

CALGB 90802 – Randomized Phase III Trial Comparing Everolimus Plus Placebo Versus Everolimus Plus Bevacizumab for Advanced Renal Cell Carcinoma Progressing After Treatment with Tyrosine Kinase Inhibitors

Fast Facts

Bevacizumab/placebo provided
CTCAE v.4; RECIST v.1.1

1. Documentation of disease:
 - a. Histologic Documentation: Renal cell carcinoma with some component of clear cell histology
 - b. Stage: Metastatic or unresectable disease
2. Prior Treatment:
 - a. Must have been treated with at least 1 prior VEGFR tyrosine kinase inhibitor treatment and have progressed or have been intolerant to treatment.
 - b. No prior systemic therapy with a VEGF binding agent (e.g., bevacizumab)
 - c. No prior systemic therapy with any mTOR inhibitor (e.g., sirolimus, temsirolimus, everolimus)
 - d. Prior cytokine therapy is allowed
 - e. Any systemic therapy must be completed at least 4 weeks prior to registration
 - f. ≥ 2 weeks since any prior radiation (including palliative)
 - g. Patients must not have had a major surgical procedure, open biopsy, or significant traumatic injury within 4 weeks prior to study registration, and must have fully recovered from any such procedure. The following are not considered to be major procedures: Thoracentesis, paracentesis, port placement, laparoscopy, thoracoscopy, bronchoscopy, endoscopic ultrasonographic procedures, mediastinoscopy, skin biopsies, incisional biopsies and routine dental procedures.
3. Patients must have Measurable Disease by RECIST criteria. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2 cm with conventional techniques or as ≥ 1 cm with spiral CT scan.
4. No active brain metastases; patients with treated, stable brain metastases for at least three months are eligible as long as they meet the following criteria:
 - a. Treated brain metastases are defined as having no ongoing requirement for steroids and no evidence of progression or hemorrhage after treatment for at least 3 months, as ascertained by clinical examination and brain imaging (MRI or CT). (Stable dose of anticonvulsants are allowed). Treatment for brain metastases may include whole brain radiotherapy (WBRT), radiosurgery (RS; Gamma Knife, LINAC, or equivalent) or a combination as deemed appropriate by the treating physician. Patients with CNS metastases treated by neurosurgical resection or brain biopsy performed within 3 months prior to Day 1 are not eligible. Baseline brain imaging (MRI/CT) is required.
5. No serious non-healing wound, ulcer, or bone fracture
6. No arterial thrombotic events within 6 months of registration, including transient ischemic attack (TIA), cerebrovascular accident (CVA), peripheral arterial thrombus, unstable angina or angina requiring surgical or medical intervention in the past 6 months, or myocardial infarction (MI). Patients with clinically significant peripheral artery disease (i.e., claudication on less than one block), significant vascular disease (i.e., aortic aneurysm, history of aortic dissection), or any other arterial thrombotic event are ineligible.
7. Patients who have experienced a deep venous thrombosis or pulmonary embolus within the past 6 months must be on stable therapeutic anticoagulation to be enrolled to this study.
8. Patients receiving anti-platelet agents and prophylactic anticoagulation are eligible.
9. No inadequately controlled hypertension (defined as a blood pressure of ≥ 160 mmHg systolic and/or ≥ 90 mmHg diastolic on medication), or any prior history of hypertensive crisis or hypertensive encephalopathy
10. No known severe impairment of lung function defined as \geq grade 2 dyspnea or cough, or either:
 - a. Requirement of supplemental oxygen, or
 - b. In cases where pulmonary function or pulse oximetry tests have been obtained, FEV1 or FVC are $< 50\%$ of predicted, or single breath DLCO is $< 35\%$ of predicted or resting room oxygen saturation is less than 90%.
11. No active or severe liver disease (e.g. acute or chronic hepatitis, cirrhosis). No positive serology for anti-HBC or anti-HCV antibodies. HBV seropositive patients (HBsAg positive) are eligible if they are closely monitored for evidence of active HBV infection by HBV DNA testing and agree to receive suppressive therapy with lamivudine or other HBV-suppressive therapy until at least 4 weeks after the last dose of everolimus.
12. No NYHA Class ≥ 2 congestive heart failure
13. No active bleeding or chronic hemorrhagic diathesis or increased risk for bleeding including but not limited to history of major bleeding within 6 months (e.g. gastrointestinal, lung, CNS sites; or required transfusion support).

14. No history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 6 months prior to the initiation of treatment.
15. No ongoing immunosuppressive therapy including chronic systemic treatment with corticosteroids (≥ 10 mg/day prednisone equivalent).
16. Archival tissue must be available for submission, though it is optional patients to choose to participate in the correlative substudies or not.
17. Patients who are pregnant or nursing are not eligible. Women of child bearing potential must have a negative serum or urine pregnancy test within 16 days prior to registration. This is because the effects of everolimus and bevacizumab on a developing fetus at the recommended therapeutic doses are unknown.

Women of child-bearing potential include:

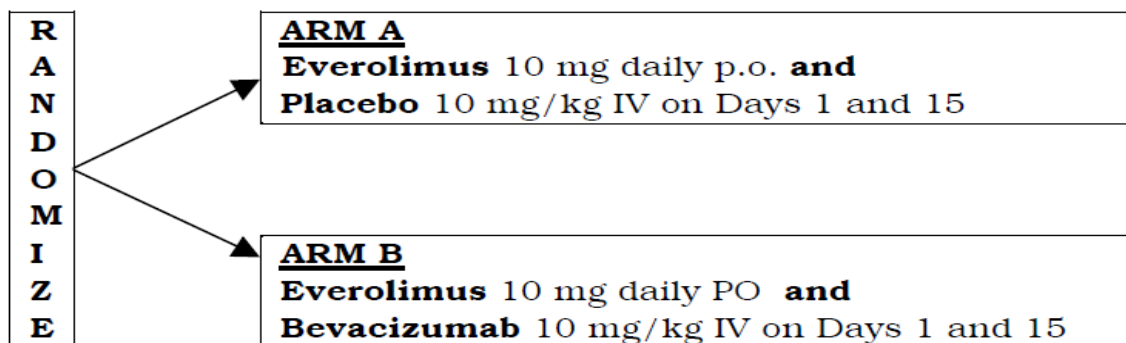
- Any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhea ≥ 12 consecutive months].
 - Women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35 m IU/mL.
 - Women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g., vasectomy).
18. Age ≥ 18 years of age
 19. Performance Status ECOG 0-2 or Karnofsky Score $\geq 60\%$
 20. Required Initial Laboratory Values:
 - Granulocytes $\geq 1,500/\mu\text{L}$
 - Platelet count $\geq 100,000/\mu\text{L}$
 - Calculated Creatinine clearance ≥ 30 mL/minute (modified Cockcroft and Gault formula)
 - Bilirubin ≤ 1.5 x upper limits of normal
 - AST ≤ 2.5 x ULN
 - Fasting serum triglycerides ≤ 200 mg/dL
 - Serum cholesterol ≤ 300 mg/dL
 - Fasting serum glucose ≤ 1.5 x ULN
 - Urine protein to creatinine ratio* < 1.0 or Urine protein $\leq 1+$

Pre-Study Parameters

1. History and physical including weight, pulse, blood pressure, performance status
2. Labs including CBC with differential, serum creatinine, albumin, AST, ALT, Alk Phos, bilirubin, fasting glucose, triglycerides, serum cholesterol, LDH, serum or urine HCG, UPC ratio/dipstick
3. Hepatitis B screening: HBsAg, HBsAb, HB core antibody; HVC Ab, HBV DNA testing only if hepatitis B seropositive
4. Brain CT or MRI; CT chest/abdomen/pelvis; bone scan

Schema

1 Cycle = 28 Days



* See Section 8.0 for complete treatment details.

Treatment is to continue until disease progression or unacceptable toxicity.
Bevacizumab/placebo provided.