Long-Term PFS From TIVO-3: Tivozanib (TIVO) vs Sorafenib (SOR) in Relapsed/Refractory (R/R) Advanced RCC

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Background

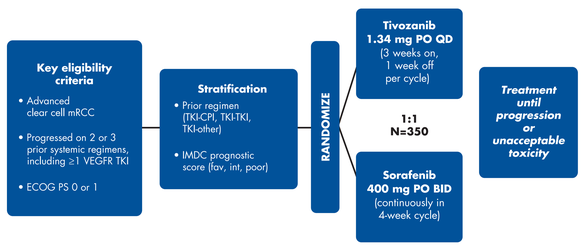
- Tivozanib (TIVO) is an oral vascular endothelial growth factor tyrosine kinase inhibitor that is approved by the US Food and Drug Administration (FDA) for treatment of patients with relapsed/refractory (R/R) renal cell carcinoma (RCC) following ≥2 prior systemic therapies[1,2]
- Long-term progression-free survival (LT-PFS) is a clinically meaningful outcome for evaluating efficacy in patients with R/R metastatic RCC (mRCC) who received ≥2 prior lines of therapy
- The TIVO-3 trial supported FDA approval of TIVO in R/R advanced RCC by demonstrating significantly improved efficacy outcomes over sorafenib (SOR), including:
  - Significantly longer independent review committee (IRC)–assessed PFS with TIVO vs SOR (unstratified hazard ratio [HR], 0.672; 95% CI, 0.52-0.87; stratified HR, 0.73; 95% CI, 0.56-0.95)
  - A higher overall response rate with TIVO compared with SOR as evaluated by IRC (18% vs 8%; *P*=.02)[1]
  - 1-year duration of response (DOR) was 71% (95% CI, 53%-88%) with TIVO and 46% (95% CI, 19%-73%) with SOR[3]
    - The median DOR by IRC was not reached (NR; 95% CI, 9.8-NR) with TIVO and was 5.7 months (95% CI, 5.6-NR) with SOR[1]
    - The median DOR by investigator (INV) assessment was 20.3 months (95% CI, 9.8-29.9) for TIVO and 9.0 months (95% CI, 3.7-16.6) with SOR[4]
- In this analysis, we assessed the proportion of TIVO-3 patients with R/R mRCC who achieved LT-PFS at regular intervals up to 4 years after initiation of TIVO or SOR

Methods

Study Design

- TIVO-3 (NCT02627963) is a phase 3, global, open-label, parallel-arm study comparing TIVO with SOR in patients with R/R advanced mRCC (**Figure 1**)

Figure 1. TIVO-3 Study Design



BID, twice daily; CPI, checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; fav, favorable; IMDC, International Metastatic RCC Database Consortium; int, intermediate; mRCC, metastatic renal cell carcinoma; PO, oral; QD, once daily; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

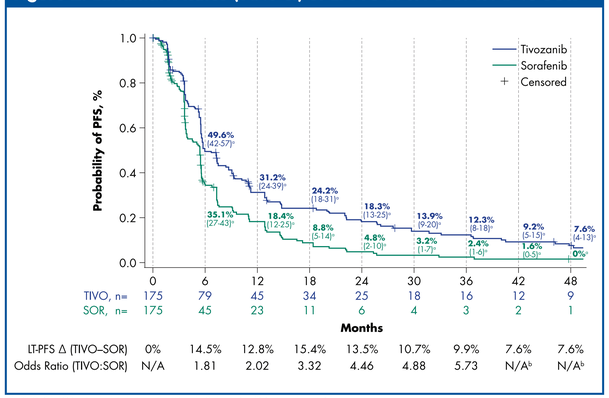
Exploratory Endpoint and Statistical Analyses

- Exploratory analysis of INV-assessed LT-PFS and long-term overall survival (OS) used a data cutoff of May 24, 2021. Unstratified PFS and OS HR for the intent-to-treat (ITT) population and prespecified subgroups (data not shown), as well as landmark values of LT-PFS at 6, 12, 24, 30, 36, 42, and 48 months are reported.
- Results include findings from the ITT population, with censoring for missing assessments and discontinuations without progressive disease
- Cox proportional hazards and log-rank statistics were used to estimate the HR and 95% CI for INV PFS and OS; odds ratios (ORs) are reported for landmark time points of LT-PFS up to 36 months
  - Due to low patient numbers at the month 42 and 48 time points (data cutoff), no inferential statistical analyses were conducted. Data are presented descriptively
- LT-PFS rates across prespecified subgroups were analyzed descriptively and are presented at 1-year intervals, up to 4 years

Results

- 350 patients were randomized 1:1 to receive TIVO (n=175) or SOR (n=175)
- The INV PFS HR analyzed with extended follow-up (data cutoff: May 24, 2021) favored TIVO compared with SOR (HR, 0.624; 95% CI, 0.49-0.79), which was comparable to the primary IRC PFS HR reported at the original October 2018 data cutoff (HR, 0.672; 95% CI, 0.52-0.87)
- Mature OS was also analyzed, and a nonsignificant trend favoring TIVO continued to emerge with accumulation of events (HR, 0.89; 95% CI, 0.70-1.14)
- Landmark INV LT-PFS rates up to 48 months were consistently higher with TIVO vs SOR: 12.3% vs 2.4% (36 months) and 7.6% vs 0% (48 months, **Figure 2**)

Figure 2. Landmark Rates (95% CI) of LT-PFS in TIVO-3: TIVO vs SOR



a% (95% CI). bOR not calculated at months 42 and 48 due to insufficient number at risk.
HR: 0.624 (95% CI: 0.49–0.79); log-rank *P*<.0001

- Despite low numbers of patients at risk, subgroups with ≥15% INV LT-PFS at 3 years included International mRCC Database Consortium (IMDC) favorable risk, female sex, ECOG PS of 0, age ≥65 years, and geographic region of North America. Three-year INV LT-PFS rates ≥15% were only observed in the TIVO (and not SOR) arm (**Table 1**)

Table 1. Landmark INV LT-PFS by Subgroup

Subgroup	TIVO N	SOR N	12-month PFS, %		24-month PFS, %		36-month PFS, %		48-month PFS, %	
			TIVO	SOR	TIVO	SOR	TIVO	SOR	TIVO	SOR
IMDC risk										
Favorable	34	36	44.0	33.6	24.0	8.4	**17.1**	0	NE	NE
Intermediate	109	105	30.9	18.7	19.9	5.3	14.8[b]	4.0	11.9	0
Poor	32	34	18.3	NE	7.3	NE	NE	NE	NE	NE
Prior treatment										
Any IO	47	44	27.0	18.6	19.1	3.7	9.8[b]	NE	6.5	NE
TKI-TKI only	79	80	31.6	9.8	18.6	2.0	13.5	NE	NE	NE
No IO	128	131	32.7	18.3	18.1	5.1	13.0	2.0	7.9	NE
Sex										
Female	49	47	32.5	12.3	25.0	0	**17.5[b]**	NE	12.5	NE
Male	126	128	30.7	20.3	15.6	6.4	10.1	3.2	5.4	NE
Age										
<65 years	98	95	26.4	13.8	12.9	4.2	10.0	2.8	5.7	NE
≥65 years	77	80	37.3	24.2	24.9	5.6	**15.3**	NE	9.9	NE
ECOG PS[a]										
0	85	83	39.0	17.4	20.5	6.3	**16.0**	3.2	10.9	NE
≥1	88	86	23.3	19.7	NE	3.3	8.7	NE	4.4	NE
Geographic region										
Europe	144	148	31.0	18.6	15.7	4.2	10.5	1.7	6.9	NE
NA	31	27	32.2	14.3	NE	NE	**16.5[c]**	NE	11.0	NE
LOT										
2	108	104	32.4	21.0	17.2	5.6	12.3	1.4	6.1	NE
≥3	67	71	29.0	14.8	19.9	3.7	12.2[b]	NE	9.8	NE

Data cutoff of May 24, 2021. Bold-faced yellow-highlighted numbers indicate values ≥15% INV LT-PFS at 36 months.
ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, International mRCC Database Consortium; INV, investigator; IO, immuno-therapy; LOT, lines of treatment; LTPFS, long-term progression-free survival; NA, North America; NE, not estimable; TKI, tyrosine kinase inhibitor.
[a] excludes n=8 unknown PS
[b] 30-month value.
[c] 42-month value.

Conclusions

- INV PFS analyzed with extended follow-up was consistent with the primary IRC PFS analysis
- OS continued to mature with longer follow-up, now demonstrating a nonsignificant trend in favor of TIVO
- Overall, the rates of INV LT-PFS were higher with TIVO compared with SOR at every time point evaluated
- The odds of experiencing LT-PFS at 36 months with TIVO were over 5 times higher than with SOR
- The higher LT-PFS rates with TIVO vs SOR were observed across subgroups, with clinically meaningful effects in the TIVO group (defined as ≥15% INV LT-PFS at 36 months) in patients with favorable risk status evaluated by IMDC, female sex, ECOG PS of 0, age ≥65 years, and North American residence

A clinically relevant proportion of patients were alive and progression free at 3 and 4 years after initiating TIVO therapy compared with SOR, and this difference was consistent across all clinical and demographic subgroups evaluated

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