Results From a Phase I Trial of Tivozanib (AV-951) Combined With Temsirolimus in Patients With Renal Cell Carcinoma

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Introduction

Tivozanib (AV-951) is an oral, potent and selective microtubule kinase inhibitor designed to provide optimal blockade of the vascular endothelial growth factor (VEGF) pathway by inhibiting all three VEGF receptors (VEGFR) - in cell-based models of published data, tivozanib has inhibitory activity against the VEGFR-1, -2, and -3 kinases of adenocarcinomas (70% inhibition of maximal VEGF-induced cell migration at 0.1, 0.2, and 0.4 μM, respectively).

Results from a Phase I study of tivozanib demonstrated a maximum tolerated dose (MTD) of 1.5 mg/day, 3 mg/day, and 6 mg/day respectively, with responses observed in patients with renal cell carcinoma (RCC) and other tumor types. Tivozanib, a monophasic target of receptor (mTOR) inhibitor, is approved for treatment of advanced RCC.

Methods

Key Eligibility Criteria

• Adults aged 18 years or older
• Histologically or cytologically confirmed RCC with a clear cell component
• Measurable disease by standard Response Evaluation Criteria in Solid Tumors (RECIST)
• No more than one prior VEGF-targeted therapy
• No prior treatment with tivozanib or other mTOR-targeted therapy
• Karnofsky performance status greater than 70%, with a life expectancy of at least 3 months
• No central nervous system primary malignancy or active metastasis

Study Design

Tivozanib was administered orally once daily for 3 weeks, followed by a 1-week break (4 weeks = 1 cycle, Figure 1).

Table 1. Tivozanib dose escalation cohorts

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Tivozanib dose</th>
<th>Patients enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5 mg/d</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>1.0 mg/d</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>1.5 mg/d</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>2.0 mg/d</td>
<td>15</td>
</tr>
<tr>
<td>MTD expansion</td>
<td>2.5 mg/d</td>
<td>15</td>
</tr>
</tbody>
</table>

An expansion cohort of 12 additional patients was enrolled at the MTD for further safety and efficacy analyses.

The MTD of tivozanib plus temsirolimus was determined as the maximum dose at which no more than one patient experienced dose-limiting toxicity, defined as:

• Grade 3 non-hematologic toxicity lasting more than 3 days (except alopecia, rash, and self-limiting/reversibly controllable events); grade 4 non-hematologic toxicity
• Grade 3/4 neutropenia (associated with fever and requiring antibiotics); grade 3/4 thrombocytopenia
• Any toxicity requiring treatment interruption for longer than 2 weeks

Key Study Endpoints

• Responses were evaluated per RECIST 1.0
• Blood samples were collected for evaluation of PK parameters for tivozanib and temsirolimus concentrations

Statistical Analysis

• PK parameters were determined by non-compartmental methods using Phoenix WinNonlin, version 6.2 (Pharsight Corporation, Cary, NC).

• Adverse Events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for AEs, version 3.0

Results

Patients

• A total of 27 patients with RCC received at least one dose of study medication and were evaluable for safety (Table 2).
• Median duration of treatment was 21.9 weeks (range, 6.9-97.9 weeks).

Table 2. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 27</th>
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</thead>
<tbody>
<tr>
<td>Median age (y)</td>
<td>61 (43-71)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>20 (74)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>1: White 24 (89) 2: African American 1 (4) 3: Black/African American 1 (4)</td>
</tr>
<tr>
<td>Karnofsky performance status, n (%)</td>
<td>100% 70% 80% 90%</td>
</tr>
<tr>
<td>No. of prior VEGF-targeted therapies, n (%)</td>
<td>1 0 2 3</td>
</tr>
<tr>
<td>Stages</td>
<td>1: Stable disease 15 (68) 2: Partial response 5 (23) 3: Complete response 0</td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td>1: Tivozanib monotherapy 6 (22) 2: Tivozanib + temsirolimus 21 (78)</td>
</tr>
</tbody>
</table>

The mean (± standard deviation) maximum plasma concentration (Cmax) and area under the curve extrapolated to the last time point (AUC∞) for tivozanib were lower and higher, respectively, than previously reported (3), most likely due to the sparse sampling schedule employed in this study - Cmax, 164.3 ± 88.1 ng/mL; AUC∞, 413 ± 127 microgram hour/mL; t1/2, 99.4 ± 33.4 ng/mL; tmax, 25 ± 9 week; n=19 |

Results from a Phase I study of tivozanib determined a maximum tolerated dose (MTD) of 1.5 mg/day, with responses observed in patients with renal cell carcinoma (RCC) and other tumor types. Tivozanib, a monophasic target of receptor (mTOR) inhibitor, is approved for treatment of advanced RCC.

Pharmacokinetics

• Tivozanib had an effect on tivozanib serum concentration (Figure 3 and 4).

Conclusions

• Tivozanib and temsirolimus can safely be combined at the full recommended doses of each agent, 1.5 mg/day and 25 mg/week, respectively, and the combination of tivozanib and temsirolimus was well tolerated in this study.

• The incidence of AEs associated with tivozanib and temsirolimus in combination was similar to that observed in previous clinical trials of each agent administered as monotherapy in patients with advanced RCC, suggesting no evidence of additive toxicity.

• In patients with advanced RCC, the combination of tivozanib and temsirolimus demonstrated encouraging evidence of clinical activity, with 23% of patients achieving a partial response, 68% maintaining stable disease, 66% demonstrating tumor reduction, and a median duration of treatment of 21.9 weeks, with 2 patients remaining on treatment for 80 and 95 weeks.

• Tivozanib is the first selective VEGF kinase inhibitor to be successfully combined with an mTOR inhibitor at the full recommended dose and schedule of both agents.

• Data suggest no PK interaction between tivozanib and temsirolimus.

• The clinical activity and manageable AE profile observed with this combination of tivozanib and temsirolimus further supports exploration in patients with RCC.

References


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