

TYPE OF CANCER: Metastatic Renal Cancer
TYPE OF TRIAL: Phase III
TRIAL SPONSOR: Pfizer

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STUDY SUMMARY

Axitinib (AG-013736) As Second Line Therapy For Metastatic Renal Cell Cancer:
AXIS TRIAL

TREATMENT OVERVIEW

- Each cycle is 4 weeks long
- Patient should be seen by the physician every 2 weeks x2, then every 4 weeks
- Patients may continue to participate in the study unless they experience unacceptable toxicity or disease progression.

PRETREATMENT ASSESMENT

The following screening procedures must be performed within 28 days prior to treatment on-study unless otherwise stated on schedule of events:

- Patient signature on current IRB-approved informed consent form prior to any study specific procedure (may be done >28 days prior to treatment);
- Medical history including cancer history, history of other disease processes (active or resolved), concomitant illnesses, and demographics;
- Physical examination including examination of major body systems, ECOG performance status, body weight, height (screening only), and vital signs (temperature, blood pressure, heart rate, respiratory rate) and 12 Lead EKG/ ECG
- Hematology, Chemistry, Thyroid function tests
- Urinalysis
- Pregnancy test (serum or urine), if applicable.
- CT or MRI scans of chest, abdomen and pelvis in addition to any other applicable sites of disease

- Brain CT or MRI scan
- Bone scan
- Assessment of concomitant medications and treatments
- Assessment of ongoing symptoms/events (serious adverse events must be recorded from time of signed consent)
- Study randomization.

ENTRANCE CRITERIA FOR PARTICIPATION IN TRIAL

Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the trial:

1. Histologically confirmed metastatic renal cell cancer with a component of clear cell histology.
2. Evidence of unidimensionally measurable disease (ie, ≥ 1 malignant tumor mass that can be accurately measured in at least 1 dimension ≥ 20 mm with conventional computerized tomography [CT] scan or Magnetic Resonance Imaging [MRI], or ≥ 10 mm with spiral CT scan using a 5 mm or smaller contiguous reconstruction algorithm). Bone lesions, ascites, peritoneal carcinomatosis or miliary lesions, pleural or pericardial effusions, lymphangitis of the skin or lung, cystic lesions, or irradiated lesions are not considered measurable.
3. Must have failed (experienced disease progression as defined below) one prior systemic first-line regimen for metastatic renal cell cancer. The prior regimen must have contained one or more of the following: sunitinib, bevacizumab + IFN α , temsirolimus, or cytokine(s).
 - Disease progression will be defined by RECIST documented by 2 sets of CT/MRI (or sets of chest x-rays, bone scans, or x-rays of bone lesion) performed any time within period of 4 weeks prior to the first dose of prior therapy to 4 months after the last dose of prior treatment showing objective evidence of disease progression. These pre-study scans or x-rays documenting disease progression must be confirmed by the Principal Investigator prior to enrollment in the study (after patient enrollment, pre-study scans or x-rays must be submitted to independent third-party imaging core laboratory for retrospective review). Patients who discontinue first-line therapy without evidence of disease progression whilst on first-line therapy must subsequently have documented evidence (eg, CT/MRI scan) of disease progression within 4 months after the last dose of their previous regimen.

4. Adequate organ function as defined by the following criteria:
 - absolute neutrophil count (ANC) ≥ 1500 cells/mm³;
 - platelets $\geq 75,000$ cells/mm³.
 - Hemoglobin ≥ 9.0 g/d.
 - AST and ALT ≤ 2.5 x upper limit of normal (ULN), unless there are liver metastases in which case AST and ALT ≤ 5.0 x ULN;
 - Total bilirubin ≤ 1.5 x ULN;
 - Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance ≥ 60 mL/min;
 - Urinary protein $< 2+$ by urine dipstick. If dipstick is $\geq 2+$ then a 24-hour urine collection can be done and the patient may enter only if urinary protein is < 2 g per 24 hours.
5. Male or female, age ≥ 18 years.
6. ECOG performance status of 0 or 1 (See Appendix 4).
7. Life expectancy of ≥ 12 weeks.
8. At least 2 weeks since the end of prior systemic treatment (4 weeks for bevacizumab + FN α), radiotherapy, or surgical procedure with resolution of all treatment-related toxicity to NCI CTCAE Version 3.0 grade ≤ 1 or back to baseline except for alopecia.
9. No evidence of preexisting uncontrolled hypertension as documented by 2 baseline blood pressure readings taken at least 1 hour apart. The baseline systolic blood pressure readings must be ≤ 140 mm Hg, and the baseline diastolic blood pressure readings must be ≤ 90 mm Hg. Patients whose hypertension is controlled by antihypertensive therapies are eligible.
10. Women of childbearing potential must have a negative serum or urine pregnancy test within 3 days prior to treatment.
11. Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all pertinent aspects of the trial prior to enrollment.
12. Willingness and ability to comply with scheduled visits, treatment plans (including willingness to take either AG-013736 or sorafenib according to randomization), laboratory tests, and other study procedures, including completion of patient-reported outcome measures (FKSI and EQ-5D questionnaires).

Exclusion Criteria

Subjects presenting with any of the following will not be included in the trial:

1. Prior treatment of mRCC with more than one systemic first-line regimen.
2. Patients treated with any neoadjuvant or adjuvant systemic therapy.
3. Major surgery <4 weeks or radiation therapy <2 weeks of starting the study treatment. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided there is at least one measurable lesion that has not been irradiated.
4. Gastrointestinal abnormalities including:
 - inability to take oral medication;
 - requirement for intravenous alimentation;
 - prior surgical procedures affecting absorption including total gastric resection;
 - treatment for active peptic ulcer disease in the past 6 months;
 - active gastrointestinal bleeding, unrelated to cancer, as evidenced by hematemesis, hematochezia or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy;
 - malabsorption syndromes.
5. Current use or anticipated need for treatment with drugs that are known potent CYP3A4 inhibitors (ie, grapefruit juice, verapamil, ketoconazole, miconazole, itraconazole, erythromycin, telithromycin, clarithromycin, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir and delavirdine).
6. Current use or anticipated need for treatment with drugs that are known CYP3A4 or CYP1A2 inducers (ie, carbamazepine, dexamethasone, felbamate, omeprazole, phenobarbital, phenytoin, amobarbital, nevirapine, primidone, rifabutin, rifampin, and St. John's wort).
7. Requirement of anticoagulant therapy with oral vitamin K antagonists. Low-dose anticoagulants for maintenance of patency of central venous access device or prevention of deep venous thrombosis is allowed. Therapeutic use of low molecular weight heparin is allowed.
8. Active seizure disorder or evidence of brain metastases, spinal cord compression, or carcinomatous meningitis.
9. A serious uncontrolled medical disorder or active infection that would impair their ability to receive study treatment.
10. Any of the following within the 12 months prior to study drug administration: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack and 6 months for deep vein thrombosis or pulmonary embolism.

11. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

12. History of a malignancy (other than renal cell cancer) except those treated with curative intent for skin cancer (other than melanoma), in situ breast or in situ cervical cancer, or those treated with curative intent for any other cancer with no evidence of disease for 2 years.

13. Dementia or significantly altered mental status that would prohibit the understanding or rendering of informed consent and compliance with the requirements of this protocol.

14. Female patients who are pregnant or lactating, or men and women of reproductive potential not willing or not able to employ an effective method of birth control/contraception to prevent pregnancy during treatment and for 6 months after discontinuing study treatment. The definition of effective contraception should be in agreement with local regulation and based on the judgment of the principal investigator or a designated associate.

15. Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for entry into this study.