Efficacy and safety data from patients with advanced renal cell cancer treated with tivozanib hydrochloride after progression on sorafenib

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Abstract/Poster No: 364

Introduction

- Tivozanib hydrochloride (tivozanib) is a potent, selective inhibitor of vascular endothelial growth factor receptors (VEGFRs)-1, -2, and -3 with a long half-life that is designed to optimize blockade while minimizing off-target toxicities[1,2]
- Tivozanib is given orally (PO), once daily at 1.5 mg for 3 weeks followed by a one week rest
  - The half-life of 4.5–5.1 days allows once-daily administration with a consistent serum concentration[2,3]
- A Phase III trial (TIVO-1) in advanced renal cell carcinoma (RCC) patients met its primary endpoint progression-free survival (PFS), with a median PFS of 11.9 months in the tivozanib arm vs 9.1 months in the sorafenib control arm (P=0.042)[4]
  - In a pre-specified subgroup analysis of treatment-naïve patients for metastatic disease, the PFS benefit of tivozanib was 12.7 months vs 9.1 months with sorafenib (P=0.037)

Objectives

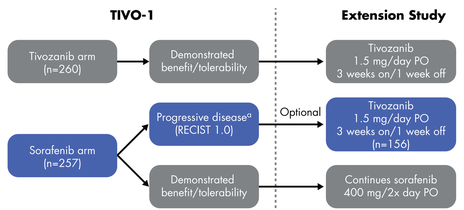
- The primary objectives of the study were:
  - To allow long-term access to either tivozanib or sorafenib for patients who participated in TIVO-1 and experienced clinical benefit and acceptable tolerability within their randomly assigned treatment arm
  - To allow access to tivozanib for patients who participated in TIVO-1 and failed sorafenib treatment (progressive disease per RECIST 1.0) on protocol
- The secondary objectives of the study were to assess response rate, PFS, OS, and safety and tolerability for all participants

Methods

Study Design

- This was an interim analysis of the open-label, multi-center extension study (NCT01076010) of TIVO-1 (A Phase III, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib to Sorafenib in Subjects With Advanced Renal Cell Carcinoma [NCT01030783])
- Planned enrollment in this extension study was to include the following:
  - Patients who were randomized to either tivozanib or sorafenib and demonstrated clinical benefit and acceptable tolerability in TIVO-1 and were offered long-term access to their respective study drug
  - Patients who progressed on sorafenib (had documented progressive disease [PD] per RECIST [Version 1.0]) in TIVO-1 and were offered tivozanib
- Patients who did not tolerate sorafenib and previously discontinued for adverse events (AEs), or for any other reason besides radiographic progressive disease, were not eligible to receive tivozanib in the extension study

Figure 1. Extension study schema.



[a]Only patients with RECIST-defined progression on sorafenib in TIVO-1 who then chose to receive tivozanib in the extension study were included in this analysis

- Patients were to have been no more than 4 weeks from last dose of sorafenib until initiation of tivozanib, and have an ECOG performance status of ≤2 **(Figure 1)**

Analysis

- Only patients with RECIST-defined progression on sorafenib in TIVO-1 who then chose to receive tivozanib in the extension study were included in this analysis
- This interim analysis included data through August 27, 2012 in 156 patients who received tivozanib after progression on sorafenib by this date
- ORR, PFS, overall survival (OS), and AEs were evaluated in patients who received tivozanib after progression on sorafenib
- Ongoing AEs at the time of crossover were considered medical history and were only recorded as an AE in the extension study if they worsened in severity from baseline

Results

- Patient population was predominantly male, white, and from Central/Eastern Europe **(Table 1)**
- Dose interruptions due to AEs were observed in 20 patients (13%) and dose reductions due to AEs in 15 patients (10%)
- Of the 156 patients, 101 (65%) discontinued study drug and 55 patients (35%) were ongoing at the time of the analysis
- Median PFS was 8.4 months (95% confidence interval [CI]: 5.5–12.4 months), measured from the first dose of tivozanib in the extension study **(Figure 2)**
- Median OS was 19.6 months (95% CI: 14.1–NR), measured from the first dose of tivozanib in the extension study **(Figure 3)**
- Tumor shrinkage was apparent in 74% of patients **(Figure 4)**
- The confirmed ORR was 13% (95% CI: 8.5–19.8; **Table 2)**

Table 1. Baseline Characteristics

Characteristic	Tivozanib After Sorafenib (n=156)
Gender, n (%)	
Male	111 (71)
Female	45 (29)
Age (years)	
Median	60
Range	23–86
Age group, n (%)	
<65 years	115 (74)
≥65 years	41 (26)
Race, n (%)	
White	151 (97)
Asian	5 (3)
Geographic region,[a] n (%)	
Central/Eastern Europe	138 (88)
North America/Western Europe	10 (6)
Rest of world	8 (5)

[a]Due to rounding, total does not equal 100%.

Figure 2. PFS by investigator assessment for tivozanib after sorafenib.

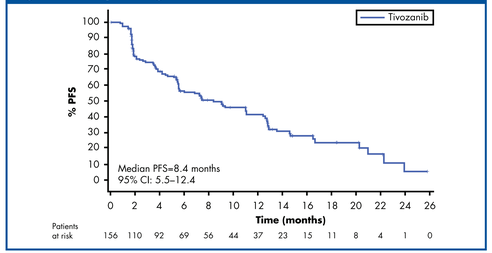


Figure 3. OS since starting tivozanib after progression on sorafenib.

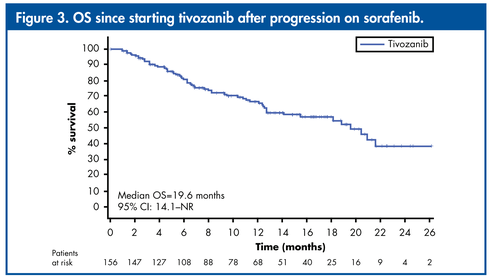
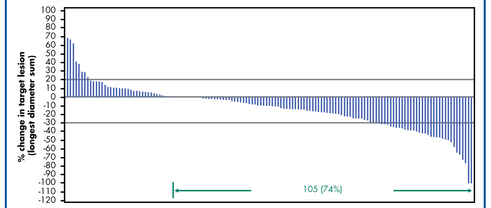


Figure 4. Change from extension study baseline for target lesions (investigator assessment).



141 patients had measurable disease at baseline and at least one subsequent scan.

Table 2. Summary of Best Overall Response (investigator assessment)

	Tivozanib After Sorafenib
Best overall response (confirmed), n (%)	
CR	0
PR	21 (13)
SD	94 (60)
PD	28 (18)
Not evaluable	13 (8)
Confirmed ORR (CR + PR),[a] n (%)	21 (13)
95% CI	(8.5–19.8)

[a]There were 9 additional unconfirmed responses recorded.
CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

- Study is ongoing, and patients are continuing to cross over to tivozanib after progression on sorafenib, impacting response rate, PFS, and OS
- Most commonly reported treatment-emergent AEs are shown in **Table 3**

Table 3. Percent Most Frequently Reported AEs (occurring in ≥5% of patients)

Preferred Term[a]	All Grades	Grade 3 (4)
Hypertension	24	12 (0)
Diarrhea	13	2 (0)
Fatigue	12	3 (0)
Palmar-plantar erythrodysesthesia syndrome	10	1 (0)
Asthenia	9	3 (0)
Dysphonia	6	0 (0)
Decreased appetite	6	0 (0)
Dyspnea	5	1 (0)
Peripheral edema	5	0 (0)

AEs ongoing at the time of cross over were recorded as medical history and only reported as on-study AE if severity increased.
[a]AEs are listed by MedDRA (Version 14.0) preferred term in decreasing frequency for total patients.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities.

Discussion and Conclusions

- In this interim report, tivozanib has demonstrated anti-tumor activity after radiographic progression on sorafenib
  - Confirmed ORR: 13% (95% CI: 8.5–19.8)
  - Tumor shrinkage in 74% of patients
  - PFS: 8.4 months (95% CI: 5.5–12.4)
  - The anti-tumor activity of tivozanib may be contributing to the OS of patients randomized to sorafenib in TIVO-1 **(see Motzer et al. Poster #350)**
- Rates of dose reduction and dose interruption due to AEs for tivozanib as second line VEGF inhibitor in this study were low (10% and 13%)
  - These were consistent with the low rates of dose reduction and interruption observed in TIVO-1 patients who received tivozanib as a first-line targeted therapy (12% and 18%, respectively)[4]
- The AE profile of next-line tivozanib after sorafenib was similar to that of tivozanib as first-line targeted therapy in TIVO-1, with the exception of hypertension
- Hypertension on next-line tivozanib was approximately half as common as observed in TIVO-1
  - All grades in this study were 24% vs 44% in TIVO-1
  - Grade 3/4 in this study were 12% vs 26% in TIVO-1
  - The low rate of reported hypertension in the extension study may be related to effective management of this class-effect on prior sorafenib
- Study is currently in progress and patient follow-up is ongoing

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