FAST FACTS

S2200 - A Phase II Randomized Trial of Cabozantinib (NSC #761968) with or without Atezolizumab (NSC #783608) in Patients with Advanced Papillary Renal Cell Carcinoma (PAPMET2)

ELIGIBILITY CRITERIA

1. Disease Related Criteria
   a. Participants must have a histologically confirmed diagnosis of metastatic papillary renal cell carcinoma (PRCC), either type 1 or type 2. (NOTE: A designation of type 1 or type 2 should be made by the local pathologist if possible but is not required). Mixed histologies which contain type 1 or type 2 along with any other RCC histology/histologies will be allowed provided that they contain a papillary component.
   b. Participants must have measurable disease per RECIST 1.1 criteria (see Section 10.1). All measurable lesions must be assessed by CT or MRI within 28 days prior to registration. All non-measurable lesions must be assessed by CT or MRI, or nuclear medicine bone scan within 42 days prior to registration. The CT from a combined PET/CT may be used to document only non-measurable disease unless it is of diagnostic quality as defined in S2200 Section 10.1.c. If there is clinical suspicion for bone metastases at the time of enrollment (at the discretion of the investigator), bone scan must be performed at baseline (within 42 days prior to registration).
   c. Participants with new or progressive brain metastases (active brain metastases) must not require immediate CNS specific treatment at the time of study registration or anticipated during the first cycle of therapy. Patients with leptomeningeal disease are excluded from enrolling.
   d. Participants with measurable disease, per RECIST v1.1, must be present outside the CNS.
   e. Participants must have no history of intracranial hemorrhage or spinal cord hemorrhage.
   f. Participants must not have undergone stereotactic radiotherapy within 7 days prior to initiation of study treatment, whole-brain radiotherapy within 14 days prior to initiation of study treatment, or neurosurgical resection within 28 days prior to initiation of study treatment.
   g. Participants must not have ongoing requirements for corticosteroids as therapy for CNS disease.
   h. Participants, if needed, must receive a stable dose of anti-convulsant therapy.
   i. Participants must not have cavitating pulmonary lesions.
   j. Participants must not have uncontrolled pleural effusions, pericardial effusions, or ascites requiring recurrent drainage procedures (once monthly or more frequently. Participants with indwelling catheters (e.g., PleurX) are allowed
   k. Participants must not have tumor invading the GI tract or evidence of endotracheal or endobronchial tumor within 28 days prior to registration.
   l. Participants must not have evidence of tumor invading or encasing any major blood vessels.

2. Prior/Concurrent Therapy Criteria
   a. Participants must not have had major surgery within 28 days prior to registration, and participants must have recovered from any adverse effects of surgery.
   b. Participants must not have had prior treatment with cabozantinib for any reason.
   c. Participants must not have had prior treatment or adjuvant therapy with PD-1/PD-L1 checkpoint inhibitors for any reason within the past 6 months.
   d. Participants must not have received more than 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 participant 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.
   e. Participants must not take within 14 days prior to registration, nor plan to take while on protocol treatment, any 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,); Please refer to https://drug-interactions.medicine.iu.edu/MainTable.aspx for the updated CYP3A4 inhibitors or inducers.

f. Participants must not take within 14 days prior to registration, nor plan to take while on protocol treatment, any strong CYP3A4 inducers (e.g. avasimibe, phenytoin, rifampin, rifabutin); Please refer to https://drug-interactions.medicine.iu.edu/MainTable.aspx for the updated CYP3A4 inhibitors or inducers.

g. Participants must complete all prior radiation therapy at least 14 days prior to registration. Participants must have recovered to ≤ grade 1 from all associated toxicities at the time of registration unless the toxicity is determined to be not clinically significant by the registering investigator.

h. Participants must not be receiving or planning to receive any other investigational agents at time of registration.

i. Participants must not have been diagnosed with a clinically significant autoimmune disease, exceptions such as diabetes, eczema, and vitiligo are allowed. Other non- clinically significant autoimmune diseases are allowed if approved by the registering investigator.

j. Participants must not be on steroid doses >10 mg prednisone equivalent. Replacement steroid doses for adrenal insufficiency will be allowed. Also, short duration steroid therapy to prevent allergic reactions are acceptable (eg prior to CT imaging).

3. Clinical/Laboratory Criteria

a. Participants must be ≥ 18 years of age.

b. Participants must have a complete physical examination and medical history within 28 days prior to registration.

c. Participants must have a Zubrod performance status of 0-2 (see Section 10.6).

d. Participants must have adequate hematologic function within 28 days prior to registration, as documented by:
- WBC ≥ 2 x 10^3/uL
- ANC ≥ 1.5 x 10^3/uL,
- Platelet count ≥ 100 x 10^3/uL.
- Lymphocyte count ≥ 0.5 x 10^3/uL
- Hemoglobin (≥ 9 g/dL) Participants may be transfused to meet this criterion.

e. Participants must have adequate hepatic function within 28 days prior to registration as documented by:
- Total Serum bilirubin ≤ 1.5 x the institutional upper limit of normal (ULN) unless history of Gilbert's disease. Participants with history of Gilbert's disease must have total bilirubin ≤ 5 x institutional ULN.
- Aspartate aminotransferase (AST) must be ≤ 3 x the institutional ULN unless the liver is involved with the tumor, in which case serum transaminase (SGOT) must be ≤ 5 x the institutional ULN.
- Alanine aminotransferase (ALT), must be ≤ 3 x the institutional ULN unless the liver is involved with the tumor, in which case serum transaminase (SGPT) must be ≤ 5 x the institutional ULN

f. Participants must have serum creatinine ≤ 2 x the institutional ULN OR creatinine clearance (either measured or calculated) > 30 mL/min and obtained within 28 days prior to registration.
Calculated Creatinine Clearance = (140 - age) X (weight in kg)†
72 x serum creatinine*
Multiply this number by 0.85 if the participant is a female.
† The kilogram weight is the participant weight with an upper limit of 140% of the IBW.
* Actual lab serum creatinine value with a minimum of 0.7 mg/dL.

g. Participants 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. See Section 18.5.

h. Participants must not have known history of congenital long QT syndrome and must not have experienced unstable angina pectoris, clinically significant cardiac arrhythmias, or stroke (TIA or other ischemic event) within 90 days prior to registration.

i. Participants must not have experienced myocardial infarction or thromboembolic event requiring anticoagulation within 90 days of registration, unless clinically stable with ongoing medical management.

j. Participants must have urine protein < 3+ 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.

Protein	Trace	30	100	≥ 300
mg/dL	Tr	+1	+2	3+

k. Participants must have documented blood pressure of SBP < 150 mm Hg or DBP < 100 mm Hg within 14 days prior to registration.

l. Participants with known human immunodeficiency virus (HIV) must be on effective anti-retroviral therapy at registration and have undetectable viral load within 6 months of registration.

m. Participants with evidence of chronic hepatitis B virus (HBV) infection must have undetectable HBV viral load while on suppressive therapy within 6 months prior to registration, if indicated.

n. Participants with a history of hepatitis C virus (HCV) infection must have been treated and cured. Participants currently being treated for HCV infection must have undetectable HCV viral load within 6 months prior to registration..

o. Participants must be able to take oral medications (i.e., swallow pills whole). Participants 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. Participants with intractable nausea or vomiting are not eligible.

p. Participants must not have had any clinically-significant GI bleeding within 3 months prior to registration and participants must not have a GI disorder which (at the discretion of the investigator) bears a high risk of perforation or fistula (e.g. Crohn's disease).

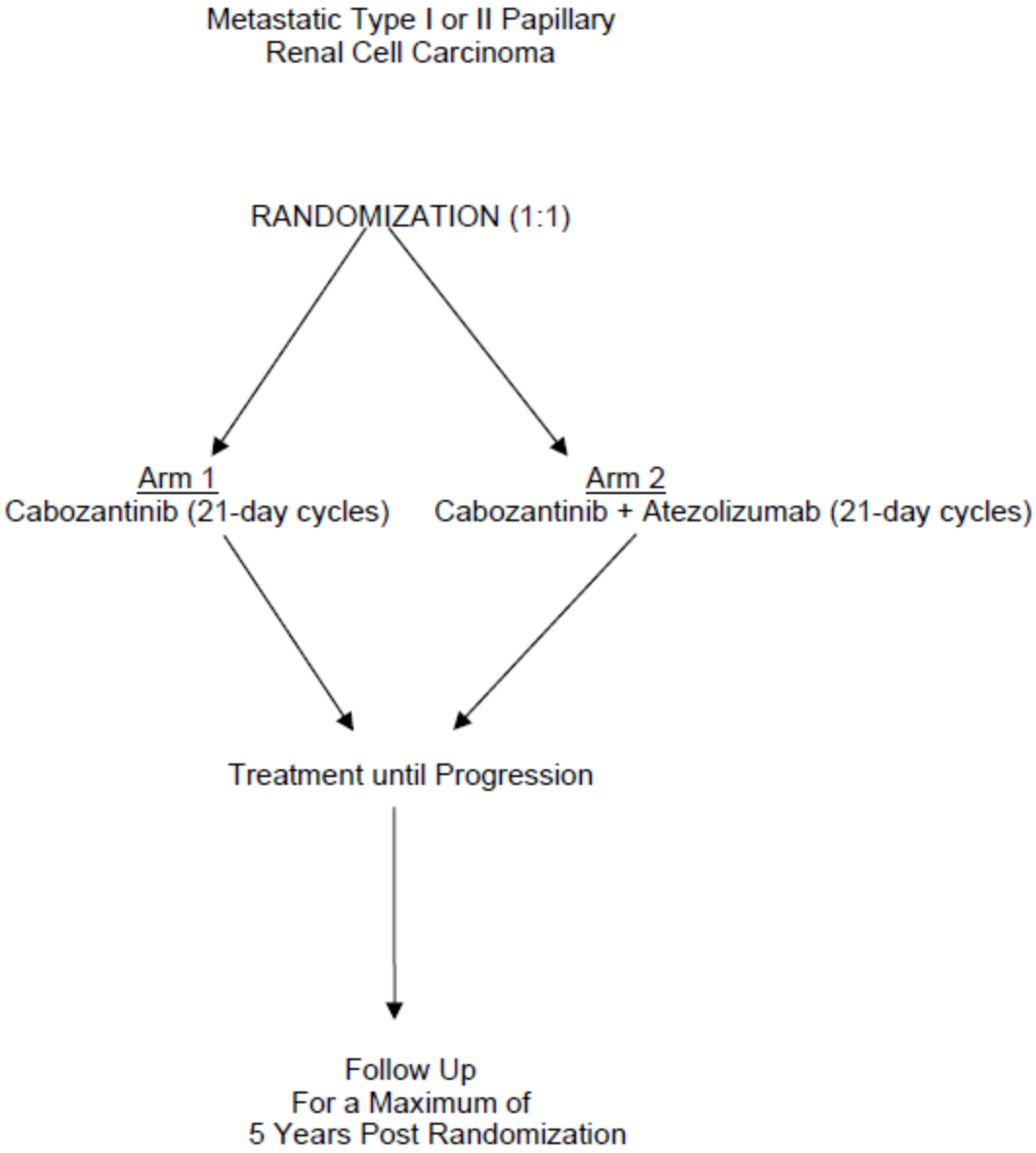
q. Participants must not have had hemoptysis of ≥ (2.5 mL) of red blood, and do not demonstrate any other signs indicative of pulmonary hemorrhage within 3 months prior registration.

r. Participants with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

s. Participants must not be pregnant or nursing, due to VEGF therapy being toxic to embryogenesis. Individuals who are of reproductive potential must have agreed to use an effective contraceptive method with details provided as a part of the consent process. A person who has had menses at any time in the preceding 12 consecutive months or who has semen likely to contain sperm is considered to be of "reproductive potential." In addition to routine contraceptive methods, "effective contraception" also includes refraining from sexual activity that might result in pregnancy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) including hysterectomy, bilateral oophorectomy, bilateral tubal ligation/occlusion, and vasectomy with testing showing no sperm in the semen.

t. Participants must not be on warfarin, at therapeutic doses. Low dose aspirin for cardio-protection (per local applicable guidelines) and low molecular weight heparin (LMWH) are allowed.

SCHEMA


Metastatic Type I or II Papillary
Renal Cell Carcinoma
RANDOMIZATION (1:1)
Arm 1
Cabozantinib (21-day cycles)
Arm 2
Cabozantinib + Atezolizumab (21-day cycles)
Treatment until Progression
Follow Up
For a Maximum of
5 Years Post Randomization