Circulating neuropilin-1 as a potential biomarker of progression-free survival benefit for tivozanib in metastatic clear cell renal cell carcinoma (RCC): post-hoc biomarker analysis of tivozanib RCC trials

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Abstract Reference: A-17

Introduction

• Tivozanib has been investigated in renal cell carcinoma (RCC)

- In the Phase 2 study of tivozanib in patients with RCC (Study 201), median progression-free survival (PFS) was 11.7 months in the intention-to-treat (ITT) population and 14.8 months in patients who discontinued treatment due to RCC (aRCC)
- In the TIVO-1 Phase 3 trial in patients with advanced RCC, the primary endpoint of median PFS was 11.9 months vs 9.1 months for sorafenib (HR) 0.79, 95% confidence interval (CI) 0.64-0.99, P=0.0425

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- The identification of biomarkers in targeted VEGFR cancer therapy has been challenging
- Biomarker analyses were performed for patients in the 201 and TIVO-1 studies
- Serum biomarker analysis was performed using RiboLase-Based Methodology (RBMM) Human Oncology
- The objective of this study was to investigate potential biomarkers of tivozanib benefit in patients with advanced ccRCC

Objective

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Methods

• The 201 study (NCT00502307) was a Phase 2, placebo controlled, randomized, double-blind, discontinuation trial in patients with RCC
- Patients had recurrent or metastatic RCC not amendable to surgery, no more than 3 prior systemic treatments for RCC, and no prior VEGF-targeted therapy
- Patients were randomized (1:1) to tivozanib 1.5 mg once daily for 3 weeks followed by 1 week off, or placebo for 12 weeks
- All patients were unblinded after 12 weeks of double-blind treatment
- Following the completion of the 201 and TIVO-1 trials, post-hoc exploratory serum biomarker analyses, including NRP-1, were performed to identify and validate candidate biomarkers of increased tivozanib benefit

Results

• Serum samples from 50 patients with ccRCC were profiled on RBM to identify and analyze serum factors that correlate with response to tivozanib
- Maximum percent tumor reduction (MPR) and independent assessment of PFS were used
- Biomarker analyses were performed for patients in the 201 and TIVO-1 studies
- Serum biomarker analysis was performed using RiboLase-Based Methodology (RBMM) Human Oncology
- Tivozanib was the only serum protein significantly different between responders and nonresponders
- A Cox proportional hazard model was used to assess the association between serum biomarkers and PFS and overall survival (OS)

Conclusions

- In the exploratory analysis, controls were unavailable to determine whether NRP-1 was a potential prognostic or response biomarker
- NRP-1 was further investigated in the TIVO-1 trial

- Tivozanib was further investigated in the TIVO-1 trial
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Table 1. Serum Protein Biomarkers Investigated in Study 201

<table>
<thead>
<tr>
<th>Serum protein</th>
<th>P value</th>
<th>Q value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuripilin (NRP-1)</td>
<td>0.0033</td>
<td>0.2389</td>
</tr>
<tr>
<td>Leptin</td>
<td>0.0130</td>
<td>0.3864</td>
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<tr>
<td>Insulin-like growth factor binding protein 2 (IGFBP2)</td>
<td>0.2534</td>
<td>0.3664</td>
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<tr>
<td>Kallikrein 5</td>
<td>0.3086</td>
<td>0.3664</td>
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<tr>
<td>Endoglin</td>
<td>0.0316</td>
<td>0.3664</td>
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<tr>
<td>Phosphoserine aminotransferase (PASTA)</td>
<td>0.3622</td>
<td>0.3664</td>
</tr>
<tr>
<td>Insulin-like growth factor binding protein 1 (IGFBP1)</td>
<td>0.3638</td>
<td>0.3664</td>
</tr>
<tr>
<td>Interferon-gamma induced protein 10 (P10)</td>
<td>0.0449</td>
<td>0.3910</td>
</tr>
<tr>
<td>Monokine induced by gamma interferon (MIG)</td>
<td>0.0392</td>
<td>0.4651</td>
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<tr>
<td>Fibulin 1C (Fib-1c)</td>
<td>0.0708</td>
<td>0.4656</td>
</tr>
</tbody>
</table>

Figure 1. Study Design of Trial 201 (A) and TIVO-1 (B).

Figure 2. NRP-1 Levels in Tivozanib Responders vs Nonresponders

Figure 3. PFS of Tivozanib-Treated Patients With High vs Low NRP-1 Levels Based on a Median Cutoff

Figure 4. OS of Tivozanib-Treated Patients With High vs Low NRP-1 Levels Based on a Median Cutoff

Acknowledgments

This study was sponsored by AVEO Oncology. Editorial assistance was provided by Scientific Connections, onAshfield Company, and was funded by AVEO Oncology. The authors would like to thank Brooke Esteves, a former employee of AVEO Oncology, for her contributions to this study.