# Testing the Addition of an Anti-Cancer Drug, Cabozantinib to the Immunotherapy Drug Cemiplimab (REGN2810), in Adolescents and Adults With Advanced Adrenocortical Cancer

**Status:** RECRUITING

## Eligibility Criteria

**Age:** 12 years and over

This study is NOT accepting healthy

**Healthy Volunteers:** volunteers

**Inclusion Criteria:**

* STEP 1: Patients must have documented histologically or cytologically confirmed adrenocortical carcinoma * STEP 1: Locally advanced unresectable or recurrent/metastatic disease * STEP 1: Evaluable disease as defined by RECIST v 1.1 * STEP 1: Up to 3 prior lines of systemic therapy will be allowed in the unresectable/recurrent/metastatic setting. Treatment naïve patients will be allowed. * Note: Combination etoposide, doxorubicin, cisplatin, and mitotane (EDP-M) is considered 1 line of therapy. For patients who received mitotane ≤ 6 months prior to registration, mitotane should be discontinued 28 days prior to study registration AND a mitotane level must be documented to be \< 2 mg/L prior to registration. Patients who have received mitotane within 6 months of enrollment and who have mitotane levels ≥ 2 mg/L will not be eligible to enroll * STEP 1: No prior treatment with cabozantinib or other cMET inhibitors, or anti-CTLA-4, or anti-PD-1/PD-L1 therapy * STEP 1: Prior external beam radiation therapy (any area radiated within a month prior to study registration cannot be used as an index lesion and only growth outside of the radiation field can be considered for disease progression), systemic cytotoxic chemotherapy, targeted therapies will be allowed, as long as not administered within 14 days before study registration, and provided any acute treatment-related associated toxicities have recovered to ≤ grade 1 except for alopecia, peripheral neuropathy or other residual toxicities that are not deemed clinically significant * STEP 1: Potential trial participants should have recovered from clinically significant adverse events, and wound healing is clinically adequate of their most recent therapy/intervention prior to enrollment * STEP 1: Age 12 years and above; and BSA ≥ 1.2m\^2 * STEP 1: * Eastern Cooperative Oncology Group (ECOG) performance 0

•2 (age 18 and above); or * Patients 12 to \<16 years of age will be assessed by the Lansky scale and should have a score ≥ 50; or * Patients ≥ 16 to \<18 years of age will be assessed by the Karnofsky scale, and should have a score ≥ 50 * STEP 1: Absolute neutrophil count (ANC) ≥ 1,000/mcL without colony stimulating factor support within 2 weeks prior * Transfusion support is allowed if ≥ 7 days from obtaining required initial laboratory * STEP 1: Platelet count ≥ 100,000/mcL * Transfusion support is allowed if ≥ 7 days from obtaining required initial laboratory * STEP 1: Hemoglobin ≥ 8 g/dL * Transfusion support is allowed if ≥ 7 days from obtaining required initial laboratory * STEP 1: Total bilirubin ≤ 1.5 x upper limit of normal (ULN) * For patients with known Gilbert's disease, bilirubin ≤ 3 mg/dL * STEP 1: Aspartate aminotransferase (AST)(serum glutamic oxaloacetic transaminase \[SGOT\])/ alanine aminotransferase (ALT) (serum glutamic pyruvic transaminase \[SGPT\]) ≤ 3 x upper limit of normal (ULN) * STEP 1: Random Urine Creatinine Ratio (UPCR) ≤ 1 mg/mg * STEP 1: Calculated (Calc.) creatinine clearance ≥ 30 mL/min * STEP 1: Mitotane level \< 2 mg/L* * Only applicable for patients who have received mitotane ≤ 6 months prior to registration * STEP 1: Must have assessment of adrenal steroid production within 3 months prior to registration as patients will be stratified based on corticosteroid production * Patients will be classified as corticosteroid producing if random plasma adrenocorticotropic hormone (ACTH) is \< 20 pg/mL plus random serum cortisol is \> 20 mcg/dL in the absence of anti-cortisol therapy. Patients already on anti-cortisol therapy will be classified as having corticosteroid producing tumors regardless of their plasma ACTH and serum cortisol levels, as these levels can be affected by anti-cortisol therapy * STEP 1: Not pregnant and not nursing, because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects based on animal reproduction studies. Therefore, for women of childbearing potential only, a negative urine or serum pregnancy test, per institution standard, done ≤ 14 days prior to registration is required * STEP 1: Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional within 28 days of registration. To be eligible for this trial, patients should be class II or better * STEP 1: No known history of congenital long QT syndrome * STEP 1: No known history of myocarditis * STEP 1: No myocardial infarction (MI) or unstable angina within 6 months of registration * STEP 1: No clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding within 6 months of registration including, but not limited to: active peptic ulcer, known endoluminal metastatic lesion(s) with history of bleeding, inflammatory bowel disease, or other gastrointestinal conditions with increased risk of perforation * STEP 1: No history of gastrointestinal (GI) perforation within 6 months of registration * STEP 1: No known tumor with invasion into the GI tract from the outside causing increased risk of perforation or bleeding within 28 days of registration * STEP 1: No current radiologic or clinical evidence of pancreatitis * STEP 1: No history of clinically significant non-healing wounds or ulcers within 28 days of registration * STEP 1: No uncontrolled hypertension within 14 days of registration (defined as sustained systolic blood pressure (SBP) ≥ 150 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg despite optimal medical management) * STEP 1: No known endobronchial lesions involving the main or lobar bronchi and/or lesions infiltrating major pulmonary vessels that increase the risk of pulmonary hemorrhage. (CT with contrast is recommended to evaluate such lesions.). No hemoptysis greater than ½ teaspoon (2.5 mL) or any other signs of pulmonary hemorrhage within the 3 months prior to registration * STEP 1: No history of pneumonitis * STEP 1: No known tumor invading or encasing any major blood vessels * STEP 1: No history of fracture within 28 days of registration * STEP 1: No known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 4 weeks after major surgery (e.g., removal or biopsy of brain metastasis) before registration. Eligible patients must be neurologically asymptomatic and without corticosteroid treatment at the time of the start of study treatment * STEP 1: Major surgery (e.g., laparoscopic nephrectomy, GI surgery, within 2 weeks before registration. Minor surgeries within 10 days before registration. Patients with clinically relevant ongoing complications from prior surgery are not eligible * STEP 1: Verbalizes the ability to swallow oral tablet formulation * STEP 1: No history of allergic reaction attributed to compounds of similar chemical or biological composition to cabozantinib * STEP 1: Patients 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 will be eligible * STEP 1: HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months prior to registration are eligible for this trial * STEP 1: For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated * STEP 1: Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load * STEP 1: No active autoimmune disease: or history of autoimmune disease that might recur, and 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 (GBS), myasthenia gravis, * systemic autoimmune disease such as systemic lupus erythematosus (SLE), * connective tissue diseases, * scleroderma, inflammatory bowel disease (IBD), * Crohn's, ulcerative colitis, * 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, * Patients with vitiligo, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible, * Patients with rheumatoid arthritis and other arthropathies, Sjögren's syndrome, and psoriasis controlled with topical medication and patients with only positive serology, such as antinuclear antibodies (ANA) or anti-thyroid antibodies, should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible * STEP 1: No steroid use \> 10 mg prednisone equivalents daily. A brief course of corticosteroids for prophylaxis or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by contact allergen) is permitted, as is steroid pre-medication for contrast allergy * STEP 1: Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed on this study. Patients on strong CYP3A4 inhibitors must discontinue the drug for 14 days prior to registration on the study * STEP 1: Chronic concomitant treatment with strong CYP3A4 inducers is not allowed. Patients must discontinue the drug 14 days prior to the start of study treatment * STEP 1: Herbal supplements and traditional Chinese medicines are not allowed * STEP 1: Active treatment with coumarin agents (e.g., warfarin), direct thrombin inhibitors (e.g., dabigatran), direct Xa inhibitor betrixaban or platelet inhibitors (e.g., clopidogrel) within 5

days of registration. Allowed use of anticoagulants include: prophylactic use of low-dose aspirin for cardio-protection (per local applicable guidelines) and low-dose low molecular weight heparins (LMWH), therapeutic doses of LMWH or anticoagulation with direct factor Xa inhibitors rivaroxaban, edoxaban, apixaban. Also use of anticoagulants is allowed in patients with known brain metastases who are on a stable dose of the anticoagulant for at least 1 week prior to registration without clinically significant hemorrhagic complications from the anticoagulation regimen or the tumor * STEP 2 (CROSSOVER): Patients must have demonstrated radiographic progression of disease on cabozantinib monotherapy (Arm A) per RECIST version 1.1 criteria * Patients must cross-over to Arm C within 4 weeks (+/- 1 week) after radiographic documented progression and do not need to have a repeat radiographic assessment prior to starting cabozantinib and cemiplimab (REGN2810). The progression CT may serve as eligibility for crossover and as the baseline tumor measurement * STEP 2 (CROSSOVER): Patients that were discontinued on cabozantinib, or currently meet criteria for discontinuation of cabozantinib due to toxicity are not eligible to cross-over. * Note: Patients who underwent dose reduction of cabozantinib during treatment on Arm A will not re-escalate dose at or after cross-over to Cabo-Cemiplimab (REGN2810) (Arm B) * STEP 2 (CROSSOVER): Not pregnant and not nursing, because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects. Therefore, for women of childbearing potential only, a negative serum or urine pregnancy test done ≤ 14 days prior to re-registration is required

## Conditions & Interventions

**Interventions:**
PROCEDURE: Biospecimen Collection, DRUG: Cabozantinib, BIOLOGICAL: Cemiplimab, PROCEDURE: Computed Tomography, PROCEDURE: Magnetic Resonance Imaging
**Conditions:**
Locally Advanced Adrenal Cortical Carcinoma, Metastatic Adrenal Cortical Carcinoma, Recurrent Adrenal Cortical Carcinoma, Stage III Adrenal Cortical Carcinoma AJCC v8, Stage IV Adrenal Cortical Carcinoma AJCC v8, Unresectable Adrenal Cortical Carcinoma

## More Information

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