Temporal Characteristics of Treatment-Emergent Adverse Events and Dose Modifications With Tivozanib and Sorafenib in the Phase 3 TIVO-3 Study of Relapsed or Refractory mRCC

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Background

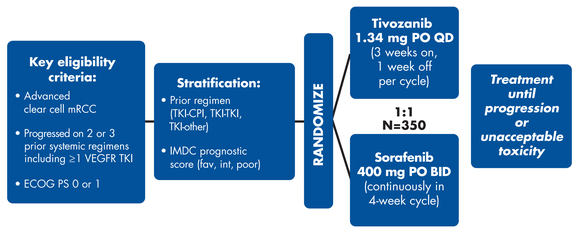
- Tivozanib is a potent and highly selective vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) with a long half-life that represents an effective treatment option for patients with previously treated metastatic RCC (mRCC)[1,2]
- In the phase 3 TIVO-3 trial, tivozanib demonstrated favorable tolerability and significant progression-free survival (PFS; median, 5.6 vs 3.9 mo; hazard ratio, 0.73; *P*=0.016) and overall response rate (ORR) compared with sorafenib in patients with mRCC[1]
- Based on these findings, tivozanib was approved by the US Food and Drug Administration 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 had not been previously treated with a VEGFR TKI or an mTOR inhibitor
- Tivozanib was associated with fewer dose reductions, interruptions, and discontinuations than sorafenib despite a longer time on therapy. Greater insight into temporal characteristics of treatment-emergent adverse events (TEAEs) may enable proactive supportive care strategies and improve patient experience
- Here we describe time to onset (TTO) of the most commonly reported TEAEs and TTO of first dose reduction, interruption, and discontinuation occurring with tivozanib and sorafenib

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 RCC Database Consortium (IMDC) risk category (favorable, intermediate, or poor) and type of prior therapy (2 prior VEGFR TKIs, VEGFR TKI plus checkpoint inhibitor (CPI), VEGFR TKI plus any other systemic agent) then randomized 1:1 to receive tivozanib or sorafenib
  - Data cutoff for these updated safety analyses was August 15, 2019

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.

Patients in the TIVO-3 trial had longer duration of treatment exposure with tivozanib than sorafenib, but fewer all-grade and grade ≥3 TEAEs

Temporal characteristics of TEAEs were generally similar, but time to dose modifications was longer with tivozanib than with sorafenib

Among those with the same TEAE, dose modifications were required more frequently with sorafenib than tivozanib

Results

Treatment Exposure and Dose Modifications

- Patients in the safety analysis randomly assigned to tivozanib (n=173) or sorafenib (n=170) received 11.9 cycles (336 mean days of treatment exposure) and 6.7 cycles (192 mean days of treatment exposure), respectively

Table 1. Dose Modification Due to TEAEs

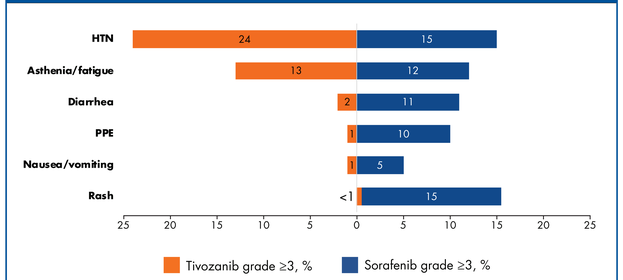
	Tivozanib n=173		Sorafenib n=170	
	%	Time to onset, days	%	Time to onset, days
Dose reduction	25	85	39	45
Dose interruption	50	81	64	50
Dose discontinuation	21	114	30	49

- Overall, dose reductions, interruptions, and discontinuations due to TEAEs were less frequent with tivozanib than sorafenib, and time to onset of first dose reduction, interruption, and discontinuation was longer for tivozanib than sorafenib (**Table 1**)

VEGFR TKI Class Effect TEAEs

- VEGFR TKI class effect all-grade TEAEs were reported in 87% and 92% of patients in the tivozanib and sorafenib arms, respectively
  - Incidence of grade ≥3 VEGFR TKI class effect TEAEs are shown in **Figure 2**

Figure 2. Incidence of VEGFR TKI Class Effect Grade ≥3 TEAEs

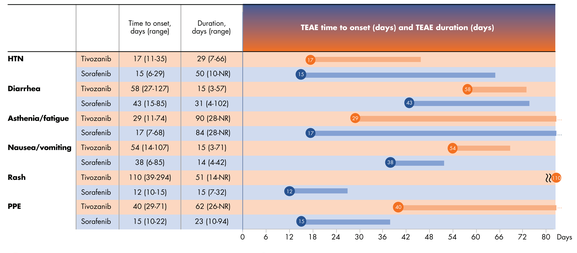


HTN, hypertension; PPE, palmar-plantar erythrodysesthesia.

Time to TEAE Onset and Durations

- Time to onset and duration of TEAEs were generally similar with tivozanib and sorafenib, with the exception of rash and PPE, which occurred more rapidly with sorafenib (**Figure 3**)

Figure 3. TEAEs Time to Onset and Duration



NR, not reached.

Table 3. TEAE Dose-Modification Rate and Associated Drug Exposure

	TEAE dose modification rate, %[a]		Mean study drug exposure in patients with TEAEs and dose modification			
			Tivozanib		Sorafenib	
	Tivozanib	Sorafenib	Cycles	Days	Cycles	Days
HTN	20	26	18	523	6.6	191
Diarrhea	18	34	20.5	575	9.5	273
Asthenia/fatigue	24	37	12.4	359	6	178
Nausea/vomiting	25	58	18.3	515	5	150
Rash	18	55	15.8	440	5.8	177
PPE	14	46	13.8	391	8.4	238

[a] Proportion of patients with a TEAE that resulted in study drug dose interruption, reduction, or discontinuation.

- While mean study drug exposure was 11.9 cycles (336 days) for tivozanib in the overall safety population, patients who experienced VEGFR TKI class effect TEAEs requiring dose modification generally had a longer than average duration of tivozanib treatment (**Table 3**)

Conclusions

- Tivozanib has demonstrated clinically meaningful and statistically significant improvement in PFS[1]
- Patients in the TIVO-3 trial had longer duration of treatment exposure with tivozanib than sorafenib, but fewer all-grade and grade ≥3 TEAEs
  - Temporal characteristics of TEAEs were generally similar, but time to dose modifications was longer with tivozanib than with sorafenib
  - Among those with the same TEAEs, dose reductions, interruptions, or discontinuations were required more frequently with sorafenib than tivozanib
- The dose modification rate due to each VEGFR TKI class effect TEAE was consistently lower with tivozanib compared with sorafenib
  - In the face of dose modification, patients on tivozanib experienced longer treatment exposure than the overall population, while patients with dose modification of sorafenib generally had the same or shorter duration

References

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

Acknowledgments

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