Patient preference for tivozanib hydrochloride or sunitinib in the treatment of metastatic renal cell carcinoma (mRCC): TAURUS study design

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Background

- Vascular endothelial growth factor receptors (VEGFRs) play a critical role during tumor angiogenesis via the promotion of endothelial cell proliferation, migration, and survival[1]
- Most cases of renal cell carcinoma (RCC) are characterized by a loss of function of the von Hippel-Lindau tumor suppressor gene, which results in an increase in expression of vascular endothelial growth factor (VEGF) and a subsequent increase in tumor angiogenesis[2]
- Tivozanib hydrochloride (tivozanib) is a potent and selective inhibitor of VEGFRs 1, 2, and 3[3]
- Previous Phase II and Phase III studies have demonstrated the efficacy and safety of tivozanib in patients with mRCC[4,5]
- Currently, sunitinib is a commonly used first-line treatment in patients with mRCC[6]
- With the availability of multiple approved therapies for mRCC, treatment choices may be influenced by the adverse event profiles of different therapies
- Patient preference may be an important tool to help patients and physicians in selecting an appropriate treatment[7]
- The goal of this study is to investigate the patient treatment preference for tivozanib or sunitinib for the treatment of mRCC

Key Eligibility Criteria

Inclusion Criteria

- Unresectable mRCC
- Histologically or cytologically confirmed RCC of any histology
- Patients with or without prior nephrectomy
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

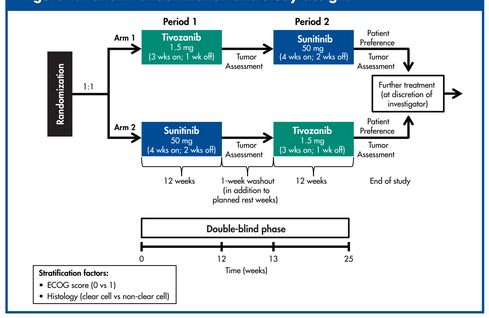
Exclusion Criteria

- Any prior systemic therapy for treatment of mRCC (including investigational or licensed drugs that target VEGF or VEGF receptors/pathway, or are mammalian target of rapamycin [mTOR] inhibitors)
- Central nervous system malignancies or metastases
- Significant hematologic, gastrointestinal, thromboembolic, vascular, bleeding, or coagulation disorders
- Significant serum chemistry or urinalysis abnormalities
- Significant cardiovascular disease
  - Uncontrolled hypertension
  - Myocardial infarction or severe angina within 6 months prior to administration of first dose of study drug
- Corrected QT interval of >480 msec using Bazett's formula
- Currently active second primary malignancy

Study Design

- Phase II, randomized, double-blind, multinational, multicenter, two-arm crossover study
- One hundred and sixty patients in Western Europe and the United States
- Patients are stratified for ECOG score (0 vs 1) and histology (clear cell vs non-clear cell) and then randomized 1:1 to one of two treatment arms
- Patients randomized to Arm 1 will receive 1.5 mg oral tivozanib daily on a 3 weeks on/1 week off schedule for 12 weeks (3 cycles) followed by 50 mg oral sunitinib daily on a 4 weeks on/2 weeks off schedule for 12 weeks (2 cycles)
- Patients randomized to Arm 2 will receive 50 mg oral sunitinib daily on a 4 weeks on/2 weeks off schedule for 12 weeks (2 cycles) followed by 1.5 mg oral tivozanib daily on a 3 weeks on/1 week off schedule for 12 weeks (3 cycles)
- Patients will receive double-blinded (over-encapsulated) tivozanib and sunitinib
  - Over-encapsulated placebo will be given during the treatment off-weeks in order to maintain the blind
- There will be a 1-week washout period, in addition to the treatment off-week(s), between the two treatment periods, as shown in **Figure 1**

Figure 1. Patient randomization and study design.



ECOG, Eastern Cooperative Oncology Group.

- Upon completion of the first 12 weeks of study treatment, all patients will have a tumor assessment and will be informed of their disease assessment result
- Assessment of adverse events (AEs) will be done to establish a baseline AE profile prior to initiation of Drug 2
- All patients are planned to continue the study and to cross over to the second treatment period regardless of their tumor response
  - However, patients with a significant clinical response may continue receiving the same treatment as during the first 12 weeks if the patient prefers it. The patient will continue treatment open-label off the study (sunitinib) or as part of a separate, long-term follow-up study (tivozanib)
- Patients with controlled disease or progressive disease (PD) at the end of the first 12-week treatment period will remain blinded and will cross over as planned to the second treatment for 12 weeks, following the washout period
- Patients who experience PD or unacceptable toxicities during the first treatment period may withdraw early and cross over once toxicities have resolved
- At the end of the study, further treatment is at the discretion of the investigator and patient preference

Dose Interruption and Reduction

- Patients with clinically significant Grade 3/4 AEs that are assessed as being study drug related by the investigator should have their dose interrupted to allow for resolution of toxicities to baseline
- Upon resolution of toxicities, dosing may resume at the initial dose or a reduced dose at the investigator's discretion
- Dose reduction to 1.0 mg/day for tivozanib and to 37.5 mg/day for sunitinib will be allowed
  - Once a dose is reduced, it may not be re-escalated
- Hypertension must be treated with antihypertensive drugs prior to dose reduction

Study Objectives

Primary Objective

- To compare patient treatment preference of tivozanib vs sunitinib

Secondary Objectives

- To compare overall safety and tolerability
- To assess the frequency of dose modifications
- To evaluate quality of life (QoL), including kidney-specific symptoms and fatigue

Exploratory

- To assess anti-tumor activity of tivozanib and sunitinib at 12 weeks
- To compare progression-free survival (PFS) at 25 weeks
- To assess QoL using the Functional Assessment of Cancer Therapy-Anti-Angiogenic (FACT-AntiA) questionnaire

Criteria for Evaluation and Statistical Analysis

Patient Treatment Preference

- A questionnaire will be used to document patient treatment preference and reason(s) at the end of the 25-week treatment period. After the questionnaire is completed, the patients will be unblinded and informed of the result of the end-of-treatment disease assessment

Efficacy

- Response Evaluation Criteria In Solid Tumors (version 1.1) will be used to assess disease status
- Radiology assessments will be performed after the end of each 12-week period
- Patients who withdraw early from either treatment period will have their disease status assessed immediately

Safety

- National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) will be used for grading toxicities
- Patients will be monitored for occurrence of AEs from the time of signing the informed consent form throughout study treatment and at the 30-day post-treatment safety visit

Quality of Life

- The Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS), EQ-5D, Functional Assessment of Chronic Illness Therapy-Diarrhea (FACIT-D), FACIT-Fatigue, and FACT-AntiA questionnaires will be used throughout the study to measure patients' health-related QoL

Statistical Methods

- The proportion of patients who prefer tivozanib will be calculated and presented along with the 95% confidence interval based on the exact binomial distribution
- The reason(s) for treatment preference also will be reported for each arm
- The health-related QoL questionnaires also will be summarized and compared between arms using analysis of variance. The analysis regarding the FACT-AntiA will be exploratory
- Safety analyses will be based on the patients who receive at least one dose of either tivozanib or sunitinib
  - The primary safety analyses will be conducted on the first 12-week treatment period of the study
  - Analyses of safety data after the first 12 weeks will be exploratory
- The safety endpoints include study drug exposure, incidence of AEs, vital signs, clinical laboratory parameters, electrocardiogram measurements, and ECOG performance status
- Study drug modifications and interruptions will be compared between the two arms
- Anti-tumor activity and rate of PFS will be analyzed in the intent-to-treat population and summarized descriptively
- No interim analyses are planned for this study. Ongoing safety assessments will be performed by the sponsor throughout the trial

Discussion

- **In a Phase III clinical trial, tivozanib was well tolerated, with superior efficacy (improved PFS and objective response rate), lower rates of off-target toxicity, and fewer dose adjustments compared with sorafenib in mRCC patients**
- **This Phase II trial is the first, direct comparison of tivozanib vs sunitinib in the same study population, e.g. first-line mRCC**
- **Enrollment of patients has recently begun**

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