# Maturation of Overall Survival in TIVO-3 With Long-Term Follow-Up

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## Background

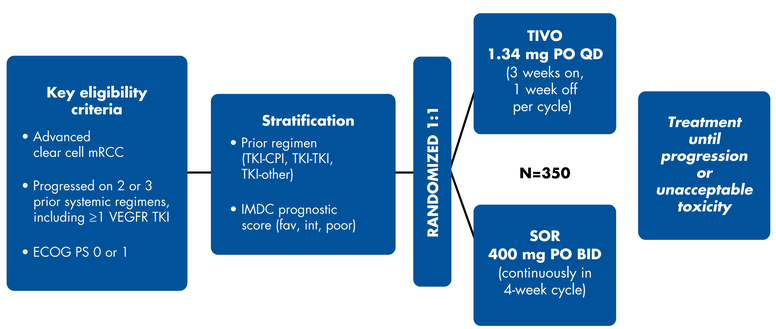
- Tivozanib (TIVO) is an oral vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) that is approved by the US Food and Drug Administration for treatment of patients with relapsed/refractory (R/R) renal cell carcinoma (RCC) following ≥2 prior systemic therapies[1,2]
- In the TIVO-3 study (NCT02627963), treatment with TIVO demonstrated a significantly improved independent review committee–assessed progression-free survival (PFS) compared with those treated with sorafenib (SOR), with a stratified HR of 0.73 (95% CI, 0.56-0.95)[3]
- Similarly, long-term follow-up analyses revealed that the investigator-assessed PFS rate at 3 years was higher in patients treated with TIVO compared with those treated with SOR (12% vs 2%, respectively)[4]
- Maturity of survival data is a key analytic when evaluating the clinical application of oncology therapies[5]
- Here, we report the impact of event accumulation and data maturation on the stability of Kaplan-Meier (KM) survival estimates at serial time points of extended mean follow-up

## Methods

### *Study Design*

- TIVO-3 is a phase 3, global, open-label, parallel-arm study comparing TIVO with SOR in patients with R/R metastatic RCC (**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.

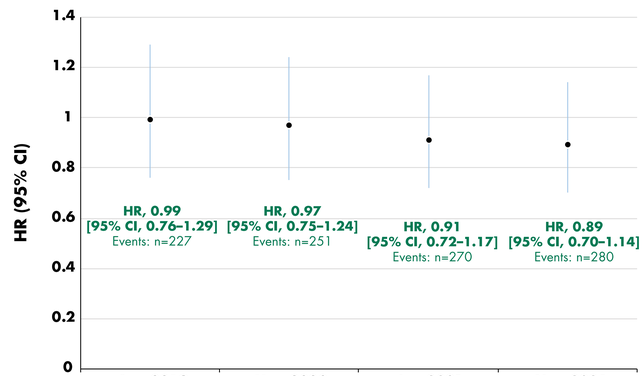
### *Endpoints and Statistical Analyses*

- To evaluate for effects of maturation of OS, Cox proportional hazards and log-rank statistics were used to estimate HR (95% CI) for OS using prespecified (2 years after last-patient-in [LPI], August 2019; 251 events, May 2020) and exploratory intent-to-treat (ITT) analyses (extended follow-up: 270 events, January 2021; database closure, May 2021)
- At the final data cutoff (database closure), conditional analyses of Cox proportional hazards and stratified log-rank statistics, using data from patients achieving 12-month and 18-month PFS in either arm, were used to estimate the HR and 95% CI for OS
- Patients were followed up for survival until death, consent withdrawal, or loss to follow-up

## Results

- At baseline, 350 patients were randomized to receive TIVO (n=175) or SOR (n=175)
- At 2 years following LPI, the mean follow-up was 17.9 months (data cutoff, August 2019), and 65% of patients had experienced an event, with an OS HR of 0.99 (95% CI, 0.76-1.29; **Figure 2**)
- With subsequent prespecified and exploratory OS analyses, and with mean follow-up extended to 22.8 months, 80% of patients had experienced an event, and the HR of OS lowered to 0.89 (95% CI, 0.70-1.14) in favor of TIVO (**Figure 2**)

**Figure 2. Serial OS With Extended Follow-Up**




| Mean follow-up (95% CI), months | 17.9 (16.7-19.1) | 20.3 (18.8-21.8) | 21.9 (20.2-23.6) | 22.8 (20.9-24.6) |
|---|---|---|---|---|

- When OS was conditioned on clinically relevant landmark PFS time points, a statistically significant improvement in OS was observed in patients treated with TIVO compared with those treated with SOR
  - **Table 1** shows the unconditioned OS in the ITT population results and the landmark PFS conditional OS results analyzed at final database closure (data cutoff, May 2021)
  - The HR for conditional OS significantly favored TIVO over SOR in patients with PFS ≥12 months (HR, 0.445) and trended in favor of TIVO over SOR in patients with PFS ≥18 months (HR, 0.461)
  - Median OS was 48.3 (TIVO) vs 32.8 (SOR) months when conditioned on PFS ≥12 months, and was 54.3 (TIVO) vs 50.0 (SOR) months when conditioned on PFS ≥18 months

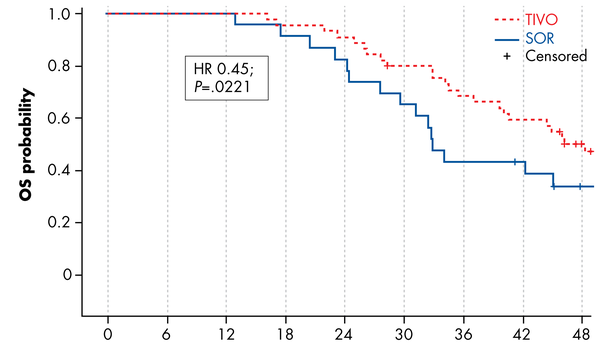
**Table 1. Unconditioned (ITT Population) and Landmark PFS-Conditioned OS in TIVO-3**

| Population | Group | At risk, n | Events | Median OS (95% CI), months | HR (95% CI) | Stratified log-rank *P* value |
|---|---|---|---|---|---|---|
| **Unconditioned (ITT population)** | TIVO | 175 | 138 | 16.4 (13.4-21.9) | 0.89 (0.70-1.14) | 0.3533 |
| | SOR | 175 | 142 | 19.1 (14.9-24.2) | | |
| **Conditioned on PFS ≥12 months** | TIVO | 45 | 25 | 48.3 (32.8-NR) | **0.45 (0.22-0.91)** | **0.0221** |
| | SOR | 23 | 17 | 32.8 (27.6-50.0) | | |
| **Conditioned on PFS ≥18 months** | TIVO | 34 | 8 | 54.3 (44.9-NR) | 0.46 (0.15-1.39) | 0.1617 |
| | SOR | 11 | 5 | 50.0 (32.4-NR) | | |

NR, not reached.

- The KM survival curves for TIVO and SOR cohorts conditioned on 12-month PFS demonstrate rapid separation shortly after 1 year that appears to remain consistent or increase over time (**Figure 3**)

**Figure 3. KM Survival Curve of Conditional OS in Patients With 12-Month PFS**




| Number at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TIVO, n= | 45 | 45 | 45 | 43 | 41 | 35 | 30 | 26 | 18 |
| SOR, n= | 23 | 23 | 23 | 21 | 19 | 15 | 10 | 9 | 5 |

## Conclusions

- Serial OS analyses using KM estimates are affected by increased curve reliability with decreased censoring and limited residual patients at risk for death
- Consistent with this concept, as events accumulated over the follow-up period, the HR for OS reduced from 0.99 to 0.89, favoring TIVO over SOR
- Conditional analysis from TIVO-3 suggests an improved OS with TIVO over SOR in the subset of patients remaining progression-free at 1 year

**Long-term follow-up in TIVO-3 suggests that early and consistent PFS benefit with TIVO over SOR may be associated with an improvement in OS HR over time as more events accumulate**

### References

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