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 advanced RCC (mRCC).

- In the phase 3 TIVO-3 trial, tivozanib demonstrated favorable tolerability and significant progression-free survival (PFS) benefits, 2.0 vs 1.6 months, respectively, and overall survival (OS) compared with sorafenib in patients with mRCC.

- Based on these findings, tivozanib was approved by the US Food and Drug Administration for the treatment of patients with advanced or irretrievably advanced RCC following failure of prior systemic therapies.

- Tivozanib was approved in the EU for use in patients with RCC who have been previously treated with sunitinib or axitinib.

- Tivozanib was associated with fewer dose reductions, interruptions, and discontinuations than sorafenib; however, dose modifications may enable proactive supportive care strategies and improve patient experience.

Methods

- TIVO-3 (NCT02489086) is a phase 3, open-label trial that enrolled patients with mRCC whose disease progressed after 2-3 prior systemic regimens, one of which included a VEGF TKI (Figure 1).

- Patients were stratified by International Metastatic RCC Database Consortium (IMDC) category (favorable, intermediate, or poor risk) and type of prior therapy (prior -VEGF, sunitinib, or placebo with concurrent immunotherapy).

- TivozanibTKI class effect all-grade TEAEs were reported in 87% and 92% of patients in the tivozanib and sorafenib arms, respectively.

- Data cutoff for these updated safety analyses was August 16, 2019.

Results

Time to onset, duration, and rate of dose modification

- 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 with tivozanib.

- In the face of dose modification, patients on tivozanib experienced longer treatment exposure than the overall study population, while patients with dose modification of sorafenib generally had the same or shorter duration.

- Greater insight into temporal characteristics of treatment-emergent adverse events (TEAEs) may enable proactive supportive care strategies and improve patient experience.

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

Table 1: TEAE Dose-Modification Rate and Associated Drug Exposure

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<thead>
<tr>
<th>TEAE Class</th>
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<th>Sorafenib</th>
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- Table 3: TEAE Dose-modification Rate and Associated Drug Exposure

- Treatment-exposure data were collected over 42 weeks (14 cycles) of treatment, from the start of treatment, to the earliest study drug discontinuation, dose modification, or end of study,

- Asthenia/fatigue, diarrhea, rash, and palmar-plantar erythrodysesthesia (PPE) were the most frequent TEAEs.

- TEAE dose modification rates were generally lower with tivozanib than with sorafenib regardless of IMDC class.

- 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.

- In the face of dose modification, patients on tivozanib experienced longer treatment exposure than the overall study population, while patients with dose modification of sorafenib generally had the same or shorter duration.

Conclusions

- Tivozanib has demonstrated favorable tolerability and statistically significant improvement in PFS compared with sorafenib.

- 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.

- Greater insight into temporal characteristics of treatment-emergent adverse events may enable proactive supportive care strategies and improve patient experience.

- Tivozanib has demonstrated statistically significant and clinically meaningful improvement in PFS compared with sorafenib.

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References


Acknowledgments

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Table 2: TEAEs and Dose-modification Rates

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