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)

Brian I. Rini,[1] Michael B. Atkins,[2] Bernard J. Escudier,[3] Thomas E. Hutson,[4] Piotr Koralewski,[5] David F. McDermott,[6] Sumanta K. Pal,[7] Michael N. Needle,[8] Camillo Porta[9]

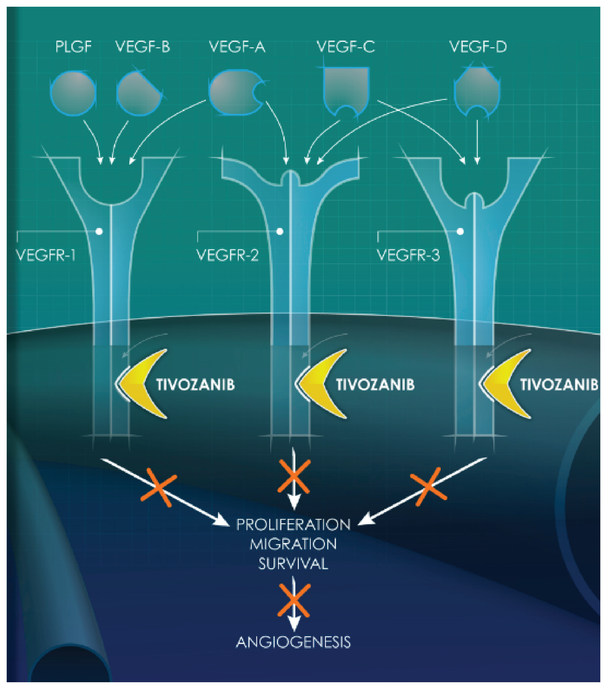
[1]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; [2]Georgetown University Hospital, Lombardi Comprehensive Cancer Center, Washington, DC; [3]Gustave Roussy Cancer Campus, Villejuif, France; [4]Baylor Sammons Cancer Center-Texas Oncology, Dallas, TX; [5]Wojewodzki Szpital Specjalistyczny im. L. Rydygiera, Krakow, Poland; [6]Beth Israel Deaconess Medical Center, Boston, MA; [7]City of Hope Comprehensive Cancer Center, Duarte, CA; [8]Aveo Oncology, Cambridge, MA; [9]IRCCS San Matteo University Hospital Foundation, Padua, Italy

Background

Tivozanib in Renal Cell Carcinoma (RCC)

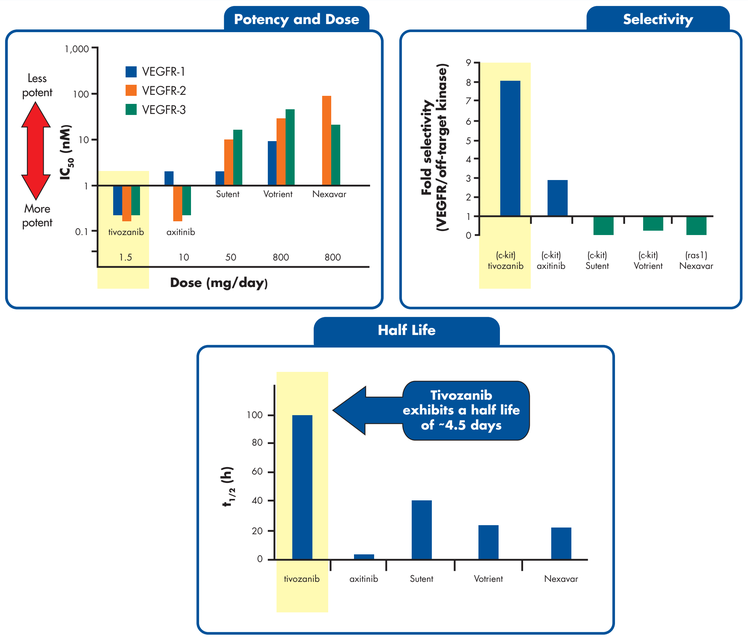
- Tivozanib is a vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor that selectively inhibits all 3 VEGF receptors (**Figure 1**), and is currently under development for the treatment of RCC because of its critical role in the pathological angiogenesis of cancer[1-3]

Figure 1. Selective inhibition of VEGFR-1, VEGFR-2, and VEGFR-3 by tivozanib[1,4]



- Tivozanib is more selective and potent compared to other VEGF TKIs (tyrosine kinase inhibitors)[5,6], and has a longer half-life[4] (**Figure 2**)
- Tivozanib was designed to optimize the VEGF blockade while minimizing off-target toxicities, which may enable more tolerable combinations with other therapies[1,4]

Figure 2. Potency, selectivity, and half-life of tivozanib[1,4-6]



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[7]
  - Superior progression-free survival (PFS) was demonstrated for the primary endpoints (11.9 months and 9.1 months, with tivozanib and sorafenib, respectively)[7]
  - Median overall survival (OS) was 28.8 months for tivozanib, and 29.3 months for sorafenib (P=0.105)[7]
  - The one-way crossover design in TIVO-1 led to subsequent imbalance in second-line treatment between arms
  - 63% of patients taking sorafenib received subsequent therapy, most commonly tivozanib, which may have caused the discordance between the PFS and OS endpoints
  - Strong second-line efficacy of tivozanib was observed in patients who crossed over from sorafenib, which likely confounded the OS results from TIVO-1[7]
  - For the 163 patients who crossed over from sorafenib to tivozanib, median PFS was 11 months, and median OS was 21.6 months from the start of tivozanib[8]

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, leading to discordance between the PFS and OS endpoints
- 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

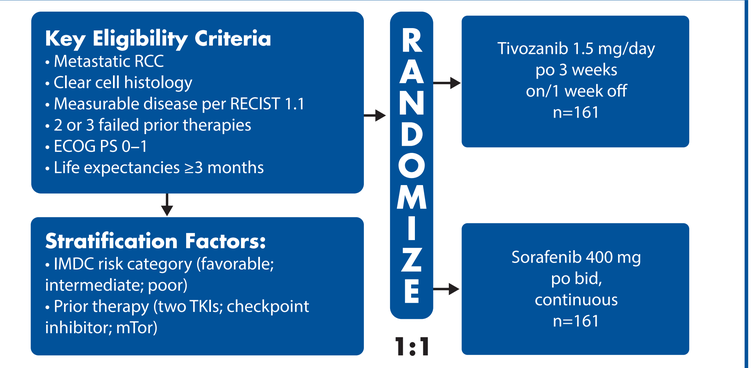
Study Hypothesis

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

Study Design

- Open-label, randomized, controlled, multi-national, 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] plus a 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 ≥ grade 3 treatment-related adverse events (AEs; 1.0 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 without 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



ECOG=Eastern Cooperative Oncology Group; IMDC=International Metastatic Renal Cell Carcinoma; RECIST=Response Evaluation Criteria in Solid Tumors; RCC=renal cell carcinoma; mTor=mammalian target of rapamycin; TKI=tyrosine kinase inhibitor.

Inclusion/Exclusion Criteria

Key Inclusion Criteria

- Adults aged ≥18 years
- Evidence of metastatic RCC with clear cell histology
- Failure on 2 or 3 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 mm^3, platelet count <100,000 per mm^3
- Significant cardiovascular disease, including left ventricular failure and uncontrolled hypertension
- History of myocardial infarction, angina, or thromboembolic/vascular disorders within 6 months prior to study enrollment

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 will provide 90% power to detect a statistically significant difference in PFS, as assessed by the Independent Radiological review, between the two treatment arms based on the following assumptions:
  - The 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 15 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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Acknowledgments

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