fuller doses. Based on these finding, Arm B was closed to further accrual, and replaced with Arm C that employs reduced starting doses of the agents.

**ARM C – (mICR)**
- Ramucirumab 6 mg/kg IV over 60 minutes q 14 days
- Cetuximab 400 mg/m2 IV q 14 days
- Irinotecan 150 mg/m2 IV over 60-90 minutes q 14 days

*Repeat cycles every 14 days until progression.*

**PRE-STUDY PARAMETERS** (refer to Section 7 for details)
- History, physical examination, weight, PS and vitals
- ECOG Performance Status (PS)
- Adverse event and disease assessment
- Pregnancy test (serum or urine β-HCG)
- CBC and CMP, magnesium
- Urine Protein:Creatinine Ratio
- PT/INR
- CT scans of chest/abdomen/pelvis
- Electrocardiogram
- K-ras mutation status
- Pathology submissions