**TIVO-3: A phase 3, randomized, controlled, multi-center, open-label study to compare tivozanib hydrochloride to sorafenib in patients with refractory advanced renal cell carcinoma (RCC)**

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**Background**

Tivozanib in Renal Cell Carcinoma (RCC)
- Tivozanib is a vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor that selectively inhibits all 3 VEGF receptors (Figure 1), and is currently under development for the treatment of RCC because of its critical role in the pathological angiogenesis of cancer.1,3

Figure 1. Selective inhibition of VEGFR-1, VEGFR-2, and VEGFR-3 by tivozanib1,4

![Figure 1](image)

**Tivozanib Efficacy and Safety—TIVO-1**
- TIVO-1 was an open-label, randomized, phase 3, multinational trial in which patients with metastatic RCC were randomized to either tivozanib or sorafenib:2
  - Superior progression-free survival (PFS) was demonstrated for the primary endpoints (11.9 months vs 9.1 months, with tivozanib and sorafenib, respectively)5
  - Median overall survival (OS) was 28.8 months for tivozanib, and 29.3 months for sorafenib (P=0.103)6
  - The one-way crossover design in TIVO-1 led to a subsequent imbalance in second-line treatment between arms.
  - 63% of patients taking sorafenib received subsequent therapy, most commonly tivozanib, which may have caused the PFS discrepancy between the tivozanib and sorafenib groups.2

**Study Rationale for TIVO-3**
- The imbalance in crossover between tivozanib and sorafenib in TIVO-1 and the strong second-line efficacy of tivozanib observed in patients who crossed over from sorafenib to tivozanib likely confounded the OS data.2
- The TIVO-3 trial was designed to demonstrate the efficacy and safety of tivozanib in patients with advanced RCC, as well as demonstrate that the negative trend in OS from TIVO-1 was an artifact.

Figure 2. Potency, selectivity, and half-life of tivozanib1,4

![Figure 2](image)

**Study Hypothesis**
- Tivozanib monotherapy will provide clinical benefit to patients with advanced RCC and will compare favorably to sorafenib.

**Study Design**
- Open-label, randomized, controlled, multinational, multi-center, parallel-arm, phase 3 study (NCT02627963) comparing the PFS, OS, objective response rate (ORR), duration of response (DOR), and safety/tolerability of tivozanib and sorafenib in approximately 322 patients diagnosed with advanced RCC (Figure 3)
- Patients randomized in a 1:1 ratio (tivozanib:sorafenib), and stratified by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk category (favorable, intermediate, poor) and prior therapy (2 prior VEGF TKIs, 1 prior checkpoint inhibitor [PD-1 or PD-L1], or prior VEGF TKI or a prior VEGF TKI plus any other systemic agent)
- Treatment will continue until verified disease progression or unacceptable toxicities.
  - Dose reductions allowed for patients with ≥3 treatment-related adverse events (AEs): 10 mg/day for tivozanib and 400 mg/day for sorafenib, and dose interruptions allowed for the management of persistent AEs.
  - Responses will be assessed based on:
    - Diagnostic imaging with measurement of target lesions, reviewed by independent radiologists
    - Measurable disease via RECIST v1.1 criteria
    - CT/MRI performed every 8 weeks from the first day of protocol treatment
  - Toxicities will be graded based on the NCI Common Terminology Criteria for Adverse Events (CTCAE Version 4.03), with continuous monitoring throughout treatment, including a 30-day follow-up period.
  - After treatment discontinuation, follow-up information for long-term survival and subsequent anti-cancer therapy, if available, will be obtained every 3 months from the End of Treatment Visit, or a 30-day follow-up visit (whichever is later) until death, withdrawal of consent, loss to follow-up, or study closure.
  - Any patients starting new anti-cancer treatments must complete the End of Treatment Visit prior to starting a new therapy.
  - The two patient populations defined for efficacy analysis included an intent-to-treat (ITT) population (all patients randomized into the trial) and a per protocol population (patients with major protocol deviations who received ≥2 cycles of treatment); primary efficacy analysis will be based on the ITT population.

Figure 3. TIVO-3 Study Design

![Figure 3](image)

**Inclusion/Exclusion Criteria**

- **Key Inclusion Criteria**
  - Adults aged ≥18 years
  - Evidence of metastatic RCC with clear cell histology
  - Failure on ≥2 prior systemic agents, one of which includes a VEGF TKI (other than tivozanib or sorafenib)
  - Measurable disease per RECIST criteria 1.1
  - ECOG PS 0–1
  - A life expectancy of ≥3 months

- **Key Exclusion Criteria**
  - Prior treatment with tivozanib or sorafenib, or more than 3 prior regimens for metastatic RCC
  - Metastatic central nervous system metastases other than stable/treated metastases
  - Hemoglobin < 9.0 g/dL, absolute neutrophil count <1500 per mm3, platelet count <100,000 per mm3
  - Significant cardiovascular disease, including left ventricular failure and uncontrolled hypertension
  - History of myocardial infarction, angina, or thromboembolic/vascular disorders

- **Statistical Methods**
  - The distribution of the primary endpoint for the two treatment arms, PFS, will be compared using a log-rank test with two-sided 5% significance level (α).
  - 322 patients (161 for tivozanib, 161 for sorafenib) with a total of 255 events compared using a log-rank test with two-sided 5% significance level (α).
  - Median PFS for subjects receiving sorafenib and tivozanib will be 4 months and 6 months, respectively (an increase of 2 months, or 50%)
  - An equal number of subjects will be assigned to each treatment arm
  - Enrollment will take 18 months
  - The dropout percentage per treatment arm will be 3%

**Study Objectives**

- **Primary Objective**
  - PFS
- **Secondary Objectives**
  - OS
  - ORR and DoR
  - Safety
- **Exploratory Objectives**
  - Relationship between tivozanib and sorafenib drug levels and activity
  - Relationship between tivozanib and sorafenib drug levels and AEs

**References**

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