

MCCRC I4T-MC-JVBT – A Randomized, Placebo-Controlled, Double-Blind Phase 2 Study of mFOLFOX6 Chemotherapy Plus Ramucirumab Drug Product (IMC-1121B) versus mFOLFOX6 Plus Placebo for Advanced Adenocarcinoma of the Esophagus, Gastroesophageal Junction, or Stomach

Fast Facts

Ramucirumab provided
CTCAE v.4; RECIST v1.1;

Inclusion Criteria

1. Histologic or cytologic confirmation of adenocarcinoma of the esophagus, gastroesophageal junction (GEJ) or stomach. NOTE: adenosquamous histology or poorly differentiated carcinoma (not otherwise specified) is eligible.
2. Metastatic or locally advanced, unresectable disease at time of randomization
3. Provided signed informed consent and is amenable to compliance with protocol schedules and testing
4. Males or females at least 18 years of age
5. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-1 at time of randomization
6. Measurable or non-measurable disease at the time of randomization
 - a. Measurable or nonmeasurable disease must be outside a previously irradiated field or, if within a radiation field, there must be documented progression.
7. Resolution to Grade ≤ 1 by the CTCAE Version 4.0, of all clinically significant toxic effects of prior locoregional therapy, surgery, or other anticancer therapy, except where otherwise mentioned in the eligibility criteria.
8. Adequate organ function obtained ≤ 14 days prior to randomization, defined as:
 - a. Total bilirubin less than or equal to 1.5 x institutional upper limit of normal value (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN or, if liver metastases are present, ≤ 5.0 x ULN)
 - b. Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 50 ml/min per the Cockcroft-Gault formula or equivalent and/or 24-hour urine collection
 - c. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$, hemoglobin $\geq 9g/dl$, and platelets $\geq 100 \times 10^9/L$
 - d. Adequate coagulation function as defined by International Normalized Ratio (INR) ≤ 1.5 , prothrombin time (PT) and partial thromboplastin time (PTT/aPTT) ≤ 1.5 x ULN, (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 (that is, no bleeding within 14 days prior to randomization) or pathological condition present that carries a high risk of bleeding (for example, tumor involving major vessels or known varices). Patients on anticoagulation therapy with unresected primary tumors or luminal tumor recurrence following resection are eligible, provided that the tumor does not present a significant bleeding risk in the opinion of the investigator or consulting gastroenterologist.
9. Routine urinalysis showing $\leq 1+$ protein or protein/creatinine ratio < 0.5 . For proteinuria $\geq 2+$ or urine protein/creatinine ratio ≥ 0.5 , 24-hour urine protein should be obtained, and the level must be < 1 gram of protein in 24 hours for patient enrollment.
10. Eligible patients of reproductive potential (both sexes) must agree to use adequate contraceptive methods (hormonal or barrier methods) during the study period and at least 12 weeks after the last dose of study therapy.
11. Life expectancy of ≥ 3 months
12. Willingness to provide blood and tissue samples for research purposes. Submission of tumor specimen is mandatory for participation in this study, if a histologic, paraffin-embedded specimen exists (either from a surgical resection or biopsy); submission of paraffin block or a minimum of 8 unstained slides is required, if sufficient sample exists. NOTE: If insufficient additional tissue exists (that is, all tissue has been utilized for prior diagnostic purposes), participation in the study is allowable without the requirement for an additional biopsy; this situation must be discussed with the study principal investigator and/or the Sponsor physician or designee and will not be considered a protocol violation.

Exclusion Criteria

1. The patient has received prior first-line systemic therapy for advanced/unresectable and/or metastatic disease (prior adjuvant or neoadjuvant therapy is permitted).

2. Progressive disease \leq 12 months of completing oxliplatin treatment, if given previously in the perioperative (adjuvant or neoadjuvant) setting
3. The patient is receiving chronic therapy with nonsteroidal anti-inflammatory agents (NSAIDs; for example, indomethacin, ibuprofen, naproxen, or similar agents) or other antiplatelet agents (for example, clopidogrel, ticlopidine, dipyridamole, anagrelide). Aspirin use at doses up to 325 mg/day is permitted.
4. The patient has significant third-space fluid retention (for example, ascites or pleural effusion), and is not amenable for required repeated drainage.
5. Previous or concurrent malignancy except for basal or squamous cell skin cancer and/or in situ carcinoma of the cervix or any other organ, or other solid tumors treated curatively and without evidence of recurrence for at least 3 years prior to randomization
6. The patient is pregnant (confirmed by urine or serum beta human chorionic gonadotropin test within 7 days prior to randomization), or breastfeeding.
7. Uncontrolled intercurrent illness including, but not limited to, active or uncontrolled clinically serious infection, cardiac arrhythmia, psychiatric illness or other comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens or would limit compliance with study requirements
8. Immunocompromised patients (other than that related to the use of corticosteroids) including patients known to be HIV positive
9. Received prior therapy with an antiangiogenic agent (including but not limited to ramucirumab DP, bevacizumab, sunitinib, or sorafenib)
10. Currently enrolled in, or discontinued within the last 28 days form a clinical trial involving an investigational product or non-approved use of a drug (other than the study drug used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study. Patients participating in surveys or observational studies are eligible to participate in this study.
11. Major surgical procedure or significant traumatic injury $<$ 28 days prior to randomization, or anticipated elective or planned major surgical procedure during the course of the study. Subcutaneous venous access device placement within 7 days prior to randomization.
12. Radiation therapy within 14 days prior to randomization
13. Clinically significant peripheral neuropathy at the time of randomization (defined in the NCI CTCAE Version 4.0 as \geq Grade 2 neurosensory or neuromotor toxicity)
14. Known brain or leptomeningeal metastases
15. New York Heart Association classification III-IV congestive heart failure
16. Greater than normal risk of bleeding or coagulopathy in the absence of therapeutic anticoagulation; Grade 3/4 gastrointestinal bleeding within 3 months prior to randomization; active bleeding (that is, within 14 days prior to randomization); or pathological condition present that carries a high risk of bleeding (for example, tumor involving major vessels or known varices)
17. Patient has experienced any arterial thromboembolic events, including but not limited to myocardial infarction, stroke, transient ischemic attack, cerebrovascular accident, or unstable angina, \leq 6 months prior to randomization.
18. Clinically significant vascular disease (for example, aortic aneurysm, aortic dissection) for which more than minimal intervention is being administered or planned
19. History of hypertensive crisis or hypertensive encephalopathy or current poorly controlled hypertension (BP systolic \geq 160 mmHg and/or diastolic \geq 100 mmHg) despite standard medical management
20. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess $<$ 6 months prior to randomization. History of poorly controlled or recurrent inflammatory bowel disease (including Crohn's Disease or Ulcerative Colitis)
21. Known hypersensitivity to any of the treatment components of mFOLFOX6 or ramucirumab DP
22. All patients receiving concurrent anticancer therapy, including trastuzumab

Pre-Study Parameters

1. History and physical including height, weight, performance status, vital signs, review of concomitant medications, toxicity assessment, review of prior treatments, demography
2. Labs including CBC with differential, CMP, direct bilirubin, Mg, LDH, phosphorous, PT/INR, PTT, pregnancy test within 7 days of randomization, urine analysis/UPC ratio
3. ECG, Imaging for tumor assessment

Treatment

Arm A

Ramucirumab 8 mg/kg + mFOLFOX6 every 14 days

Arm B

Placebo + mFOLFOX6 every 14 days

Treatment continues until progression, unacceptable toxicity or patient/investigator decision.

See section 9 for complete treatment instructions.

Ramucirumab/placebo provided.