Overall survival results from a Phase III study of tivozanib hydrochloride vs sorafenib in patients with renal cell carcinoma

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Abstract/Poster No: 350

Introduction

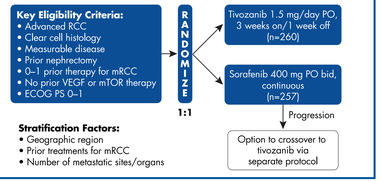
- Multiple vascular endothelial growth factor (VEGF) receptor inhibitors have been approved for treatment of renal cell carcinoma (RCC) on the basis of progression-free survival (PFS)[1–4]
- Overall survival (OS) results from pivotal trials of other VEGF receptors (VEGFR; e.g., sunitinib, pazopanib, sorafenib) have been confounded by cross-over study design and next-line cancer therapies[2,4]
- Tivozanib hydrochloride (tivozanib) is a potent, selective inhibitor of VEGFR-1, -2, and -3 with a long half-life that is designed to optimize blockade while minimizing off-target toxicities[5,6]
- Tivozanib is taken 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[6,7]
- A Phase III trial (TIVO-1; NCT01030783) in advanced RCC patients met its primary endpoint of median PFS of 11.9 (95% confidence interval [CI]: 9.3–14.7) months in the tivozanib arm versus 9.1 (95% CI: 7.3–9.5) months in the sorafenib control arm (P=0.042)[8]
  - In a pre-specified subgroup analysis of treatment-naïve patients for metastatic disease, the PFS benefit of tivozanib was 12.7 months versus 9.1 months with sorafenib (P=0.037)
- Here we present OS results from TIVO-1 and next-line cancer therapy data that contribute to OS

Methods

Study Design

- TIVO-1 was an open-label, Phase III, randomized, controlled, multinational, multi-center, parallel-arm study comparing tivozanib with sorafenib in patients with metastatic RCC (mRCC) who had a prior nephrectomy, received ≤1 prior systemic treatment for mRCC, had no prior VEGF-targeted therapy or mammalian target of rapamycin-targeted therapy (mTOR), and had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1. Patients were randomized (1:1) to tivozanib 1.5 mg PO once daily for 3 weeks followed by a 1-week break, or sorafenib 400 mg PO twice daily continuously in a 4-week cycle **(Figure 1)**
- Safety data were collected from consent to 30 days after last dose

Figure 1. TIVO-1: Phase III superiority study of tivozanib vs sorafenib as first-line targeted therapy for mRCC.



- Response was assessed every 2 cycles (8 weeks)
- Eligible patients who progressed on sorafenib (per RECIST 1.0) were given the option to receive tivozanib in an extension protocol

Analysis Plan

- PFS was the primary endpoint, which was assessed by independent review and stratified by log-rank test with a two-sided significance level of α=0.05
- OS was a secondary endpoint. OS analysis would have a 70% power to demonstrate longer OS for tivozanib using the log-rank test (2.5% type 1 error, one-sided), with an interim analysis at the time of the PFS analysis and the final analysis after a minimum follow-up of 2 years, assuming HR=0.75 and 300 total events at the final analysis
- The same stratification factors were to be used for the OS and the PFS analyses:[8]
  - Number of prior therapies for metastatic disease (0 versus 1)
  - Number of metastatic sites/organs (1 versus ≥2)
- The HR for treatment was estimated using the Cox proportional hazard (PH) regression model
- The protocol-specified, final OS analysis is reported here, after all patients in follow-up had been on study for at least 2 years (data sweep: August 27, 2012)
- To better understand the impact of next-line cancer therapies on OS, descriptive Kaplan-Meier curves of post-hoc, exploratory subset analyses are presented
- Patients continued to be followed for OS and subsequent cancer therapy

Results

OS Results

- OS was estimated for the intent-to-treat (ITT) population **(Table 1)** and included data from the extension study (for patients who chose to receive tivozanib after RECIST-defined tumor progression on sorafenib in TIVO-1; **see Motzer et al. Poster #364**; NCT01076010)

Table 1. Baseline Characteristics

Characteristic	Tivozanib	Sorafenib
No. of patients	260	257
Median age (range)	59 (23–83)	59 (23–85)
Gender, male (%)	71	74
ECOG score,* %		
0	45	54
1	55	46
MSKCC prognostic group,[10] %		
Favorable	27	34
Intermediate	67	62
Poor	7	4
Prior systemic therapy for metastatic RCC, %		
0	70	70
1	30	30

ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan-Kettering Cancer Center; RCC, renal cell carcinoma. *Imbalance between arms. P<0.05 by Fisher exact test.

Figure 2. Protocol-specified, final OS analysis.

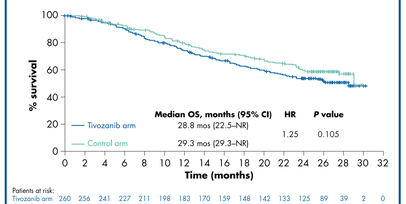
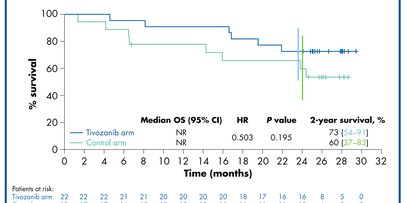


Figure 3. OS in patients from North America/Western Europe.

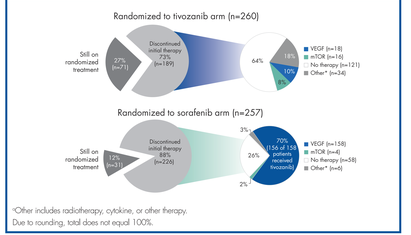


- The protocol-specified, final OS sweep included a total of 219 deaths (42% of patients)
  - 118 deaths on tivozanib arm
  - 101 deaths on control arm
- OS over time is shown in **Figure 2**
- Patients in North America/Western Europe (a prespecified subgroup for primary endpoint) did not reach median survival, but a trend toward longer survival was observed for patients in the tivozanib arm versus the control arm **(Figure 3)**

Next-line therapy

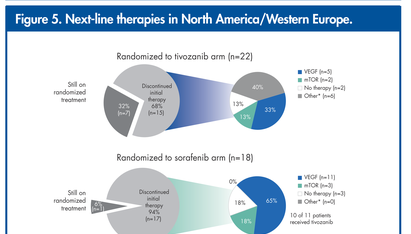
- More patients in the tivozanib arm continued on initial randomized therapy over time compared with sorafenib, consistent with the results of the primary endpoint, PFS **(Figure 4)**
  - 27% of patients were alive and had not discontinued tivozanib versus 12% of patients alive and without discontinuation of sorafenib at the time of this protocol-defined final analysis
- Among patients who discontinued randomized therapy, patients in the sorafenib arm were much more likely to receive next-line therapy, almost all of which was tivozanib
- Of the 189 tivozanib patients who discontinued initial therapy, 36% of patients (corresponding to 26% of the tivozanib ITT population) received next-line therapy
  - 10% received next-line VEGF inhibitors

Figure 4. Next-line therapies.



*Other includes radiotherapy, cytokine, or other therapy.
Due to rounding, total does not equal 100%.

Figure 5. Next-line therapies in North America/Western Europe.



*Other includes radiotherapy, cytokine, or other therapy.
Due to rounding, total does not equal 100%.

- Of the 226 sorafenib patients who discontinued initial therapy, 74% of patients (corresponding to 65% of the sorafenib ITT population) received next-line therapy
  - 70% received next-line VEGF inhibitors (156 of 158 patients received tivozanib)
- After discontinuation of initial therapy, 64% of patients in the tivozanib arm received no next-line therapy compared with 26% of patients in the control arm
- Among those who received any next-line therapy, OS was longer in the control arm as compared to the tivozanib arm (2 vs 2; **Figure 6A**)
  - Results are similar when restricted to next-line VEGF therapy **(Figure 6B)**
- In a pooled analysis of patients who were still on randomized treatment or discontinued treatment and received no next-line therapy (comparison of 1 therapy vs 1 therapy), OS was similar in both the tivozanib arm and the control arm **(Figure 7A)**
- In the North America/Western Europe subgroup, where a trend toward longer survival was observed for patients in the tivozanib arm versus the control arm **(Figure 3)**, a higher percentage of patients received next-line therapy in both arms and the difference in next-line therapy between arms was less pronounced **(Figure 5)** than in the ITT population
  - This subset was small and further study is needed to confirm these findings

Figure 6. OS Analysis of "2 vs 2" lines of therapy.

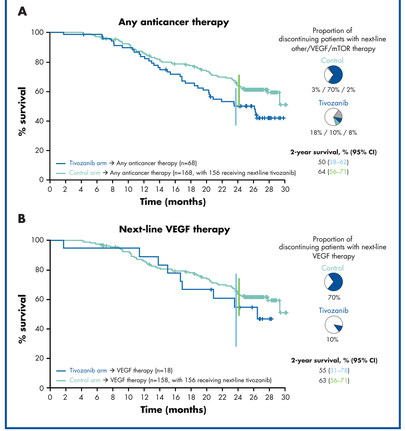
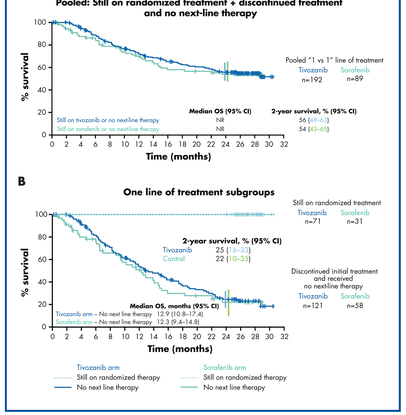


Figure 7. OS analysis of "1 vs 1" line of therapy.



Discussion and Conclusions

- In the protocol-specified final OS analysis, a trend toward longer OS was observed in the control arm compared with the tivozanib arm (HR=1.25, P=0.105)
  - Median OS in the tivozanib arm was 28.8 months; median OS in the control arm was 29.3 months
- The OS comparison between study arms was confounded by differential use of next-line cancer therapies
  - This result was consistent with the study's well utilized one-way crossover to the experimental therapy after disease progression in the control arm
  - Predominant enrollment in Central and Eastern Europe may have also contributed to this result, as access to subsequent effective treatment options for RCC is limited in this region
- More patients in the tivozanib arm remained progression-free, still on randomized treatment (27%) than in the control arm (12%)
- Following discontinuation of initial treatment, fewer tivozanib patients received next-line VEGF therapy (10%) than patients in the control arm (70%)
  - 156 of 158 patients received tivozanib in the control arm
- In North America/Western Europe, a trend toward longer OS was observed with tivozanib compared to sorafenib (HR=0.503; P=0.195); median OS was not reached at the time of analysis in either arm. Compared with the ITT population:
  - A higher percentage of North America/Western Europe patients received next-line therapy in both arms and the difference in use of next-line therapy between the two arms was less pronounced

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