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 designed to provide optimal blockade of the vascular endothelial growth factor (VEGF) pathway by inhibiting all 3 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 (IC_{50} of 0.21, 0.16, and 0.24 nM, respectively)[1]
- Results from a phase 1 study[1] 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
- In a phase 2 randomized discontinuation trial[2] in advanced RCC, tivozanib 1.5 mg/day (3 weeks on, 1 week off) demonstrated
  - Median overall progression-free survival in all patients of 11.7 months and in patients with clear cell RCC who had undergone nephrectomy (retrospective subset analysis) of 14.8 months
  - Best overall objective response rate of 30% (95% confidence interval, 25%–36%) for all patients based on independent radiology review
  - Favorable safety profile; hypertension and dysphonia, which are established VEGF-related side effects, were the most commonly reported treatment-related side effects
- Temsirolimus (Torisel®), a mammalian target of rapamycin (mTOR) inhibitor, is approved for the treatment of advanced RCC
- Preclinical data support the combination of VEGFR and mTOR inhibitors for the treatment of RCC and other solid tumors[3]

Objectives

Primary Endpoint

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

Secondary Endpoints

- To characterize the pharmacokinetic (PK) profile of tivozanib and temsirolimus when administered in combination
- To evaluate the antineoplastic activity of tivozanib and temsirolimus when administered in combination

Methods

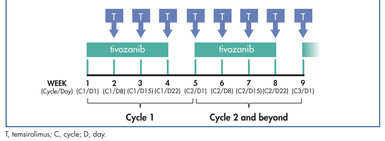
Key Eligibility Criteria

- 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) criteria
- No more than 1 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

- Phase 1b, open-label, dose-escalation trial
- Tivozanib was administered orally once daily for 3 weeks, followed by a 1-week break (4 weeks = 1 cycle; **Figure 1**)

Figure 1. 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 Levels

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

MTD, maximum tolerated dose.

- 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 1 patient experienced a dose-limiting toxicity (DLT), defined as
  - Grade 4 nonhematologic toxicity or grade 3 nonhematologic toxicity lasting more than 3 days (except alopecia, rash, transaminase elevations, and self-limiting/medically controllable events)
  - Grade 4 neutropenia lasting longer than 5 days; grade 3/4 neutropenia associated with fever and requiring antibiotics; grade 4 thrombocytopenia
  - Any toxicity requiring treatment interruption for longer than 2 weeks

Study Endpoints

- Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0
- Antitumor activity was evaluated using standard RECIST criteria, version 1.0
- Blood samples were collected for evaluation of tivozanib, temsirolimus, and sirolimus serum concentrations; PK parameters were determined by non-compartmental methods using Phoenix WinNonlin, version 6.2

Results

Patients

- A total of 27 patients with RCC received at least 1 dose of study medication and were evaluable for safety (**Table 2**)

Table 2. Patient Demographic

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)

VEGF, vascular endothelial growth factor.
[a]Percentages may not total 100% due to rounding.

Safety and Tolerability

- The MTD for the combination was tivozanib 1.5 mg/day plus 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 adverse events, including 3 who withdrew due to drug-related adverse events: left ventricular dysfunction (possibly related to tivozanib), fatigue (possibly related to temsirolimus), and 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 adverse events (any causality) were fatigue (74%), stomatitis (59%), diarrhea (56%), decreased appetite (52%), and nausea (48%; **Table 3**)
  - Fatigue was also the most common grade 3 or greater adverse event, reported by 4 patients
- Grade 3 or greater treatment-emergent laboratory abnormalities (any causality) are shown in **Table 4**
  - Hyperglycemia and hypophosphatemia were the most common grade 3/4 laboratory abnormalities, reported by 4 patients each

Efficacy

- A total of 22 patients received at least 2 cycles of tivozanib treatment and were included in the efficacy analyses
  - Of the remaining 5 patients, 2 received less than 2 cycles of tivozanib before withdrawing for reasons other than progressive disease and 3 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; **Figure 2**)
- The objective response rate was 23% (95% confidence interval, 8%–45%; **Table 5**)
- An additional 15 patients maintained stable disease and 86% of patients demonstrated tumor shrinkage (**Figure 3**)

Table 5. 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]Using standard Response Evaluation Criteria In Solid Tumors.
[b]Objective response = complete + partial response.
[c]Unconfirmed response in 1 patient.

Table 3. Treatment-emergent Adverse Events in ≥20% of Patients, Any Causality

Adverse event, all grades/ grade 3/4, n (%)	Tivozanib 0.5 mg/day, temsirolimus 15 mg/week (n = 5)	Tivozanib 1.0 mg/day, temsirolimus 15 mg/week (n = 4)	Tivozanib 1.5 mg/day, temsirolimus 15 mg/week (n = 3)[a]	Tivozanib 1.5 mg/day, temsirolimus 25 mg/week (n = 15)[b]	Total (N = 27)
Fatigue	1/1	3/0	3/0	13/3	20 (74)/4 (15)
Stomatitis	2/0	4/1	1/0	9/1	16 (59)/2 (7)
Diarrhea	1/0	2/0	3/0	9/2	15 (56)/2 (7)
Decreased appetite	3/0	2/0	2/0	7/0	14 (52)/0
Nausea	2/0	2/0	1/0	8/1	13 (48)/1 (4)
Constipation	0	2/0	2/0	7/1	11 (41)/1 (4)
Dyspnea	0	1/0	2/0	7/1	10 (37)/1 (4)
Decreased weight	0	1/0	2/0	5/0	8 (30)/0
Dehydration	0	1/0	1/0	5/2	7 (26)/2 (7)
Vomiting	2/0	1/0	1/0	3/1	7 (26)/1 (4)
Cough	1/0	1/0	1/0	4/0	7 (26)/0
Hypertension	1/0	0	1/0	5/0	7 (26)/0
Abdominal pain	0	0	1/0	5/2	6 (22)/2 (7)
Back pain	1/1	0	1/0	4/0	6 (22)/1 (4)
Rash erythematous	1/0	1/1	1/0	3/0	6 (22)/1 (4)
Anemia	0	1/0	2/0	3/0	6 (22)/0
Dysphonia	0	1/0	1/0	4/0	6 (22)/0
Epistaxis	0	0	1/0	5/0	6 (22)/0
Pyrexia	0	0	2/0	4/0	6 (22)/0
Rash	0	1/0	0	5/0	6 (22)/0

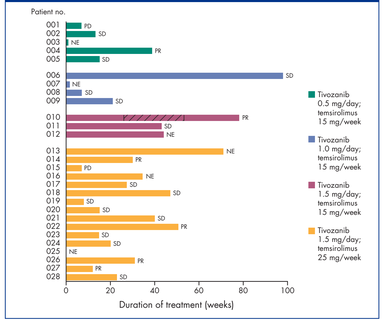
[a]Patient 010 experienced an extended treatment interruption (9/2009 to 3/2010) before restarting study treatment. None of the listed adverse events occurred during this treatment interruption.
[b]Includes the maximum tolerated dose expansion cohort.

Table 4. Grade 3/4 Laboratory Abnormalities in ≥5% of Patients, Any Causality

Laboratory abnormality, grade 3/4, n (%)	Tivozanib 0.5 mg/day, temsirolimus 15 mg/week (n = 5)	Tivozanib 1.0 mg/day, temsirolimus 15 mg/week (n = 4)	Tivozanib 1.5 mg/day, temsirolimus 15 mg/week (n = 3)[a]	Tivozanib 1.5 mg/day, temsirolimus 25 mg/week (n = 15)[b]	Total (N = 27)
Hyperglycemia	1	1	0	2	4 (15)
Hypophosphatemia	0	0	1	3	4 (15)
Elevated GGT	1	0	0	2	3 (11)
Lymphopenia	0	1	0	2	3 (11)
Thrombocytopenia	1	0	0	2	3 (11)
Hypertriglyceridemia	0	0	0	3	3 (11)
Hypokalemia	0	0	0	2	2 (7)
Hyponatremia	0	1	0	1	2 (7)

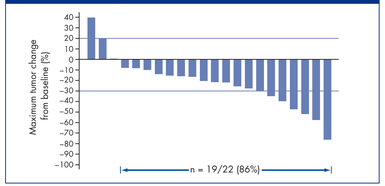
GGT, gamma-glutamyl transpeptidase.
[a]Patient 010 experienced an extended treatment interruption (9/2009 to 3/2010) before restarting study treatment. None of the listed laboratory abnormalities occurred during this treatment interruption.
[b]Includes the maximum tolerated dose expansion cohort.

Figure 2. Duration of treatment and best overall response.



PD, progressive disease; SD, stable disease; NE, not evaluable; PR, partial response.
Patient 010 experienced an extended treatment interruption (9/2009 to 3/2010) before restarting study treatment.

Figure 3. Waterfall plot of maximum tumor change from baseline.

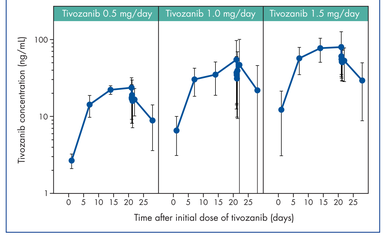


Maximum change in tumor size from baseline was not available for 5 patients.

Pharmacokinetics

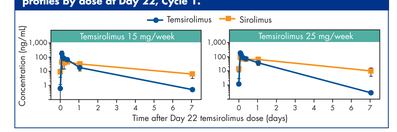
- Tivozanib serum concentrations over time were similar to those previously reported for tivozanib monotherapy (**Figure 4**),[4] indicating no effect of temsirolimus on tivozanib serum concentration
- Temsirolimus and sirolimus concentration-time profiles for the Day 22, Cycle 1 dose are shown in **Figure 5**

Figure 4. Mean (± SD) tivozanib concentration-time curves for Cycle 1.



SD, standard deviation.

Figure 5. Mean (± SD) temsirolimus and sirolimus concentration-time profiles by dose at Day 22, Cycle 1.



SD, standard deviation.

- Preliminary PK parameters for temsirolimus and sirolimus are displayed in **Table 6**
  - Sirolimus was evaluated because it is the principal active metabolite of temsirolimus in plasma
  - Maximum plasma concentration (C_{max}) and area under the curve (AUC_{0-last}) for temsirolimus are lower and higher, respectively, than previously reported,[5,6] most likely due to the sparse sampling schedule employed in this study
  - The ratio for sirolimus AUC to temsirolimus AUC was lower than previously reported, most likely due to the overestimated AUC_{0-last} for temsirolimus, resulting from the sparse sampling schedule

Table 6. Pharmacokinetic Parameters of Temsirolimus and Sirolimus at Day 22, Cycle 1

Parameter, mean (SD)	Temsirolimus 15 mg/week	Temsirolimus 25 mg/week
Temsirolimus		
Evaluable, n	7	9
C_{max}, ng/mL	164.3 (88.1)	199.6 (33.4)
AUC_{0-last}, h•ng/mL	3,191 (1,925)	4,245 (2,033)
Sirolimus		
Evaluable, n	7	9
C_{max}, ng/mL	51.3 (25.4)	93.8 (25.0)
AUC_{0-last}, h•ng/mL	3,559 (1,629)	6,566 (4,110)
Ratio of sirolimus AUC_{0-last}/ temsirolimus AUC_{0-last}	1.2 (0.7)	1.5 (0.7)

SD, standard deviation; C_{max}, maximum plasma concentration; AUC_{0-last}, area under the concentration-time curve from the time of dosing to the last measurable observation.

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**
  - **The combination of tivozanib and temsirolimus was well tolerated in the study**
  - **The incidence of adverse events associated with combination tivozanib and temsirolimus therapy in this study were similar to the safety profiles of these agents administered as monotherapy in patients with advanced RCC,[2,7] 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 side effect profile observed with this combination warrants further exploration in patients with RCC**

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