Tivozanib hydrochloride pharmacokinetic/pharmacodynamic analysis of blood pressure and soluble vascular endothelial growth factor receptor 2 (sVEGFR2) in patients with advanced renal cell carcinoma

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Introduction

Among tivozanib-treated patients, diastolic blood pressure increased a median of 5 mm Hg on Cycle 1 Day 15 and Cycle 2 Day 1 compared with baseline. No significant relationship was seen between the measured changes in diastolic blood pressure and the differences in tivozanib exposure. These findings are consistent with previous reports that decreases of 5 mm Hg on Cycle 1 Day 15 and Cycle 2 Day 1 compared with baseline. No significant association of tivozanib exposure and blood pressure is likely, but has not been found in the present analysis. This might be due to infrequent monitoring of blood pressure in the Phase III study.

Methods

Pharmacokinetic, blood pressure, and sVEGFR2 data from tivozanib-treated RCC patients in a Phase II (n=21) and a Phase II (n=28) study were pooled and analyzed.

The Phase II study (AV-951-07-20; NCT00502307) was a randomized, placebo-controlled discontinuation trial to determine the safety and efficacy of tivozanib, and the Phase II study (AV-09-30; NCT00530527) was a randomized controlled, open-label study to compare tivozanib with sorafenib.

In both studies, patients were treated with 1.5 mg tivozanib daily for 21 days followed by a 7-day rest (28-day treatment cycle). Patients in both trials were treated for multiple cycles.

The following clinical and biological endpoints were analyzed based on a time-dependent relationship:

sVEGFR2

Diastolic blood pressure

Systolic blood pressure

Blood pressure measurements taken on Cycle 1 Day 1 (predose baseline) and on Cycle 1 Day 15, Cycle 2 Day 1, and Cycle 3 Day 0 were used in this analysis. Measurements were repeated to the nearest 0.5 mm Hg, and the analysis focused on blood pressure shifts in 5 mm Hg increments.

Serum samples for sVEGFR2 Phase II study only were collected on Cycle 1 (predose) and on Cycle 1 Day 15, Cycle 2 Day 1, and Cycle 2 Days 22-28.

Models of drug exposure as predictors of longitudinal changes in sVEGFR2 were constructed by non-linear, mixed-effects modeling.

The change in diastolic blood pressure as a function by study day after the start of tivozanib treatment is shown in Table 1 and Figure 2.

Table 1: Change in Systolic Blood Pressure (mm Hg) by Cycle and Study Day

<table>
<thead>
<tr>
<th>Cycle and Study Day</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>Median</th>
<th>25th Quartile</th>
<th>75th Quartile</th>
</tr>
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<tr>
<td>Cycle 1 Day 1</td>
<td>-25</td>
<td>0.00</td>
<td>4.30</td>
<td>5.00</td>
<td>3.33</td>
<td>6.60</td>
</tr>
<tr>
<td>Cycle 2 Day 1</td>
<td>255</td>
<td>-50</td>
<td>-5.00</td>
<td>0.00</td>
<td>-10.00</td>
<td>9.00</td>
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<tr>
<td>Cycle 3 Day 1</td>
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<td>-25</td>
<td>0.00</td>
<td>4.30</td>
<td>10.00</td>
<td>18.00</td>
</tr>
<tr>
<td>Cycle 3 Day 15</td>
<td>253</td>
<td>-50</td>
<td>-5.00</td>
<td>0.00</td>
<td>-10.00</td>
<td>9.00</td>
</tr>
</tbody>
</table>

No significant relationship was seen between the measured changes in diastolic blood pressure and the differences in tivozanib exposure. These findings are consistent with previous reports that decreases of 5 mm Hg on Cycle 1 Day 15 and Cycle 2 Day 1 compared with baseline. No significant association of tivozanib exposure and blood pressure is likely, but has not been found in the present analysis. This might be due to infrequent monitoring of blood pressure in the Phase III study.

Results

No significant relationship was seen between the measured changes in diastolic blood pressure and the differences in tivozanib exposure. These findings are consistent with previous reports that decreases of 5 mm Hg on Cycle 1 Day 15 and Cycle 2 Day 1 compared with baseline. No significant association of tivozanib exposure and blood pressure is likely, but has not been found in the present analysis. This might be due to infrequent monitoring of blood pressure in the Phase III study.

Pharmacokinetics and sVEGFR2

AVG942 declined as a non-linear function of time from Day 1 to Cycle 2 Days 22-28 among tivozanib-treated patients, and the decrease appeared retardable with time. The curvilinear decrease in sVEGFR2 over time is shown in Figure 4.

Figure 4. Mean change in sVEGFR2 vs time in tivozanib-treated patients.

Conclusions

Pharmacokinetic/pharmacodynamic analysis of data from patients treated with tivozanib in Phase II and III studies showed that patients had a median increase in diastolic blood pressure of 5 mm Hg on Cycle 1 Day 15 and Cycle 2 Day 1 compared with baseline.

Levels of serum sVEGFR2 were found to decrease with time, and the effect size increased with tivozanib exposure. These findings are consistent with previous reports that decreases of sVEGFR2 may serve as a pharmacodynamic marker of VEGFR inhibition.

A significant association of tivozanib exposure and blood pressure is likely, but has not been found in the present analysis. This might be due to infrequent monitoring of blood pressure in the Phase III study.

References


Acknowledgments

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