

**TYPE OF CANCER:** Locally Advanced and/or Metastatic Renal Cell Carcinoma  
**TYPE OF TRIAL:** Phase III  
**TRIAL SPONSOR:** GlaxoSmithKline

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### **STUDY SUMMARY**

Study VEG108844, a Study of Pazopanib versus Sunitinib in the Treatment of Subjects with Locally Advanced and/or Metastatic Renal Cell Carcinoma

### **TREATMENT OVERVIEW**

- Patients will be randomized to receive either Pazopanib by mouth daily, continuously or Sunitinib by mouth daily in 6 week cycles of dosing for 4 weeks of treatment and 2 weeks off
- On treatment assessments will be performed on day 14 of cycle 1 and then days 28 and 42 of all cycles
- After disease progression, survival status will be assessed every 3 months

### **PRE-TREATMENT ASSESSMENTS**

- Informed consent
- Eligibility
- Demography
- Medical history
- Serum pregnancy test (if applicable)
- Disease assessments by CT scan or MRI
- Bone scan
- Physical exam
- Vital signs
- Performance status
- ECG
- Echocardiogram
- Clinical Chemistry
- Hematology
- Coagulation tests
- Urine protein to creatinine ratio
- Amylase and Lipase
- Lipid panel
- Thyroid function tests

## **ENTRANCE CRITERIA FOR PARTICIPATION IN TRIAL**

### *INCLUSION CRITERIA*

1. Subjects must provide written informed consent prior to performance of any study-specific procedures or assessments, and must be willing to comply with treatment and follow up. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol. **Note:** It is not necessary that informed consent be obtained within the protocol-specified screening window.
2. Diagnosis of renal cell carcinoma with clear-cell component histology.
3. Received no prior systemic therapy (interleukin-2, interferon- $\alpha$ , chemotherapy, bevacizumab, mTOR inhibitor, sunitinib, sorafenib or other VEGF TKI) for advanced or metastatic RCC
4. Locally advanced (defined as disease not amenable to curative surgery or radiation therapy) or metastatic RCC (equivalent to Stage IV RCC according to AJCC staging).
5. Must have measurable disease per RECIST. A measurable lesion is defined as a lesion that can be accurately measured in at least one dimension with the longest diameter  $\geq 20$  mm using conventional techniques, or  $\geq 10$  mm with spiral CT scan.  
**Note:** Subject should be excluded if all baseline measurable lesions are within previously irradiated areas.
6. KPS of  $\geq 70$
7. Age  $\geq 18$  years old
8. A female is eligible to enter and participate in this study if she is of:  
Non-childbearing potential (i.e., physiologically incapable of becoming pregnant), including any female who has had:
  - A hysterectomy
  - A bilateral oophorectomy (ovariectomy)
  - A bilateral tubal ligation
  - Is post-menopausal

Subjects not using hormone replacement therapy (HRT) must have experienced total cessation of menses for  $\geq 1$  year and be greater than 45 years in age, OR, in questionable cases, have a follicle stimulating hormone (FSH) value  $>40$  mIU/mL and an estradiol value  $<40$ pg/mL ( $<140$  pmol/L).

Subjects must discontinue HRT prior to study enrolment due to the potential for inhibition of Cytochrome P450 (CYP) enzymes that metabolize estrogens and progestins. For most forms of HRT, at least 2-4 weeks must elapse between the cessation of HRT and determination of menopausal status; length of this interval depends on the type and dosage of HRT. If a female subject is determined not to

be post-menopausal, they must use adequate contraception, as defined immediately below.

Childbearing potential, including any female who has had a negative serum pregnancy test within 2 weeks prior to the first dose of study treatment, preferably as close to the first dose as possible, and agrees to use adequate contraception. GSK acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follow:

- An intrauterine device with a documented failure rate of less than 1% per year.
- Vasectomized partner who is sterile prior to the female subject’s entry and is the sole sexual partner for that female.
- Complete abstinence from sexual intercourse for 14 days before exposure to investigational product, through the dosing period, and for at least 21 days after the last dose of investigational product.
- Double-barrier contraception (condom with spermicidal jelly, foam suppository, or film; diaphragm with spermicide; or male condom and diaphragm with spermicide).

**Note:** Oral contraceptives are not reliable due to potential drug-drug interactions.

Female subjects who are lactating should discontinue nursing prior to the first dose of study drug and should refrain from nursing throughout the treatment period and for 14 days following the last dose of study drug.

A male with a female partner of childbearing potential is eligible to enter and participate in the study if he uses a barrier method of contraception or abstinence during the study.

#### 9. Adequate organ system functions

System	Laboratory Values
<b>Hematologic</b>	
Absolute neutrophil count (ANC)	$\geq 1.5 \times 10^9/L$
Hemoglobin <sub>1</sub>	$\geq 9 \text{ g/dL}$
Platelets	$\geq 100 \times 10^9/L$
International normalized ratio (INR)	$\leq 1.2 \times \text{upper limit of normal (ULN)}$
Partial thromboplastin time (PTT)	$\leq 1.2 \times \text{ULN}$
<b>Hepatic</b>	
Total bilirubin	$\leq 1.5 \times \text{ULN}$
AST and ALT	$\leq 2.5 \times \text{ULN}$
<b>Renal</b>	
Calculated creatinine clearance	$\geq 30 \text{ mL/min}$
Urine Protein to Creatinine Ratio (UPC) <sub>2</sub>	$< 1$

1. Subjects may not have had a transfusion within 7 days of screening assessment.

2. If UPC  $\geq$ 1, then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value  $<$ 1g to be eligible.

10. Total serum calcium concentration  $<$ 12.0mg/dL

11. Left ventricular ejection fraction (LVEF)  $\geq$ lower limit of institutional normal (LLN) as assessed by echocardiography or multigated acquisition (MUGA) scan. The same modality used at baseline must be applied for subsequent evaluations.

### **EXCLUSION CRITERIA**

1. Pregnant or lactating female

**Note:** Lactating females who discontinue nursing prior to the first dose of study drug and agree to refrain from nursing throughout the treatment period and for 14 days following the last dose of study drug are eligible.

2. History of another malignancy.

**Note:** Subjects who have had another malignancy and have been disease-free for 3 years, or subjects with a history of completely resected non-melanomatous skin carcinoma or successfully treated *in situ* carcinoma are eligible.

3. History or clinical evidence of central nervous system (CNS) metastases.

**Note:** Subjects who have previously-treated CNS metastases (surgery  $\pm$  radiotherapy, radiosurgery, or gamma knife) and meet all 3 of the following criteria are eligible:

a. Are asymptomatic

and,

b. Have had no evidence of active CNS metastases for  $\geq$ 6 months prior to enrolment

and,

c. Have no requirement for steroids or enzyme-inducing anticonvulsants (EIA)

4. Clinically significant gastrointestinal abnormalities including, but not limited to:

a. Malabsorption syndrome

b. Major resection of the stomach or small bowel that could affect the absorption of study drug

c. Active peptic ulcer disease

d. Inflammatory bowel disease

e. Ulcerative colitis, or other gastrointestinal conditions with increased risk of perforation

f. History of abdominal fistula, gastrointestinal perforation, or intra abdominal abscess within 28 days prior to beginning study treatment.

5. Presence of uncontrolled infection.

6. Prolongation of corrected QT interval (QTc)  $>$  480 milliseconds (msecs).

7. History of any one or more of the following cardiovascular conditions within the past 12 months:

a. Cardiac angioplasty or stenting

b. Myocardial infarction

c. Unstable angina

d. Symptomatic peripheral vascular disease

- e. Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA)
8. History of cerebrovascular accident (CVA) including transient ischemic attack (TIA)
  9. History of pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.  
Note: Subjects with recent DVT who have been treated with therapeutic anticoagulating agents for at least 6 weeks are eligible.
  10. Poorly controlled hypertension [defined as systolic blood pressure (SBP) of  $\geq 150$ mmHg or diastolic blood pressure (DBP) of  $\geq 90$ mmHg].  
Note: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. Blood pressure must be re-assessed on two occasions that are separated by a minimum of 24 hours. The mean SBP/DBP values from each blood pressure assessment must be  $< 150/90$ mmHg in order for a subject to be eligible for the study.
  11. Prior major surgery or trauma within 28 days prior to first dose of study drug and/or presence of any non-healing wound, fracture, or ulcer.
  12. Evidence of active bleeding or bleeding diathesis
  13. Hemoptysis within 6 weeks of first dose of study drug.
  14. Any serious and/or unstable pre-existing medical, psychiatric, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study.
  15. Use any prohibited medications within 14 days of the first dose of study medication.
  16. Use of an investigational agent, including an investigational anti-cancer agent, within 28 days or 5 half-lives, whichever is longer, prior to the first dose of study drug.
  17. Prior use of an investigational or licensed drug that targets VEGF or VEGF receptors (eg. bevacizumab, sunitinib, sorafenib, etc), or are mTOR inhibitors (eg. temsirolimus, everolimus, etc).
  18. Is now undergoing and/or has undergone in the 14 days immediately prior to first dose of study drug, any cancer therapy (surgery, tumor embolization, chemotherapy, radiation therapy, immunotherapy, biological therapy, or hormonal therapy)
  19. Any ongoing toxicity from prior anti-cancer therapy that is  $>$ Grade 1 and/or that is progressing in severity.
  20. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to pazopanib or sunitinib.