Cancer Research Consortium of West Michigan
P: 616.391.1230 | 800.336.6299 | www.crcwm.org

FAST FACTS

S1500: A Randomized, Phase II Efficacy Assessment of Multiple MET Kinase Inhibitors (Cabozantinib, Crizotinib, Savolitinib, and Sunitinib) in Metastatic Papillary Renal Carcinoma (PAPMET)

Provided Drugs: *Cabozantinib, Crizotinib, Savolitinib, and Sunitinib*

Eligibility Criteria

5.1. Disease Related Criteria

a. Patients must have histologically or cytologically confirmed papillary histology renal cell carcinoma which is metastatic or locally advanced disease not amenable to surgical resection. (NOTE: A designation of type I or type II should be made by the local pathologist if possible.) Mixed histologies containing type I or type II will be allowed provided that they contain ≥ 50% of the papillary component.
b. Patients must also have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (see Section 10.1). Disease X-rays, scans or physical examinations used for tumor measurement must have been completed within 28 days prior to registration. If there is clinical suspicion for bone metastases at the time of enrollment (at the discretion of the investigator), bone scan should be performed at baseline (within 42 days prior to registration). All disease must be assessed and documented on the Baseline Tumor Assessment Form.
c. Patients with a history of treated brain metastases who are asymptomatic and have not received steroid therapy in the 14 days prior to registration are eligible. Anti-seizure medications are allowed provided they are non-enzyme inducing (e.g. topiramate, levatiracetam, gabapentin).
d. Patients must not have cavitating pulmonary lesions. Patients must not have tumor invading the GI tract or evidence of endotracheal or endobronchial tumor within 28 days prior to registration.

5.2 Prior/Concurrent Therapy Criteria

a. Patients may have received prior surgery. At least 28 days must have elapsed since surgery and patient must have recovered from any adverse effects of surgery.
b. Patients may have received up to one prior systemic therapy for advanced or metastatic renal cell carcinoma with the exception of another VEGF inhibitor FDA-approved for advanced RCC (i.e., pazopanib, bevacizumab, sorafenib or axitinib). If a patient develops metastatic disease within six months of discontinuation of adjuvant therapy, this will constitute one prior systemic therapy for advanced or metastatic RCC. If a patient develops metastatic disease and more than six months has elapsed since discontinuation of adjuvant therapy, this will not constitute prior systemic therapy for advanced or metastatic RCC. Patients may have also received prior immunotherapy. Patients must not have received a MET/HGF inhibitor or sunitinib as prior therapy. At least 14 days must have elapsed since completion of prior systemic therapy. Patients must have recovered from all associated toxicities at the time of registration.
c. Patients may have received prior radiation therapy, but must have measurable disease outside the radiation port. At least 14 days must have elapsed since completion of prior radiation therapy. Patients must have recovered from all associated toxicities at the time of registration.
d. Patients must not be taking, nor plan to take while on protocol treatment, strong CYP3A4 inhibitors (e.g. boceprevir, cobicistat, danoprevir, elvitegravir/RIT, fluvoxamine, indinavir, itraconazole, ketoconazole, lopinavir/RIT, nefazodone, nelfinavir, posaconazole, ritonavir, telaprevir, telithromycin, tipravavir/RIT, or voriconazole,); strong CYP3A4 inducers (e.g.

avasimibe, phenytoin, rifampin, rifabutin); potent inhibitors of CYP1A2 (e.g. ciprofloxacin); and/or drugs known to be CYP3A4 substrates with a narrow therapeutic range (e.g., diergotamine, ergotamine) within 14 days prior to randomization. (Moderate inhibitors or inducers of isoenzyme CYP3A4 should be avoided, but if necessary can be used with caution (see Section 18.2).

e. Patients must not be receiving or planning to receive any other investigational agents.

5.3 Clinical/Laboratory Criteria

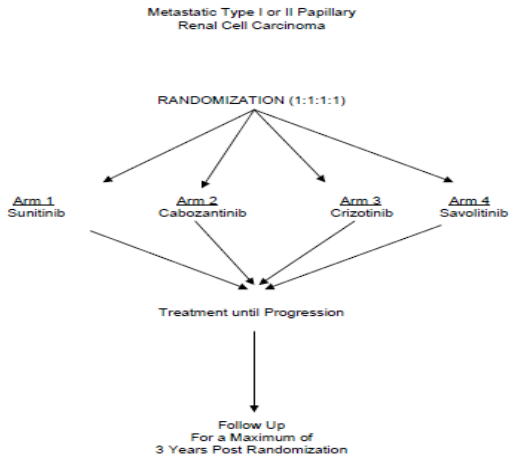
a. Patients must have a complete physical examination and medical history within 28 days prior to registration.
b. Patients must have a Zubrod performance status of 0 - 1 (see Section 10.4).
c. Patients must have adequate hematologic function as documented by a WBC ≥ 2,000/mcL, an ANC ≥ 1,000/mcL, and a platelet count ≥ 75,000/mcL. These tests must be obtained within 28 days prior to registration.
d. Patients must have adequate hepatic function as evidenced by serum bilirubin ≤ 1.5 x institutional upper limits of normal (ULN). Serum transaminase (SGOT/AST and SGPT/ALT) must be ≤ 2.5 x the institutional ULN unless the liver is involved with the tumor, in which case serum transaminase (SGOT/SGPT) must be ≤ 5 x the institutional ULN. These tests must be obtained within 28 days prior to registration.
e. Serum creatinine must be ≤ 2 x the institutional ULN OR creatinine clearance (either measured or calculated) must be > 30 mL/min and obtained within 28 days prior to registration.
f. Patients must not have any clinical evidence of congestive heart failure (CHF) (specifically, New York Heart Association [NYHA] Class III [moderate] or Class IV [severe]) at the time of registration. Baseline echocardiogram within 28 days of registration must demonstrate an EF ≥ 50%. Due to the potential cardiac toxicity of the agents utilized in this protocol, patients must have QTc interval < 500 msec on prestudy EKG and no known history of congenital long QT syndrome. Patients must not have experienced unstable angina pectoris, clinically significant cardiac arrhythmias, or stroke (TIA or other ischemic event) within 3 months prior to registration and not have experienced myocardial infarction or thromboembolic event requiring anticoagulation within 6 months of registration. Prestudy EKG must be obtained within 28 days prior to registration.
g. Baseline urinalysis should show urine protein < 3+ and must be obtained within 28 days prior to registration. If urine protein is 3+ or greater, then urine protein by 24 hour collection must show less than 3 grams of protein.
h. Patients must not have inadequately controlled hypertension. Patients must have documented blood pressures of SBP < 150 and DBP < 90 within 14 days of starting randomization. Blood pressure medications (any number) are permitted.
i. Patients must be able to take oral medications (i.e., swallow pills whole). Patients must not have gastrointestinal tract disease resulting in an inability to take oral medication or a requirement for IV alimentation, prior surgical procedures that could in the opinion of the treating investigator affect absorption, or active peptic ulcer disease. Patients with intractable nausea or vomiting are not eligible.
j. Patients must not have had any clinically-significant GI bleeding within 6 months prior to registration and patients must not have a GI disorder which (at the discretion of the investigator) bears a high risk of perforation or fistula. Examples of this include (but are not limited to) Crohn's disease or tumor with transmural extension through the gastrointestinal lining.
k. Patients must not have had hemoptysis of ≥ 0.5 teaspoon (2.5 ml) of red blood within 3 months prior registration.
l. Patients must not demonstrate any other signs indicative of pulmonary hemorrhage within 3 months prior to registration.

m. Patient's baseline imaging must not indicate the presence of tumor invading or encasing any major blood vessels.
n. Patients must not have any unresolved wounds from previous surgery.
o. Albumin, alkaline phosphatase, bicarbonate, BUN, chloride, glucose, phosphorus, and total protein must be assessed within 28 days of registration.
p. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for 3 years. Men receiving active surveillance for prostate cancer may also be enrolled.
q. Due to the unknown effects of the study drugs, patients must not be pregnant or nursing. Women/men of reproductive potential must have agreed to use an effective contraceptive method while receiving study drug and for three months after last dose of study drug. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.
r. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with cabozantinib, crizotinib, savolitinib or sunitinib. In addition these patients are at increased risk of lethal infections when treated with marrow suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.
s. Patients must be ≥ 18 years of age.

5.4 Specimen Submission Criteria

a. Patients must have tissue available and be willing to submit for central pathologic review in order to classify type I versus type II papillary disease (see Section 12.0).
b. Patients must be offered the opportunity to participate in specimen banking for future translational medicine studies (see Section 15.0).

Schema



Pre-Study Parameters

1. History & Physical exam
2. Weight & Performance Status
3. CBC w/diff, platelets
4. CMP, phosphorous, LDH
5. Urinalysis
6. Pregnancy test
7. CT of chest/abdomen/pelvis
8. Bone scan if indicated
9. EKG and ECHO