Results From a Phase 1 Trial of Tivozanib (AV-951) Combined With Temsirolimus Therapy in Patients With Renal Cell Carcinoma

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Introduction

Tivozanib (AV-951) is an oral, potent and selective small-molecule tyrosine kinase inhibitor that targets vascular endothelial growth factor (VEGF) pathway by inhibiting VEGF receptors (VEGFRs) 1, 2, and 3. In a phase 2 randomized discontinuation trial in advanced RCC, tivozanib showed promising antitumor activity, with an overall objective response rate of 15%. This study was designed to evaluate the safety and antitumor activity of tivozanib plus temsirolimus, an oral mTOR antagonist, combining a targeted agent that inhibits angiogenesis with a mTOR inhibitor that inhibits tumor cell growth. The primary objective of this study was to determine the maximum tolerated dose (MTD) and schedule of tivozanib plus temsirolimus in patients with advanced RCC, who had undergone Evanspace pretreatment (radiation therapy or surgical resection).

Methods

Patients

Patients with histologically confirmed metastatic RCC with a clear cell component were eligible for this study. Patients were allowed to receive at least 1 prior VEGF-based treatment. No prior temsirolimus or other mTOR-targeted therapy was allowed. Patients were randomized to receive AV-951 1.5 mg/day (3 weeks on, 1 week off) or AV-951 1.5 mg/day (21.0 mg/week) plus temsirolimus 25 mg/week (C1/D15) or 50 mg/week (C2/D8).

Primary Endpoint

To determine the safety, tolerability, and MTD of tivozanib administered in combination with temsirolimus.

Secondary Endpoints

To characterize the pharmacokinetics of tivozanib and temsirolimus.

To investigate the antitumor activity of tivozanib and temsirolimus when administered as a single agent.

To evaluate the antineoplastic activity of tivozanib and temsirolimus when administered in combination.

Eligibility Criteria

Advanced RCC: patients with histologically confirmed metastatic RCC and other tumors (M) and a Karnofsky performance status of ≥70%.

Prior VEGF Treatments: patients were allowed to receive at least 1 prior VEGF-based treatment. No prior temsirolimus or other mTOR-targeted therapy was allowed.

Patient Age: patients must be at least 18 years old, and no upper age limit.

Methods

Sixty patients with advanced RCC were randomized in a 2:2:2:2 ratio to receive tivozanib 0.5 mg/day, tivozanib 1.0 mg/day, tivozanib 1.5 mg/day, or tivozanib 1.5 mg/day, plus temsirolimus 25 mg/week or 50 mg/week.

Safety and Tolerability

The most common treatment-emergent adverse events (any causality) were fatigue, thrombocytopenia, elevated alanine aminotransferase (ALT), and elevated aspartate aminotransferase (AST).

Pharmacokinetics

The maximum plasma concentration (Cmax) and area under the curve (AUC) for tivozanib were increased in proportion to dose. The AUC and Cmax for temsirolimus were similar across treatment groups.

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Conclusions

Tivozanib and temsirolimus can safely be combined at the MTD of AV-951 1.5 mg/day, plus temsirolimus 25 mg/week, and a median duration of treatment of 21.9 weeks, with 2 patients withdrawing due to drug-related adverse events: left ventricular dysfunction (possibly related to tivozanib), and fatigue (possibly related to temsirolimus). The combination of tivozanib and temsirolimus demonstrated encouraging evidence of clinical activity and tolerability.

References