CTSU E2810 - Randomized, Double-Blind Phase III Study of Pazopanib vs. Placebo in Patients with Metastatic Renal Cell Carcinoma Who Have No Evidence of Disease Following Metastatectomy

Fast Facts

1. Patient must be at least 18 years of age at the time of randomization.
2. Patient must have pathologically confirmed renal cell carcinoma with a clear cell component. Pure papillary and chromophobe histologies are excluded. There must be pathologic confirmation of metastatic disease in the resected metastatectomy specimen.
3. Patient must have undergone nephrectomy or partial nephrectomy to remove primary renal cell carcinoma (at any time in the past).
4. Patient must have undergone surgical resection to remove one or more sites of metastatic disease, with successful removal of all known sites 2- 12 weeks prior to randomization. Any number of prior metastatectomies may have been performed in the past, so long as the most recent procedure was within the 12 weeks of registration. The most recent procedure may be nephrectomy for a renal primary tumor.
5. Patients with synchronous disease at initial diagnosis must have metastatic (M1) disease (AJCC 7th edition T1-4N0-1M1).
6. Positive surgical margins are permitted if the surgeon confirms complete resection of gross metastatic disease, and post operative scans are negative.
7. Patients presenting with metachronous disease may have distant metastases, regional lymph node or renal bed recurrence. Recurrences at a partial nephrectomy resection site are not eligible if it is the only site of disease.
8. Patients presenting with tumors within the kidneys (multiple synchronous or single/multiple metachronous) are not eligible if there are no extrarenal sites of disease (i.e. potential multifocal primary disease).
9. Patient must have no evidence of disease on post-operative imaging (CT and/or MRI) conducted within 4 weeks prior to randomization and an MRI without gadolinium must be done within 8 weeks prior to radiation. A CT of the brain with and without IV contrast is permitted if MRI is contra-indicated (i.e., pacemaker).
10. Patient must not have received any prior or concurrent systemic therapy for RCC. Adjuvant placebo administration is permitted.
11. Patient must have no active peptic ulcer disease.
12. Patient must have no active inflammatory bowel disease.
13. Patient must have no New York Heart Association (NYHA) class II or greater congestive heart failure.
14. Patient must have no prior history or current clinically apparent central nervous system metastases.
15. Patient must have an ECOG performance status of 0 or 1 at the time of randomization.
16. Patient must have the following baseline laboratory values within 2 weeks prior to randomization:
    a. Absolute granulocyte count > 1,500/mcL
       AGC_____ Date of Test_____
    b. Platelets > 100,000/mcL
       Platelet count_____ Date of test_____
    c. Total bilirubin < 1.5 X institutional upper limit of normal
       Total bilirubin_____ Date of test_____
    d. AST(SGOT)/ALT(SGPT) < 2.5 X institutional upper limit of normal
       ALT_____ Date of test_____ ULN_____
       AST_____ Date of test_____ ULN_____

e. Calculated creatinine clearance (CrCl) > 30mL/min (pazopanib is not cleared by the kidney). CrCl= Wt (kg) x (140-age)*/72 x Cr. Level; (*female x 0.85).
Creatinine Clearance_____ Date_____

f. Subjects must have a urine protein/creatinine ratio < 1. If UPC ≥ 1, then a 24-hour urine total protein must be obtained. Subjects must have a 24-hour urine protein value < 1g to be eligible. Use of urine dipstick for renal function assessment is not acceptable.

17. Women must not be pregnant or breast-feeding due to the unknown effects of pazopanib on the developing fetus.
All females of childbearing potential must have a blood test or urine study within 2 weeks prior to randomization to rule out pregnancy. A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

    Female? _____ (Yes or No)
    Date of blood test or urine study: _____

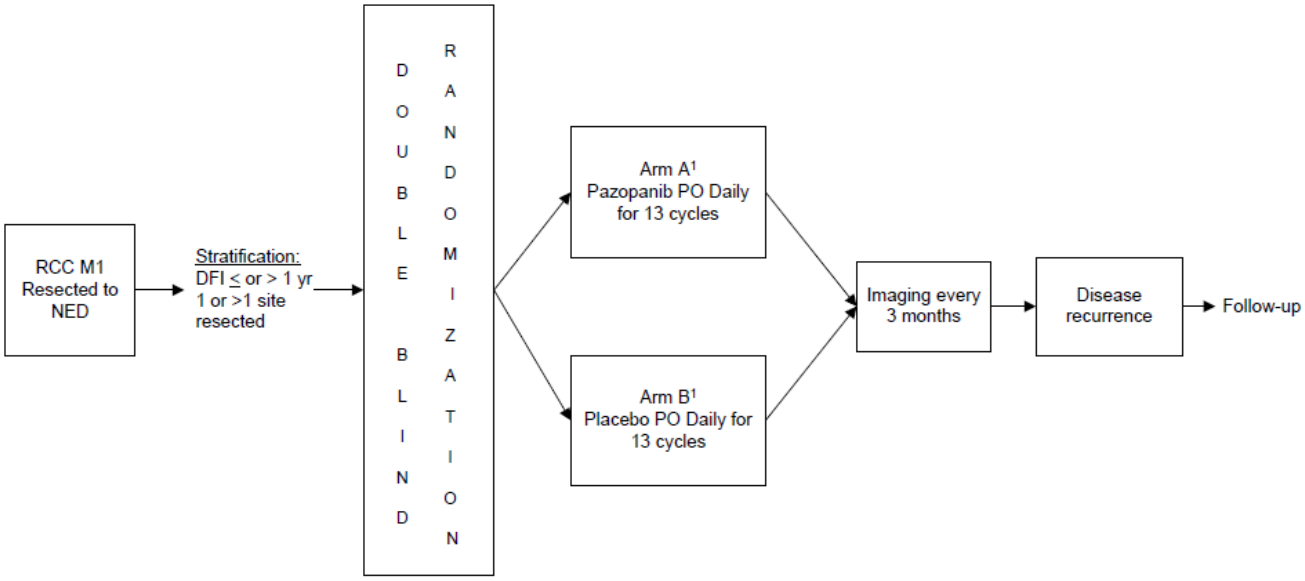
18. Women of childbearing potential and sexually active males must be strongly advised to use an accepted and effective method of contraception or to abstain from sexual intercourse for the duration of their participation in the study. Should a woman become pregnant while participating in this study, she should inform her treating physician immediately. If a man impregnates a woman while participating in this study, he should inform his treating physician immediately.
19. Patient must be able to swallow pills and have no significant impairment in gastrointestinal absorption including history of gastric bypass surgery.
20. Patient must have no history of allergic reactions attributed to compounds of similar chemical or biologic composition to pazopanib.
21. Patient must have no uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
22. Patient must have a QTc interval on ECG ≤ 0.48 seconds by Bazett's calculation (≤ CTCAE v.4 Grade 2) prior to randomization.
23. Patient must have a systolic blood pressure ≤ 140 mmHg and diastolic blood pressure must be ≤ 90 mmHg, measured within 4 weeks prior to randomization. Initiation or adjustment of anti-hypertensives prior to starting study treatment is allowed.
24. Patient must not have serious or non-healing wound, ulcer, or bone fracture at the time of randomization.
25. Patient must have no history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 4 weeks prior to randomization.
26. Patient must have no history of cerebrovascular accident (CVA) within 6 months of randomization.
27. Patient must have no history of myocardial infarction, hospital admission for unstable angina, cardiac angioplasty or stenting within 6 months of randomization.
28. Patient must have no history of venous thrombosis within 12 weeks of randomization.
29. Patient cannot be taking strong CYP3A4 inhibitors such as: (See Appendix IX for CYP interaction information)
    - Antibiotics: clarithromycin, telithromycin, troleandomycin
    - HIV antiviral protease inhibitors: ritonavir, indinavir, saquinovir, nelfinavir, amprenavir, lopinavir
    - Antifungals: itraconazole, ketoconazole, voriconazole, fluconazole
    - Antidepressants: nefazodone

30. Patient must not have history of hemoptysis in excess of 2.5 mL (1/2 teaspoon) within 8 weeks prior to randomization.

31. Patient must not be taking drugs known to prolong the QTc interval. Such drugs should be discontinued at least 5 half-lives prior to randomization. See Appendix VII for a list of agents that that are associated with a risk for QTc prolongation and/or Torsades de Pointes.

32. Patients must not have any history of other cancer within 3 years from time of randomization with the exception of basal cell skin cancer, squamous cell skin cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast, or resected non-invasive (Ta) urothelial carcinoma.

SCHEMA



Accrual Goal= 180 patients
Cycle= 28 days
NOTE: QOL will be assessed at several timepoints during this study. See Section 5.3.1 for details of the assessment schedule.

1. Blinded treatment:
Arm A= Pazopanib 4 tablets PO daily
Arm B= Placebo 4 tablets PO daily