Final Analysis of the Phase 2 Randomized Discontinuation Trial of Tivozanib (AV-951) Versus Placebo 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] determined a maximum tolerated dose of tivozanib 1.5 mg/day, with responses observed in patients with renal cell carcinoma (RCC) and other tumors
- Previously reported results from the current phase 2 trial[2] indicated that tivozanib has antitumor activity and a favorable safety profile in patients with advanced RCC
- Clear cell RCC, the most common histologic subtype, has been shown to be more responsive to anti-VEGF therapies compared with non–clear cell subtypes[3]
- Nephrectomy is a known prognostic factor in RCC[4-6]

Objective

- To evaluate the efficacy of tivozanib in patients with advanced RCC
  - Objective response rate (ORR) after 16 weeks of open-label tivozanib
  - Percentage of randomized patients remaining progression free after the 12-week phase of double-blind treatment with tivozanib or placebo
  - Secondary efficacy objectives included progression-free survival (PFS) after treatment with tivozanib or placebo and overall PFS in all treated patients
- To investigate the safety and tolerability of tivozanib

Methods

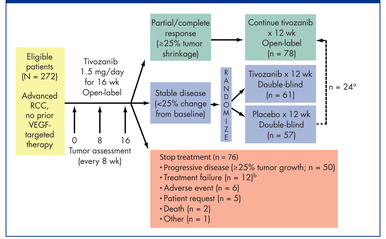
Study Design

- Phase 2 randomized discontinuation trial (**Figure 1**)
- Patients received tivozanib 1.5 mg/day orally for 3 weeks, followed by a 1-week break (4 weeks = 1 cycle)
- Patients who attained at least 25% regression during the first 16 weeks continued open-label treatment with tivozanib
- Patients with less than 25% change from baseline were randomized to double-blind tivozanib or placebo

Efficacy and Safety Analyses

- Efficacy was analyzed in all treated patients and in patients randomized to tivozanib or placebo during the double-blind phase
  - Patients underwent computed tomography (CT) scans every 2 cycles
  - Response was evaluated by independent radiology review using standard Response Evaluation Criteria In Solid Tumors (RECIST) criteria, version 1.0
  - Kaplan-Meier methodology was used to estimate PFS; between-group comparisons of PFS were performed using a log-rank test. To estimate the PFS of all treated patients, those randomized to placebo were censored after the 16-week open-label period
- A retrospective subgroup analysis evaluated efficacy by RCC histology subtype and nephrectomy status at study enrollment
- Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0

Figure 1. Study design and patient disposition.



RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor.
[a]Patients with progression during the double-blind phase were unblinded; those on placebo were allowed to restart tivozanib. All patients were unblinded after 12 weeks of double-blind treatment.
[b]Treatment failure and clinical disease progression not meeting the criteria for progressive disease (≥25% tumor growth).

Results

Patients

- A total of 272 patients with locally advanced or metastatic RCC were enrolled between October 2007 and July 2008 and received at least 1 dose of study medication (**Table 1**)
- Median duration of treatment was 8.5 months (range, 0.03–34.7 months)

Table 1. Patient Demographic

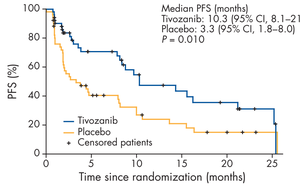
Characteristic	N = 272
Median age (range), y	56 (26–79)
Male sex, n (%)	191 (70)
Race, n (%)	
White	254 (93)
Asian	18 (7)
ECOG Performance Status, n (%)	
0	132 (49)
1	140 (51)
Prior nephrectomy, n (%)	199 (73)
Histology, n (%)	
Clear cell RCC	226 (83)
Non–clear cell RCC	46 (17)
Number of prior systemic treatments,[a] n (%)	
0	146 (54)
1	116 (43)
≥2	10 (4)
MSKCC prognostic score, n (%)	
Favorable	75 (28)
Intermediate	164 (60)
Poor	28 (10)
Not available/unknown	5 (2)

ECOG, Eastern Cooperative Oncology Group; RCC, renal cell carcinoma; MSKCC, Memorial Sloan-Kettering Cancer Center.
[a]Percentages may not total 100% due to rounding.

Efficacy

- At the end of the 16-week open-label tivozanib phase, the ORR was 18% (95% confidence interval [CI], 14%–23%)
- Following the 16-week open-label phase, patients with less than 25% change in tumor size from baseline were randomized to double-blind treatment with tivozanib (n = 61) or placebo (n = 57; **Figure 1**)
- Significantly more patients were progression free after 12 weeks of double-blind treatment with tivozanib (49%) compared with placebo (21%; $P = 0.001$)
- Median PFS was also significantly higher among patients randomized to tivozanib compared with placebo ($P = 0.010$; **Figure 2**)

Figure 2. PFS in patients randomized to tivozanib versus placebo following the 16-week open-label period.



PFS, progression-free survival; CI, confidence interval.
P value was based on a log-rank test.

- Of 24 patients with disease progression on placebo who crossed back to open-label tivozanib, 22 (92%) experienced disease control (response or stable disease) after restarting tivozanib
- Among all patients, tivozanib treatment was associated with an ORR of 24% (95% CI, 19%–30%) as best overall response throughout the study (**Table 2**)

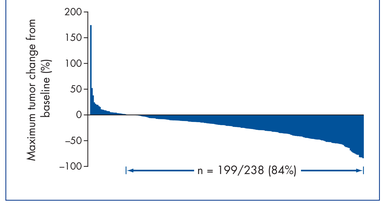
Table 2. Best Overall Response to Tivozanib Throughout the Study

Response,[a] n (%)	All patients (N = 272)	Clear cell RCC + nephrectomy (n = 176)
Objective response[b,c]	66 (24)	52 (30)
Complete response	1 (<1)	1 (1)
Partial response[c]	65 (24)	51 (29)
Stable disease	148 (54)	92 (52)
Progressive disease	21 (8)	13 (7)
Not evaluable/ determined	21 (8)	8 (5)
Median duration of response (95% CI), mo	16.1 (9.3–19.6)	16.1 (11.2–19.6)

RCC, renal cell carcinoma; CI, confidence interval.
[a]Using standard Response Evaluation Criteria In Solid Tumors; confirmed and unconfirmed responses combined.
[b]Objective response = complete + partial response.
[c]An additional 16 patients (including 11 with clear cell RCC + nephrectomy) had unconfirmed partial responses.

- In an exploratory retrospective analysis of patients with clear cell RCC who had undergone nephrectomy, ORR was 30% (95% CI, 23%–37%)
- Most (84%) patients treated with tivozanib demonstrated tumor shrinkage during the course of therapy (**Figure 3**)

Figure 3. Maximum change in tumor size from baseline.[a]

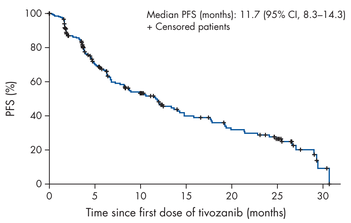


CT, computed tomography.
[a]Each bar represents one of the 238 patients with ≥1 post-baseline CT scan who were evaluable for determination of change in tumor size from baseline.

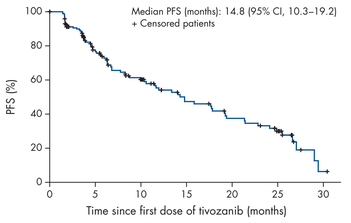
- Median PFS was 11.7 months (95% CI, 8.3–14.3 months) among all treated patients (**Figure 4A**) and 14.8 months (95% CI, 10.3–19.2 months) among those with clear cell RCC who had undergone nephrectomy (**Figure 4B**)

Figure 4. PFS throughout the study in the intent-to-treat population (N = 272).[a]

A. All patients (N = 272)



B. Clear cell RCC + nephrectomy (n = 176)



PFS, progression-free survival; CI, confidence interval; RCC, renal cell carcinoma.
[a]Patients randomized to placebo were removed from the analysis after the 16-week open-label period.

- In a subanalysis of patients with clear cell RCC who had undergone nephrectomy, median PFS was 14.3 months among treatment-naive patients and 15.8 months among patients with at least 1 prior systemic therapy (**Table 3**)

Table 3. PFS by Prior Treatment Status for the Clear Cell RCC + Nephrectomy Population

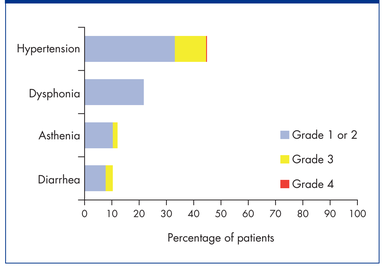
Prior treatment status	n	PFS, mo	95% CI, mo
Treatment naive	77	14.3	6.28–24
≥1 prior treatment	99	15.8	10.5–21.3

PFS, progression-free survival; RCC, renal cell carcinoma; CI, confidence interval.

Safety and Tolerability

- Hypertension (45%) and dysphonia (22%) were the most commonly reported treatment-related adverse events of any grade (**Figure 5**)
  - Hypertension was also the most common treatment-related grade 3/4 adverse event (12%)
  - Although hypertension was commonly observed, it was readily managed using standard antihypertensives and a treatment algorithm provided to investigators[7]

Figure 5. Treatment-related adverse events observed in ≥10% of patients.



- There was a low incidence of treatment-related diarrhea (12%), asthenia (10%), fatigue (8%), stomatitis (4%), and hand-foot syndrome (4%)
- Grade 3/4 laboratory abnormalities observed in at least 5% of patients included increased gamma-glutamyl transpeptidase (17%), lymphopenia (6%), and hyperuricemia (6%)
  - Grade 3/4 proteinuria was reported for 3% of patients
- Dose reductions due to adverse events were required by 8% of patients, and treatment interruptions due to adverse events were required by 4% of patients
- Treatment was discontinued by 9% of patients due to an adverse event

Conclusions

- **Tivozanib, a selective VEGFR tyrosine kinase inhibitor, shows promising efficacy and acceptable safety and tolerability for patients with advanced or metastatic RCC**
- **Significantly more patients randomized to tivozanib were progression free after 12 weeks of double-blind treatment compared with those randomized to placebo, *P* = 0.001; median PFS was also longer with tivozanib, *P* = 0.010**
- **In the overall study population, the ORR was 24% and median PFS was 11.7 months; 84% of patients experienced tumor shrinkage during tivozanib therapy**
- **In a retrospective exploratory analysis, tivozanib demonstrated the greatest efficacy in patients with clear cell RCC who had undergone nephrectomy, with a median PFS of 14.8 months and ORR of 30%**
- **Tivozanib was associated with an acceptable safety profile consistent with that of a selective VEGFR inhibitor, with low incidences of off-target toxicities such as hand-foot syndrome and proteinuria**
- **Based on these results, tivozanib is currently being evaluated in nephrectomized patients with advanced clear cell RCC in the global phase 3 TIVO-1 trial**

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