TIVO-3: Durability of Response and Updated Overall Survival of Tivozanib vs Sorafenib in Metastatic Renal Cell Carcinoma (mRCC)

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Background

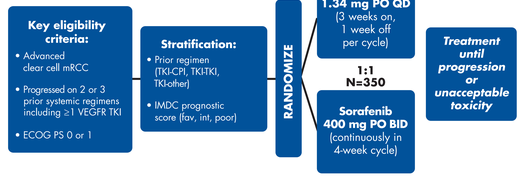
- Tivozanib is a potent and highly selective vascular endothelial cell growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) with a long half-life that is an effective treatment option for patients with previously treated mRCC[1,2]
- In the phase 3 TIVO-3 trial, tivozanib demonstrated favorable tolerability and statistically significant improvement in progression-free survival (PFS) and overall response rate (ORR) compared with sorafenib in patients with mRCC as assessed by an independent radiology review[1]
  - Median PFS, 5.6 vs 3.9 months (hazard ratio [HR], 0.73; 95% CI, 0.56-0.94; *P*=0.016)
  - ORR, 18% vs 8% (*P*=0.02)
- Based on these findings, tivozanib was approved by the FDA for the treatment of patients with relapsed or refractory advanced RCC following 2 or more prior systemic therapies
  - Tivozanib is approved in the EU for patients with RCC who are not previously treated with a VEGFR TKI or an mTOR inhibitor
- Here we report long-term durability of response based on investigator assessment and updated overall survival (OS) in patients with mRCC from the TIVO-3 trial

Methods

Study Design

- TIVO-3 (NCT02627963) is a phase 3, open-label study that enrolled patients with mRCC whose disease progressed on 2 or 3 prior systemic regimens, 1 of which included a VEGFR TKI[1] (**Figure 1**)
  - Patients were stratified by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk category (favorable, intermediate, or poor) and type of prior therapy (2 prior VEGFR TKIs, VEGFR TKI plus checkpoint inhibitor (CPI), or VEGFR TKI plus any other systemic agent) then randomized 1:1 to tivozanib or sorafenib
  - The primary endpoint was PFS, defined as the time from randomization to first documentation of objective tumor progression as assessed by blinded independent radiological review
  - Secondary endpoints included OS, ORR, duration of response (DOR), and safety
- Data cutoff for these analyses was January 15, 2021

Figure 1. TIVO-3 Study Design



BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; fav, favorable; int, intermediate; PO, orally; QD, once daily.

Median DOR was twice as long in the tivozanib arm, and the HR for OS for tivozanib relative to sunitinib continues to improve over time

Results

- Baseline patient demographics and disease characteristics were balanced and typical of those seen in patients with mRCC (**Table 1**)

Table 1. Key Baseline Patient Demographics

	Tivozanib n=175	Sorafenib n=175
Age, median (range), years	62 (34-88)	64 (30-90)
Sex, n (%)		
Male	126 (72)	128 (73)
Female	49 (28)	47 (27)
IMDC risk category, n (%)		
Favorable	34 (19)	36 (21)
Intermediate	109 (62)	105 (60)
Poor	32 (18)	34 (19)
No. of previous systemic therapies, n (%)		
2	108 (62)	104 (59)
3	67 (38)	71 (41)
Previous therapies, n (%)		
2 VEGFR TKI	79 (45)	80 (46)
CPI plus VEGFR TKI	47 (27)	44 (25)
VEGFR TKI plus other	49 (28)	51 (29)

ORR

- Per investigator assessment, 41 patients (23%) had responses with tivozanib, and 20 patients (11%) had responses with sorafenib (**Table 2**)

Table 2. ORR

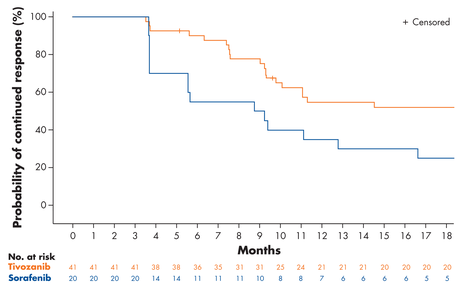
	Tizozanib n=175	Sorafenib n=175
ORR, n (%)	41 (23)	20 (11)
DCR, n (%)	144 (82)	121 (69)
PR, n (%)	41 (23)	20 (11)
SD, n (%)	103 (59)	101 (58)

DCR, disease control rate; PR, partial response; SD, stable disease.

DOR

- The median DOR by investigator assessment was 20.3 months (95% CI, 9.8-29.9 months) and 9.0 months (95% CI, 3.7-16.6 months) with tivozanib and sorafenib, respectively (**Figure 2**)
  - 3 patients in the sorafenib arm (2% of total arm; 15% of patients with responses) and 13 patients in the tivozanib arm (7%; 32%) had continued ongoing responses at time of data cutoff

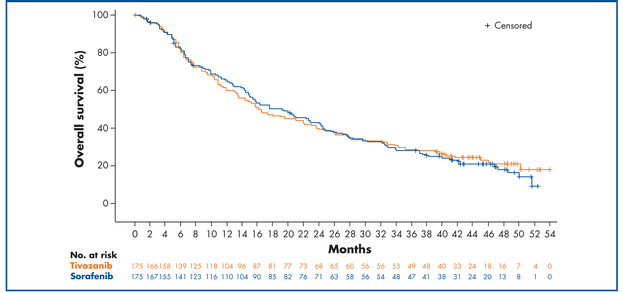
Figure 2. DOR



OS

- With prolonged follow-up, there were 270 deaths; the HR for OS favored tivozanib at 0.91 (95% CI, 0.716-1.165; *P*=0.47) (**Figure 3**) but did not reach statistical significance

Figure 3. Long-Term OS Follow-Up



Conclusions

- Tivozanib demonstrated clinically meaningful and statistically significant improvement in ORR and DOR with similar OS to sorafenib in patients with highly relapsed or refractory mRCC
  - Median DOR was 20.3 months with tivozanib, twice that observed with sorafenib
  - Statistically significant improvement in PFS and ORR had previously been shown[1,2] and continues to improve with longer follow-up
  - OS relative to sorafenib continues to improve with longer follow-up
- Collectively, these data confirm and extend previous findings for tivozanib as an evidence-based treatment option for patients with relapsed and refractory RCC, including for patients whose disease has progressed after previous checkpoint inhibitor therapy

References

1. Rini B, et al. *Lancet Oncol.* 2020;21:95-104.
2. Pal SK, et al. *Eur Urol.* 2020;78:783-785.

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