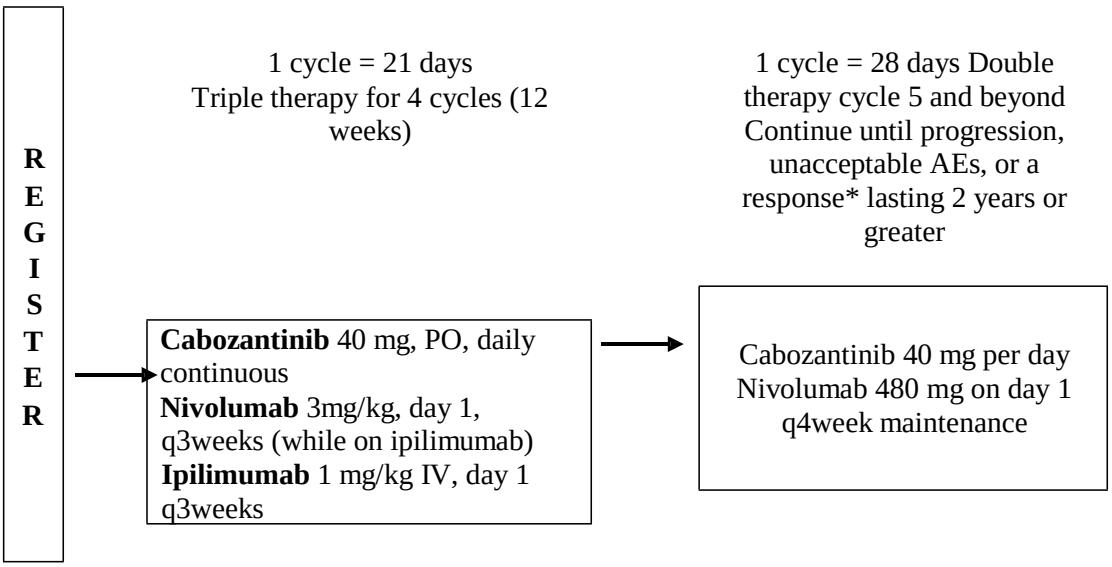
A PHASE II STUDY OF IPILIMUMAB, CABOZANTINIB, AND NIVOLUMAB IN RARE GENITOURINARY CANCERS (ICONIC)

Eligibility Criteria (For a complete listing of protocol eligibility criteria see Section 3.2)

Required Initial Laboratory Values

Absolute Neutrophil Count (ANC)	≥1,200/mcL
Platelet Count	≥75,000/mcL
Total Bilirubin	≤1.5 × ULN. For subjects with known Gilbert's disease or similar syndrome with slow conjugation of bilirubin, total bilirubin ≤ 3.0 mg/dL
AST/ALT	≤3.0 × institutional upper limit of normal (ULN) (or ≤5 x ULN for patients with liver metastases or Gilbert's disease)
Creatinine	≤ 1.5 x upper limit of normal (ULN) **OR**
creatinine clearance	≥ 40 mL/min/1.73 m^2 (calculated using the CKD-EPI equation or Cockroft-Gault formula) for patients with creatinine levels above institutional normal.
hemoglobin	≥9 g/dL (transfusion of PRBCs allowed)
serum albumin	≥2.8g/dL
lipase and amylase	≤2.0 × ULN and no radiologic (on baseline anatomical imaging) or clinical evidence of pancreatitis

Schema



*Response is defined as a complete or partial response or stable disease >9 months. Patients will be followed for a total of 5 years from the date of registration or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- No active secondary malignancy requiring systemic therapy within the previous 2 years except for locally curable cancers that have been apparently cured such as basal or squamous cell skin cancer, non-muscle-invasive bladder cancer, or carcinoma in situ of the cervix, breast or low risk Gleason 6 prostate cancer.
- Sexually active subjects (men and women) must agree to use medically accepted barrier methods of contraception (e.g., male or female condom) during the study and continue for 5 months (women) and 7 months (men) after the last dose of study drugs, even if oral contraceptives are also used. All subjects of reproductive potential must agree to use both a barrier method and a second method of birth control during the study and continue for 5 months (women) and 7 months (men) after the last dose of study drugs.

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

___ 3.2.1 Metastatic disease defined as new or progressive lesions on cross-sectional imaging or bone scan. Patients must have at least:

- One measurable site of disease as per RECIST v1.1
- One bone lesion on bone scan (tec99 or NaF PET/CT, CT or MRI) for the bone-only cohort.
- Histologically confirmed diagnosis of metastatic: small cell carcinoma of the bladder; adenocarcinoma of the bladder; squamous cell carcinoma of the bladder; plasmacytoid urothelial carcinoma; any penile cancer; sarcomatoid renal cell carcinoma; sarcomatoid urothelial carcinoma; renal medullary carcinoma or other miscellaneous histologic variants of the urothelial carcinoma, such as, but not limited to micropapillary, giant cell, lipid-rich, clear cell and nested variants, large cell neuroendocrine carcinoma, lymphoepithelioma-like carcinoma and mixed patterns will be considered, as well as small cell neuroendocrine prostate cancer, testicular Sertoli or Leydig cell tumors, and papillary and chromophobe RCC.
- H&E slides from diagnostic tumor tissue for retrospective central pathology review (See section 6.2).

___ 3.2.2 Patients may have received any number of prior anti-cancer treatments or be treatment naïve (with the exception of patients with small cell carcinoma of the bladder, whom should have received a platinum-based combination regimen either as neoadjuvant, adjuvant or first-line treatment)

___ 3.2.3 Age ≥18 years on day of consent.

___ 3.2.4 Patients must be able to swallow oral formulation of the tablets.

___ 3.2.5 Karnofsky performance status ≥70%.

___ 3.2.6 Required Laboratory Values:

Absolute Neutrophil Count (ANC)	≥1,200/mcL
Platelet Count	≥75,000/mcL
Total Bilirubin	≤1.5 × ULN. For subjects with known Gilbert's disease or similar syndrome with slow conjugation of bilirubin, total bilirubin ≤ 3.0 mg/dL
AST/ALT	≤3.0 × institutional upper limit of normal (ULN) (or ≤5 x ULN for patients with liver metastases or Gilbert's disease)
Creatinine	≤ 1.5 x upper limit of normal (ULN) **OR**
creatinine clearance	≥ 40 mL/min/1.73 m^2 (calculated using the CKD-EPI equation or Cockroft-Gault formula) for patients with creatinine levels above institutional normal.
hemoglobin	≥9 g/dL (transfusion of PRBCs allowed)
serum albumin	≥2.8g/dL

lipase and amylase	≤2.0 × ULN and no radiologic (on baseline anatomical imaging) or clinical evidence of pancreatitis

___ 3.2.7 Prior treatment with MET or VEGFR inhibitors is allowed. However, prior cabozantinib will not be allowed. Also, patients that have received both prior MET or VEGF and prior PD-1/PD-L1/CTLA-4 (sequentially or in combination) are also not allowed.

___ 3.2.8 Prior treatment with any therapy on the PD-1/PD-L1 axis or anti- CTLA-4/CTLA-4 inhibitors is allowed, either in the perioperative or in the metastatic setting. However, patients that have received both prior MET or VEGF and prior PD-1/PD-L1/CTLA-4 (sequentially or in combination) are not allowed.

___ 3.2.9 HIV-positive patients are eligible if on stable dose of highly active antiretroviral therapy (HAART), no clinically significant drug-drug interactions are anticipated with the current HAART regimen, CD4 counts are greater than 350 and viral load is undetectable.

___ 3.2.10 Patients with rheumatoid arthritis and other rheumatologic arthropathies, Sjögren's syndrome and psoriasis controlled with topical medication only and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies etc. are eligible but should be considered for rheumatologic evaluation for the presence of target organ involvement and potential need for systemic treatment.

___ 3.2.11 Patients with vitiligo, endocrine deficiencies including thyroiditis managed with replacement hormones or medications (eg thyrodidits managed with PTU or methamizole) including physiologic oral corticosteroids are eligible.

___ 3.2.12 Patients who have evidence of active or acute diverticulitis, intra-abdominal abscess, and GI obstruction, within 12 months are not eligible.

___ 3.2.13 Women of childbearing potential must have a negative pregnancy test ≤ 7 days prior to registration.

Women of childbearing potential include women who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are not postmenopausal. Post menopause is defined as amenorrhea ≥12 consecutive months. Note: women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, antiestrogens, ovarian suppression or any other reversible reason.

___ 3.2.14 Pregnant women may not participate in this study because with cabozantinib, nivolumab, and ipilimumab have potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with cabozantinib, nivolumab, and ipilimumab, breastfeeding should be discontinued if the mother is treated with these agents.

___ 3.2.15 The patient has received no cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) or biologic agents (e.g., cytokines or antibodies) within 2 weeks before the first dose of study treatment.

___ 3.2.16 The patient has received no radiation therapy:

- To the lungs and mediastinum or abdomen within 4 weeks before the first dose of study treatment, or has ongoing complications, or is healing from prior radiation therapy.
- To brain metastasis within 3 weeks for WBXRT, and 2 weeks for SBRT before the first dose of study treatment.
- To any other site(s) within 2 weeks before the first dose of study treatment.

___ 3.2.17 The patient has received no radionuclide treatment within 6 weeks of the first dose of study treatment.

___ 3.2.18 The patient has received no prior treatment with a small molecule kinase inhibitor within 14 days or five half-lives of the compound or active metabolites, whichever is longer, before the first dose of study treatment.

___ 3.2.19 The patient has received no prior treatment with hormonal therapy within 14 days or five half-lives of the compound or active metabolites, whichever is longer, before the first dose of study treatment. Subjects receiving Gonadotropin-releasing hormone (GnRH) agonists and antagonists are allowed to participate.

___ 3.2.20 The patient has not received any other type of investigational agent within 14 days before the first dose of study treatment.

___ 3.2.21 The patient must have recovered to baseline or CTCAE ≤ Grade 1 from toxicity due to all prior therapies except alopecia, neuropathy and other non-clinically significant AEs defined as lab elevation with no associated symptoms or sequelae.

___ 3.2.22 The patient may not have active brain metastases or epidural disease. Patients with brain metastases previously treated with whole brain radiation or radiosurgery or subjects with epidural disease previously treated with radiation or surgery who are asymptomatic and do not require steroid treatment for at least 2 weeks before starting study treatment are eligible. Neurosurgical resection of brain metastases or brain biopsy is permitted if completed at least 3 months before starting study treatment. Baseline brain imaging with contrast-enhanced CT or MRI scans for subjects with known brain metastases is required to confirm eligibility.

___ 3.2.23 No concomitant treatment with warfarin. Aspirin (up to 325 mg/day), thrombin or factor Xa inhibitors, low-dose warfarin (≤1 mg/day), prophylactic and therapeutic low molecular weight heparin (LMWH) are permitted.

___ 3.2.24 No chronic concomitant treatment with strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John's Wort) or strong CYP3A4 inhibitors. See Appendix IV.

Because the lists of these agents are constantly changing, it is important to regularly consult medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the patient will

be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. A patient information sheet is provided in Appendix IV.

___ 3.2.25 The patient has not experienced any of the following:

- Clinically-significant gastrointestinal bleeding within 6 months before the first dose of study treatment.
- Hemoptysis of ≥ 0.5 teaspoon (2.5 mL) of red blood per day within 1 months before the first dose of study treatment.
- Any other signs indicative of pulmonary hemorrhage within 3 months before the first dose of study treatment.

___ 3.2.26 The patient has no tumor invading any major blood vessels.

___ 3.2.27 The patient has no evidence of tumor invading the GI tract (esophagus, stomach, small or large bowel, rectum or anus), or any evidence of endotracheal or endobronchial tumor within 28 days before the first dose of cabozantinib.

___ 3.2.28 The patient has no uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

1. Cardiovascular disorders including:
   a) Congestive heart failure (CHF): New York Heart Association (NYHA) Class III (moderate) or Class IV (severe) at the time of screening.
   b) Concurrent uncontrolled hypertension defined as sustained BP > 150 mm Hg systolic, or > 90 mm Hg diastolic despite optimal antihypertensive treatment within 7 days of the first dose of study treatment.
   c) The subject has a corrected QT interval calculated by the Fridericia formula (QTcF) >500 ms within 28 days before randomization. Note: if initial QTcF is found to be > 500 ms, two additional EKGs separated by at least 3 minutes should be performed. If the average of these three consecutive results for QTcF is ≤500 ms, the subject meets eligibility in this regard.
   d) Any history of congenital long QT syndrome.
   e) Any of the following within 6 months before registration of study treatment:
      • unstable angina pectoris
      • clinically-significant cardiac arrhythmias (patients with atrial fibrillation are eligible)
      • stroke (including TIA, or other ischemic event)
      • myocardial infarction
      • cardiomyopathy
2. No significant gastrointestinal disorders particularly those associated with a high risk of perforation or fistula formation including:
   a) Any of the following that have not resolved within 28 days before the first dose of study treatment:
      • Intra-abdominal tumor/metastases invading GI mucosa

- Active peptic ulcer disease
- Diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, or malabsorption syndrome

b) None of the following within 1 year before the first dose of study treatment:

- abdominal fistula or genitourinary fistula
- gastrointestinal perforation
- bowel obstruction or gastric outlet obstruction
- intra-abdominal abscess. Note: Complete resolution of an intra-abdominal abscess must be confirmed prior to initiating treatment with cabozantinib even if the abscess occurred more than 12 months before the first dose of study treatment.

3. Disorders associated with a high risk of fistula formation including PEG tube placement are not eligible.
4. No other clinically significant disorders such as:

a) severe active infection requiring IV systemic treatment within 14 days before the first dose of study treatment

b) serious non-healing wound/ulcer/bone fracture within 28 days before the first dose of study treatment

c) history of organ or allogeneic stem cell transplant

d) concurrent uncompensated hypothyroidism or thyroid dysfunction within 7 days before the first dose of study treatment (for asymptomatic patients with an elevated TSH, thyroid replacement may be initiated if clinically indicated without delaying the start of study treatment)

5. No history of major surgery as follows:

- Major surgery within 3 months of the first dose of cabozantinib; however, if there were no wound healing complications, patients with rapidly growing aggressive cancers, may start as soon as 6 weeks if wound has completely healed post-surgery.
- Minor surgery within 1 month of the first dose of cabozantinib if there were no wound healing complications or within 3 months of the first dose of cabozantinib if there were wound complications excluding core biopsies and mediport placement.
- Complete wound healing from prior surgery must be confirmed before the first dose of cabozantinib irrespective of the time from surgery.

___ 3.2.29 No history of severe hypersensitivity reaction to any monoclonal antibody.

3.2.30 No evidence of active malignancy, requiring systemic treatment within 2 years of registration.

3.2.31 No history of allergic reactions attributed to compounds of similar chemical or biologic composition to cabozantinib, nivolumab, ipilimumab or other agents used in study.

3.2.32 No positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection.

3.2.33 No patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids. These include, but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease.