Treatment benefit of tivozanib hydrochloride vs sorafenib on health-related quality of life among patients with advanced/metastatic renal cell carcinoma (mRCC): TIVO-1 study results

David Cella,1 Cristina Ivanescu,1 Konstantina Slavkova,1 Montserrat Casamayor,2 Andrew Strahs,3 Brooke Estes,3 Anna Benkerlin,4 Robert Motzer3

1Northeastern University, Chicago, IL, USA; 2Queen’s, Huddersfield, The Netherlands; 3AWE Oncology, Cambridge, MA, USA; 4Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Introduction

A phase III randomized, double-blind, placebo-controlled study (TIVO-1; NCT01375775) was conducted to compare the efficacy and safety, as well as other patient-reported outcomes (PROs) of tivozanib hydrochloride versus placebo in patients with clear cell advanced/ metastatic renal cell carcinoma (mRCC). Tivozanib was treated as an optional therapy for patients in need of treatment or worsening of tumor size over time for patients treated with placebo. Tivozanib demonstrated significantly improved progression-free survival (PFS) compared to sorafenib, in the overall study population (11.0 months versus 7.9 months, respectively; HR: 0.73, 95% confidence interval [CI]: 0.60–0.90, P = 0.002). A post-hoc analysis of patients for treatment-naive (12.7 months versus 9.1 months, HR: 0.74, 95% CI: 0.58–0.94, P = 0.02) and in patients who previously received one prior systemic therapy for metastatic disease (15.9 months versus 9.9 months, HR: 0.69, 95% CI: 0.49–0.96, P = 0.03) were also favorable results. Patients who had a vascular access device at baseline had a significantly lower risk of tumor progression compared to those without a vascular access device (HR: 0.64, 95% CI: 0.45–0.90, P = 0.019).

At baseline, patients were categorized by the following covariates:

- Treatment group (categorical: tivozanib or sorafenib)
- Dose reduction during study (Yes; No)
- Dropouts before Month 12, defined as patients whose last completed assessment occurred prior to Month 12
- Geographic region (categorical: North America/Western Europe, Central/Eastern Europe, rest of the world)
- Time (months) from diagnosis to randomization (<1 year and ≥ 1 year)
- FACT-G total score: 6 points or less
- Number of prior treatments (categorical: 0 or 1)
- Number of metastatic sites=1
- QoL domain

Methods

- In the Phase III TIVO-1 study, patients with mRCC were randomized 1:1 to receive tivozanib (3 mg/kg once daily) or placebo (placebo once daily) for up to 2 years. Patients were randomized using stratified blocks of randomization based on the type of randomization

- In the beginning of each cycle of 28 days, the Functional Assessment of Cancer Therapy-General (FACT-G), FACT-Kidney Symptom Index Disease Related Symptoms (FKSI-DRS) and EuroQol 5-dimensional (EQ-5D) questionnaire were completed to assess baseline values of quality of life.

- These thresholds were predefined based on existing evidence of score changes that are clinically meaningful to patients. The improvement rate of tivozanib versus sorafenib was compared using a stratified Cochran-Mantel-Haenszel (CMH) test with the number of prior treatments as a stratification variable and reduction in number of metastatic sites as an independent variable

- The treatment effect of tivozanib compared to sorafenib was considered to be significant if the 95% confidence interval did not include 1.00. Sensitivity analyses were performed on the basis of a number of covariates and subgroups of interest

- Patients who did not experience HRQoL deterioration from baseline score were censored at the date of the last assessment.

- A HRQoL improvement/deterioration from baseline at any time during the study was defined as follows:

<table>
<thead>
<tr>
<th>Domain</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT-G</td>
<td>Improvement/deterioration from baseline at any time during the study</td>
</tr>
</tbody>
</table>

HRQoL was maintained at a level comparable to the baseline level up to the analysis cut-off time point in both treatment arms (i.e., decrease in scores did not exceed the established MID). These results did not reach statistical significance (HR, 0.86 (95% CI, 0.70–1.06))

Results

- The HRQoL analysis included 509 patients: 258 in the tivozanib arm and 251 in the sorafenib arm. More than 96% of patients were included in the analysis.

- The average baseline HRQoL scores differed significantly between the treatment arms (Figure 1).

- The difference in HRQoL improvement from baseline was calculated as the difference between the time to first HRQoL deterioration from baseline for tivozanib and sorafenib. The difference for physical well-being (PWB) was statistically significant (0.31 months for tivozanib and 2.79 months for sorafenib; P < 0.01)

- The difference in physical well-being (PWB) was statistically significant (0.31 months for tivozanib and 2.79 months for sorafenib; P < 0.01)

- The difference in HRQoL improvement from baseline was calculated as the difference between the time to first HRQoL deterioration from baseline for tivozanib and sorafenib. The difference for physical well-being (PWB) was statistically significant (0.31 months for tivozanib and 2.79 months for sorafenib; P < 0.01)

Discussion and Conclusions

- Comorbidities, statins, and cancer treatments were not associated with decline of HRQoL across any scale or planned analyses, providing support for the intervention benefit of HRQoL, and better tolerability as evidenced by lower dose reductions observed in the tivozanib arm.

- HRQoL was maintained at levels comparable to the baseline level up to the analysis cut-off time point in both treatment arms (i.e., decrease in scores did not exceed the established MID).

- Tivozanib showed a favorable treatment benefit on health-related quality of life compared with sorafenib in patients with advanced/metastatic renal cell carcinoma (mRCC) in the TIVO-1 study.