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

Fairooz F. Kabbinavar,[1] Sandy Srinivas,[2] Ralph J. Hauke,[3] R. J. Amato,[4] Brooke Esteves,[5] Monette M. Cotreau,[5] Andrew L. Strahs,[5] Mayer N. Fishman[6]

[1]Institute of Urologic Oncology, UCLA, Los Angeles, CA, USA; [2]Stanford Medical Center, Stanford, CA, USA; [3]Nebraska Cancer Specialists, Omaha, NE, USA; [4]University of Texas Health Science Center, Houston, TX, USA; [5]AVEO Pharmaceuticals, Inc., Cambridge, MA, USA; [6]H. Lee Moffitt Cancer Center, Tampa, FL, USA

Introduction

- Tivozanib (AV-951) is an oral, potent and selective small-molecule tyrosine kinase inhibitor designed to provide optimal blockade of the vascular endothelial growth factor (VEGF) pathway by inhibiting all three VEGF receptors (VEGFRs)
  - In cell-based models of published data, tivozanib has inhibitory activity against the VEGFR-1, -2, and -3 kinases at subnanomolar concentrations (half maximal inhibitory concentration of 0.21, 0.16, and 0.24 nM, respectively)[1]
- Results from a Phase I study of tivozanib determined a maximum tolerated dose (MTD) of tivozanib 1.5 mg/day, with responses observed in patients with renal cell carcinoma (RCC) and other tumors[1]
- Temsirolimus, a mammalian target of rapamycin (mTOR) inhibitor, is approved for treatment of advanced RCC
- Preclinical data support the combination of VEGFR and mTOR inhibitors for the treatment of RCC and other solid tumors[2]

Objectives

- To determine the safety, tolerability, and MTD of tivozanib administered in combination with temsirolimus
- To characterize the pharmacokinetic (PK) profile and antineoplastic activity of tivozanib and temsirolimus when administered in combination

Methods

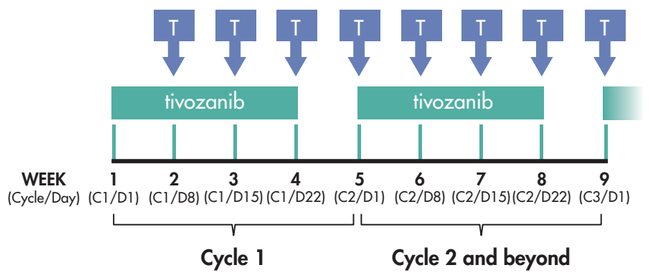
Key Eligibility Criteria

- Adults aged 18 years or older
- Histologically confirmed metastatic RCC with a clear cell component
- Measureable disease by standard Response Evaluation Criteria In Solid Tumors (RECIST)
- No more than one prior VEGF-targeted therapy
- No prior treatment with temsirolimus 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**)

Figure 1. Phase Ib, open-label, dose-escalation trial: treatment schedule.



T, temsirolimus; C, cycle; D, day.

- Temsirolimus was administered intravenously once a week starting on Day 8 of Cycle 1
- Sequential cohorts of patients were enrolled using standard 3 + 3 dose-escalation guidelines (**Table 1**); enrollment to the next dose level occurred only after acceptable tolerability was determined

Table 1. Dose-escalation Cohorts

Dose level	Tivozanib dose	Temsirolimus dose	No. of patients enrolled
1	0.5 mg/day	15 mg/week	5
2	1.0 mg/day	15 mg/week	4
3	1.5 mg/day	15 mg/week	3
4	1.5 mg/day	25 mg/week	3
MTD expansion	1.5 mg/day	25 mg/week	12

- 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 defined as the maximum dose at which no more than one patient experienced a dose-limiting toxicity, defined as:
  - Grade 3 non-hematologic toxicity lasting more than 3 days (except alopecia, rash, and self-limiting/medically controllable events); grade 4 non-hematologic toxicity
  - Grade 3/4 neutropenia (associated with fever and requiring antibiotics); grade 4 neutropenia lasting longer than 5 days; grade 4 thrombocytopenia
  - Any toxicity requiring treatment interruption for longer than 2 weeks

Key Study Endpoints

- Responses were evaluated with RECIST 1.0
- Blood samples were collected for evaluation of PK parameters for tivozanib and temsirolimus serum 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

Characteristic	N = 27
Median age (range), y	61 (43–71)
Male sex, n (%)	25 (93)
Race, n (%)	
White	24 (89)
Asian	2 (7)
Black/African American	1 (4)
Median time since diagnosis (range), mo	24 (0–146)
Karnofsky performance status,[a] n (%)	
100%	18 (67)
90%	5 (19)
80%	4 (15)
No. of prior VEGF treatments, n (%)	
0	6 (22)
1	20 (74)
2	1 (4)
Prior VEGF treatments, n (%)	
Bevacizumab	3 (11)
Sorafenib	10 (37)
Sunitinib	9 (33)

[a]Percentages may not total 100% due to rounding.

Efficacy

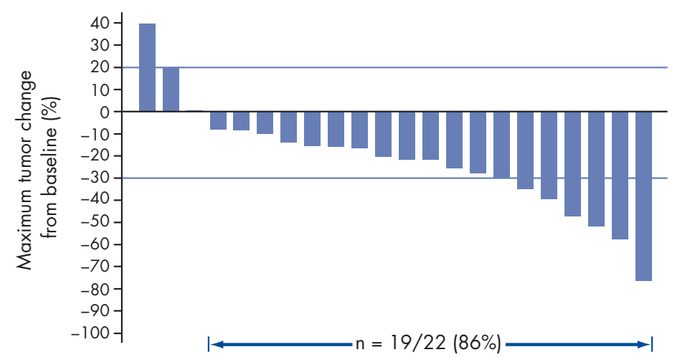
- A total of 22 patients received at least two cycles of tivozanib treatment and were included in the efficacy analyses
- Of the remaining five patients, two received less than two cycles of tivozanib before withdrawing for reasons other than progressive disease, and three patients did not satisfy the entry criteria
- Median duration of treatment, measured from Day 1 of Cycle 1 to the date of last treatment, was 21.9 weeks (range, 6.9–97.9 weeks)
- The objective response rate was 23% (95% confidence interval, 8%–45%; **Table 3**)
- An additional 15 patients maintained stable disease, and 86% of patients demonstrated tumor shrinkage (**Figure 2**)

Table 3. Best Overall Response

Response,[a] n (%)	n = 22
Objective response[b]	5 (23)
Complete response	0
Partial response	5 (23)[c]
Stable disease	15 (68)
Progressive disease	2 (9)

[a]By RECIST 1.0.
[b]Objective response = complete + partial response.
[c]Unconfirmed response in one patient.

Figure 2. Waterfall plot of maximum tumor change from baseline.

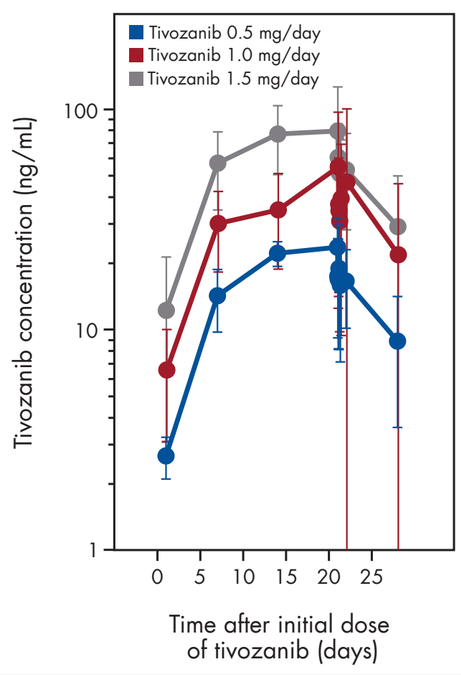


Maximum change in tumor size from baseline was not available for five patients.

Pharmacokinetics

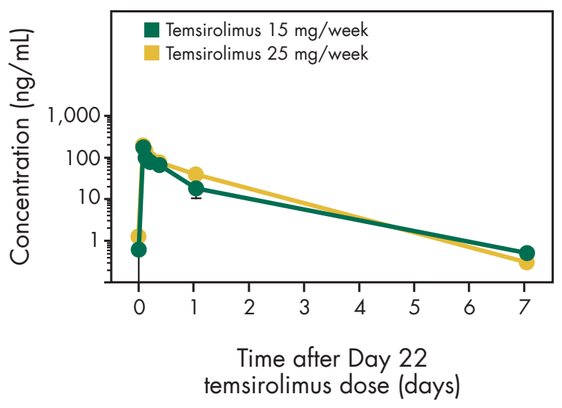
- Temsirolimus had no effect on tivozanib serum concentration (**Figures 3 and 4**)

Figure 3. Mean (± SD) tivozanib concentration-time profiles for Cycle 1.



SD, standard deviation.

Figure 4. Mean (± SD) temsirolimus concentration-time profiles by dose at Day 22, Cycle 1.



- The mean (± standard deviation) maximum plasma concentration (C_{max}) and area under the curve extrapolated to the last time point ($AUC_{0–last}$) for temsirolimus are lower and higher, respectively, than previously reported,[3,4] most likely due to the sparse sampling schedule employed in this study
  - C_{max}: 164.3 ng/mL (± 88.1; temsirolimus 15 mg/week; n=7) and 199.6 ng/mL (± 33.4 ng/mL; temsirolimus 25 mg/week; n=9)
  - $AUC_{0–last}$: 3191 h•ng/mL (± 1925 h•ng/mL; temsirolimus 15 mg/week); 4245 h•ng/mL (± 2033 h•ng/mL; temsirolimus 25 mg/week)
  - Sirolimus, the principal active metabolite of temsirolimus in plasma, had a similar pattern (results have been previously presented)[5]

Adverse Events

- The MTD for the combination was tivozanib 1.5 mg/day + temsirolimus 25 mg/week
- One patient receiving the MTD required a dose reduction of tivozanib (grade 2 fatigue), and another required reduction of temsirolimus (grade 3 hyponatremia)
- Eight patients (30%) withdrew from the study due to AEs, including three who withdrew due to drug-related AEs: left ventricular dysfunction (possibly related to tivozanib), fatigue (possibly related to temsirolimus), colitis, and rectal abscess (possibly related to tivozanib and/or temsirolimus)
- One patient died during the study due to cardiopulmonary arrest unrelated to drug administration
- The most common treatment-emergent AEs (any causality) were fatigue (74%), stomatitis (59%), diarrhea (56%), decreased appetite (52%), and nausea (48%; **Table 4**)
  - Fatigue was the most common grade 3 or greater AE, reported by four patients
  - Hyperglycemia and hypophosphatemia were the most common grade 3/4 laboratory abnormalities, reported by four patients each
- No dose-limiting toxicities were observed

Table 4. Treatment-emergent Adverse Events in >20% of Patients at the MTD[a]

	Tivozanib 1.5 mg/day + temsirolimus 25 mg/week (n=15)[b]	Total (N=27)
Adverse event	Adverse event, all grades/grade 3 and 4	Adverse event, all grades/grade 3 and 4, n (%)
Fatigue	13/3	20 (74)/4 (15)
Stomatitis	9/1	16 (59)/2 (7)
Diarrhea	9/2	15 (56)/2 (7)
Decreased appetite	7/0	14 (52)/0
Nausea	8/1	13 (48)/1 (4)
Constipation	7/1	11 (41)/1 (4)
Dyspnea	7/1	10 (37)/1 (4)
Decreased weight	5/0	8 (30)/0
Dehydration	5/2	7 (26)/2 (7)
Vomiting	3/1	7 (26)/1 (4)
Cough	4/0	7 (26)/0
Hypertension	5/0	7 (26)/0
Abdominal pain	5/2	6 (22)/2 (7)
Back pain	4/0	6 (22)/1 (4)
Rash erythematous	3/0	6 (22)/1 (4)
Anemia	3/0	6 (22)/0
Dysphonia	4/0	6 (22)/0
Epistaxis	5/0	6 (22)/0
Pyrexia	4/0	6 (22)/0
Rash	5/0	6 (22)/0

[a]Further details on the dose cohorts were previously reported.[5]
[b]Includes the maximum tolerated dose expansion cohort.

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 were similar to the safety profiles of these agents administered as monotherapy in patients with advanced RCC,[6,7] 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, 86% 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 VEGFR tyrosine 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 warrants further exploration in patients with RCC**

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