

CTSU E2804: The BeST Trial: A Randomized Phase II Study of VEGF, RAF kinase, and mTOR Combination Targeted Therapy (CTT) with Bevacizumab, Sorafenib and Temozolomide in Advanced Renal Cell Carcinoma

Fast Facts

Eligibility Criteria

- 1) Patients are required to have the clear cell variant of renal cell carcinoma with less than 25% of any other histology (including, but not limited to, papillary or chromophobe or oncocytic). There must be histologic confirmation by treating center of either primary or metastatic lesion.
- 2) Patients will be required to have measurable disease that is not curable by standard radiation therapy or surgery. All sites must be assessed within 4 weeks of study entry.
- 3) Previous nephrectomy is required with the following exceptions:
 - a) Primary tumor ≤ 5 cm, or
 - b) Extensive liver ($> 30\%$ of liver parenchymal) or multiple (> 5) bone metastases, making the nephrectomy a clinically questionable procedure.
 - c) Unresectable primary tumor due to invasion into adjacent organs or encasing the aorta or vena cava.
- 4) No prior cytotoxic chemotherapy. A maximum of one prior regimen of either vaccine or cytokine-based immunotherapy disease is permitted.
- 5) No prior anti-angiogenic therapy including, but not limited to, SU11248, ZD6474 or VEGF Trap. No prior therapy with bevacizumab, mTOR inhibitors (including, but not limited to, temsirolimus), or sorafenib will be allowed. Thalidomide or IFN α are allowed either for adjuvant or stage IV disease.
- 6) No immunotherapy within 4 weeks of randomization. Toxicities from immunotherapy must have resolved and a minimum of two weeks must pass prior to enrollment.
- 7) Prior radiation therapy is permitted, but toxicities from radiation must have resolved and a minimum of two weeks must pass prior to randomization.
- 8) No history or clinical evidence of CNS disease, including primary brain tumor, seizures not controlled with standard medical therapy, any brain metastasis, or history of stroke within the past 48 weeks.
- 9) Age ≥ 18 years of age.
- 10) ECOG performance status 0-1.
- 11) Life expectancy of greater than 12 weeks.
- 12) Patients will have the following baseline laboratory values within 2 weeks prior to randomization:
 - a) Hgb ≥ 9.0 g/dL (transfusions allowed prior to enrollment)
 - b) WBC $\geq 3,000/\text{mm}^3$
 - c) AGC $\geq 1,200/\text{mm}^3$
 - d) Platelet count $\geq 100,000/\text{mm}^3$
 - e) Serum creatinine ≤ 1.5 x upper limit of normal (ULN), or Serum creatinine clearance ≥ 55 ml/min
 - f) Total bilirubin ≤ 1.5 x ULN
 - g) AST and ALT ≤ 2.5 ULN (or ≤ 5.0 ULN in the presence of liver metastases)
 - h) INR ≤ 1.5 and aPTT within normal limits
 - i) Fasting cholesterol < 350 mg/dL (9.0 mmol/L)
Fasting triglycerides < 400 mg/dL (4.56 mmol/L)
- 13) Patients must not have other current malignancies, other than basal cell skin cancer, squamous cell skin cancer, in situ cervical cancer, and ductal or lobular carcinoma in situ of the breast. Patients with other malignancies are eligible if they have been continuously disease-free for ≥ 5 years prior to the time of registration.
- 14) No history of allergic reactions attributed to Chinese hamster ovary cell products, other recombinant human antibodies, or compounds of similar chemical or biological composition to sorafenib, temsirolimus or bevacizumab.
- 15) No history of bleeding or coagulopathy.
- 16) Any condition that impairs patient's ability to swallow pills will make patient ineligible.
- 17) No major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to randomization.
- 18) No anticipated need for major surgery during the course of the study.

- 19) No current or recent (within 4 weeks of enrollment) use of full-dose of anticoagulants or thrombolytic agents (except as required to maintain patency of preexisting or permanent indwelling IV catheters, for those patients receiving warfarin, INR must be ≤ 1.5)
- 20) No clinically significant cardiovascular disease, defined as one of the following:
 - a) Patients with uncontrolled hypertension (blood pressure $> 150/100$ mmHg at the time of enrollment). Patients with hypertension and blood pressure $\leq 150/100$ mmHg on stable antihypertensive regimen are eligible.
 - b) Myocardial infarction or unstable angina < 24 weeks prior to registration.
 - c) New York Heart Association grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication, unstable angina pectoris.
 - d) Grade II or greater peripheral vascular disease.
- 21) No serious, non-healing wound, ulcer or bone fracture.
- 22) No significant proteinuria at baseline. Urine protein must be screened within 2 weeks prior to randomization by urine analysis for Urine Protein Creatinine (UPC) ratio. If UPC ratio is > 0.5 , 24-hour urine protein is to be obtained and the level must be < 1000 mg for patient enrollment. NOTE: UPC ratio of spot urine is an estimation of 24-hour urine protein excretion. A UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm.
- 23) No uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring parenteral antibiotics on day 0 or psychiatric illness/social situations that would limit compliance with study medication requirements.
- 24) Patients currently taking any of the following cytochrome P450 enzyme-inducing drugs are ineligible: Phenytoin, Carbamazepine, Phenobarbital, Rifampin
- 25) Pregnant and breastfeeding women are excluded from the study because the agents used in this study may be teratogenic to a fetus and there is no information on the excretion of the agents or their metabolites into breast milk. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with these agents, breastfeeding should be discontinued while receiving therapy. Patients must have pregnancy tests within 7 days prior to randomization if woman is of child-bearing capacity.
- 26) HIV-positive patients receiving combination anti-viral therapy are excluded from the study because of possible pharmacokinetic interactions with sorafenib, temsirolimus or bevacizumab.

Pre-study Parameters

- 1) History and physical including blood pressure
- 2) CBC with differential, CMP, LDH, Amylase, lipase, serum phosphate, GFR, Fasting cholesterol and triglycerides, INR and aPTT (beta HCG for women of child-bearing potential)
- 3) Brain MRI, chest CT, abdominal/pelvic CT or MRI. Bone scan for pts with known bone mets, elevated alkaline phosphatase or symptoms raising suspicion of bone mets.

Treatment

Arm A

Bevacizumab 10 mg/kg IV every 2 weeks (days 1 and 15)

Arm B

Bevacizumab 10 mg/kg IV every 2 weeks (days 1 and 15)

Temsirolimus 25 mg IV weekly (days 1, 8, 15 and 22)

Arm C

Bevacizumab 5 mg/kg IV every 2 weeks (day 1 and 15)

Sorafenib 200 mg PO twice daily on day 1-5, 8-12, 15-19 and 22-26

Arm D

Sorafenib 200 mg PO twice daily (days 1-28)

Temsirolimus 25 mg IV weekly (days 1, 8, 15 and 22)

Cycle = 28 days