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 renal cell carcinoma (RCC) following prior systemic therapies. In the TIVO-3 study, 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 0.75 (95% CI, 0.56–0.95). Similarly, longer follow-up analyses revealed that the investigator-assessed PFS at 3 years was higher in patients treated with TIVO compared with those treated with SOR (12% vs 2%, respectively).

Maturity of survival data is a key analytic when evaluating the clinical application of oncology therapies. 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 follow-up.

### Study Design

TIVO-3 is a phase 3, double-blind, parallel-arm study comparing TIVO with SOR in patients with R/R metastatic RCC (Figure 1).

### Results

At baseline, 350 patients were randomized to receive TIVO (n=175) or SOR (n=175).

- At 2 years following LPI, the median follow-up was 17.9 months (data cutoff, August 2019). 65% of patients had experienced an event on 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).

### 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.
- 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).

### References


### Acknowledgments

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### Key eligibility criteria

- Advanced clear cell RCC
- ≥2 prior systemic regimens, including prior VEGFR TKI
- ECOG PS 0 or 1

### Treatment until progression or unacceptable toxicity

- TIVO 1.34 mg PO QD (6-week cycle)
- SOR 400 mg PO BID (continuously in 3-week cycle)

### Stratification

- Prior regimens
- RCC histology
- RCC type
- Presence or absence of PD-L1 expression

### Baseline demographics

- TIVO: 175 patients
- SOR: 175 patients

### Population group at risk, n, Events, Median OS

<table>
<thead>
<tr>
<th>Group</th>
<th>At risk</th>
<th>Events</th>
<th>Median OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIVO</td>
<td>175</td>
<td>45</td>
<td>45.5 (39.9–54.0)</td>
</tr>
<tr>
<td>SOR</td>
<td>175</td>
<td>45</td>
<td>34.5 (27.4–50.0)</td>
</tr>
</tbody>
</table>

### Endpoint analyses

- 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.

### Figures

Figure 1. TIVO-3 Study Design

Figure 2. KM Survival Curve of Conditional OS in Patients With 12-Month PFS

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

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