Activity of Tivozanib (AV-951) in Patients With Different Histologic Subtypes of Renal Cell Carcinoma

P. Bhargava,[1,*] B. Esteves,[1] M. Al-Adhami,[1] D. A. Nosov,[2] O. N. Lipatov,[3] A. A. Lyulko,[4] A. A. Anischenko,[5] R. T. Chacko,[6] D. C. Doval,[7] W. Slichenmyer[1]

[1]AVEO Pharmaceuticals, Inc., Cambridge, MA, USA; [2]Blokhin Oncology Research Center, Moscow, Russian Federation; [3]Bashkortostan Clinical Oncology Center, Ufa, Russian Federation; [4]Zaporizhya Medical Academy of Postgrad. Education, Zaporizhya, Ukraine; [5]Donetsk Regional Antitumor Center, Donetsk, Ukraine; [6]Christian Medical College, Vellore, India; [7]Rajiv Gandhi Cancer Institute, New Delhi, India.

*Presenting author.

Introduction

- Tivozanib (AV-951) is a potent and selective small-molecule pan–vascular endothelial growth factor receptor (VEGFR) inhibitor with 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]
- In a phase 1 study, the maximum tolerated dose of tivozanib was determined to be 1.5 mg/day, and responses were observed in patients with renal cell carcinoma (RCC) and other tumors[1]
- Previously reported results from the current phase 2 study indicated that tivozanib has antitumor activity and a favorable safety profile in patients with RCC[2]
- Clear cell RCC, the most common histologic subtype, has been shown to be more responsive to anti-VEGF therapies compared with non–clear cell (NCC) subtypes[3]
- Nephrectomy is a known prognostic marker in RCC[4-6]

Objectives

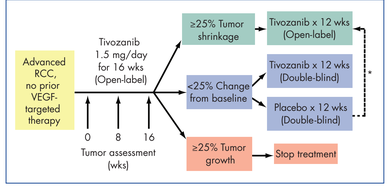
- To retrospectively explore the effect of RCC histologic subtype and nephrectomy status on the efficacy of tivozanib in patients with RCC
- To evaluate the safety and tolerability of tivozanib across histologic subtypes

Methods

Study Design

- Phase 2 randomized discontinuation trial (**Figure 1**)
- Treatment schedule: tivozanib 1.5 mg/day orally for 3 weeks, followed by a 1-week break (1 cycle = 4 weeks)

Figure 1. Study design.



RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor.
*Patients with progression during the double-blind phase were un-blinded. Patients on placebo were given the option of restarting tivozanib. All patients were un-blinded after the 12-week double-blind phase.

Subgroup Analyses

- Retrospective analyses evaluated efficacy and safety by RCC subtype and nephrectomy status at study enrollment
- Efficacy (ie, objective response rate [ORR], disease control rate [DCR; ORR + stable disease], and progression-free survival [PFS]) was analyzed in all treated patients, as well as patients who attained 25% regression during the first 16 weeks and those who had <25% change from baseline and were randomized to tivozanib or placebo
  - 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 removed from analysis after the 16-week open-label period
  - A chi-square test was used to compare ORR between groups

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, 0.03-23.8 months)

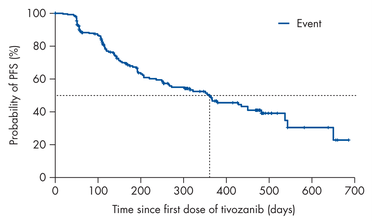
Table 1. Patient Demographics

Median age (range), y	56 (26-79)
Male sex, n (%)	191 (70.2)
Race, n (%)	
White	254 (93.4)
Asian	18 (6.6)
ECOG performance status, n (%)	
0	133 (48.9)
1	139 (51.1)
Histology, n (%)	
Clear cell RCC	226 (83.1)
NCC RCC	46 (16.9)
Papillary (chromophil) NCC	11
Other NCC	35
Prior nephrectomy, n (%)	199 (73.2)
Number of prior treatments, n (%)	
0	146 (53.7)
1	75 (27.6)
≥2	51 (18.8)
MSKCC prognostic score, n (%)	
Favorable	81 (29.8)
Intermediate	156 (57.4)
Poor	22 (8.1)
Not available/unknown	13 (4.8)

ECOG, Eastern Cooperative Oncology Group; RCC, renal cell carcinoma; NCC, non–clear cell; MSKCC, Memorial Sloan-Kettering Cancer Center.

Intent-to-treat Analysis

Figure 2. Tivozanib PFS in all patients (ITT population; N = 272), IRR.



	N	Median PFS	95% CI
ITT population	272	11.8 months (360 days)	253-450 days

PFS, progression-free survival; ITT, intent-to-treat; IRR, independent radiology review; CI, confidence interval.

Effect of RCC Histologic Subtype

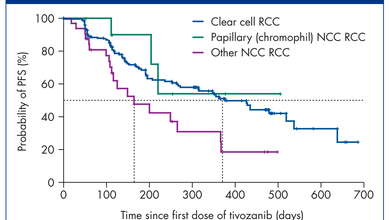
- PFS was significantly higher among patients with clear cell RCC compared with NCC RCC ($P = 0.04$). ORR was also higher among patients with clear cell RCC, although this difference was not significant (**Table 2**)
- The median PFS for patients with papillary (chromophil) NCC RCC had not yet been reached as of the data cutoff date, while the median PFS for other NCC subtypes was 5.4 months (**Table 2** and **Figure 3**)
- A high rate of disease control was observed for patients with all histologic subtypes (**Table 2**)

Table 2. Subgroup Analysis of Efficacy Response by RCC Histologic Subtype, IRR

Subgroup[a]	n	Median PFS, mo	ORR, n (%)	DCR, n (%)
All patients	272	11.8	73 (27)	229 (84)
Clear cell RCC	226	12.5	65 (29)	192 (85)
NCC RCC	46	6.7	8 (17)	37 (80)
Papillary (chromophil)	11	NA	2 (18)	11 (100)
Other	35	5.4	6 (17)	26 (74)

RCC, renal cell carcinoma; IRR, independent radiology review; PFS, progression-free survival; ORR, objective response rate; DCR, disease control rate; NCC, non–clear cell; NA, not available; RECIST, Response Evaluation Criteria In Solid Tumors.
[a]Using standard RECIST criteria. ORR = complete + partial responses. DCR = ORR + stable disease.

Figure 3. Subgroup analysis of PFS by RCC histologic subtype in all patients (N = 272), IRR.



	n	Median PFS	95% CI
Clear cell RCC	226	12.5 months (379 days)	302-537 days
Papillary (chromophil) NCC RCC	11	NA	204 days-NA
Other NCC subtypes	35	5.4 months (164 days)	112-366 days

PFS, progression-free survival; RCC, renal cell carcinoma; IRR, independent radiology review; NCC, non–clear cell; CI, confidence interval; NA, not available.

Effect of RCC Histologic Subtype and Nephrectomy Status

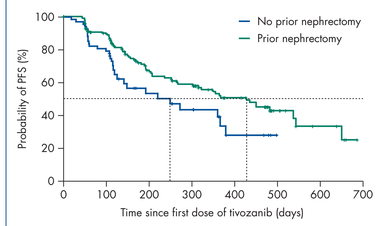
- Among all treated patients, patients who had undergone nephrectomy had a significantly higher median PFS ($P = 0.02$) and ORR ($P = 0.04$) compared with those without nephrectomy (**Table 3** and **Figure 4**)
- Median PFS was greatest among patients with clear cell RCC who had undergone nephrectomy (14.8 months; **Table 3** and **Figure 5**)
- Among patients with NCC RCC, median PFS was similar between patients without (7.2 months) and with (6.6 months) prior nephrectomy (**Table 3** and **Figure 6**)
- DCR was similar among all patient subpopulations (**Table 3**)

Table 3. Subgroup Analysis of Efficacy Response by RCC Histologic Subtype and Nephrectomy Status, IRR

Subgroup[a]	n	Median PFS, mo	ORR, n (%)	DCR, n (%)
All patients				
No prior nephrectomy	73	8.2	13 (18)	57 (78)
Prior nephrectomy	199	14.1	60 (30)	172 (86)
Clear cell RCC				
No prior nephrectomy	50	8.9	9 (18)	38 (76)
Prior nephrectomy	176	14.8	56 (32)	154 (88)
NCC RCC				
No prior nephrectomy	23	7.2	4 (17)	19 (83)
Prior nephrectomy	23	6.6	4 (17)	18 (78)

RCC, renal cell carcinoma; IRR, independent radiology review; PFS, progression-free survival; ORR, objective response rate; DCR, disease control rate; NCC, non–clear cell; RECIST, Response Evaluation Criteria In Solid Tumors.
[a]Using standard RECIST criteria. ORR = complete + partial responses. DCR = ORR + stable disease.

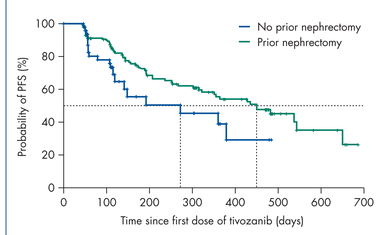
Figure 4. Subgroup analysis of PFS by nephrectomy status in all patients (N = 272), IRR.



	n	Median PFS	95% CI
No prior nephrectomy	73	8.2 months (249 days)	125-379 days
Prior nephrectomy	199	14.1 months (428 days)	302-543 days

PFS, progression-free survival; IRR, independent radiology review; CI, confidence interval.

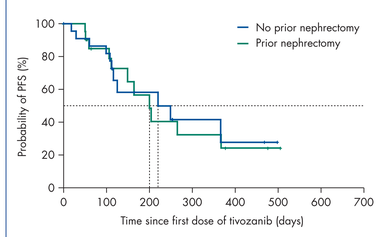
Figure 5. Subgroup analysis of PFS by nephrectomy status in patients with clear cell RCC (n = 226), IRR.



	n	Median PFS	95% CI
No prior nephrectomy	50	8.9 months (272 days)	119 days-NA
Prior nephrectomy	176	14.8 months (450 days)	322-650 days

PFS, progression-free survival; RCC, renal cell carcinoma; IRR, independent radiology review; CI, confidence interval; NA, not available.

Figure 6. Subgroup analysis of PFS by nephrectomy status in patients with NCC RCC (n = 46), IRR.



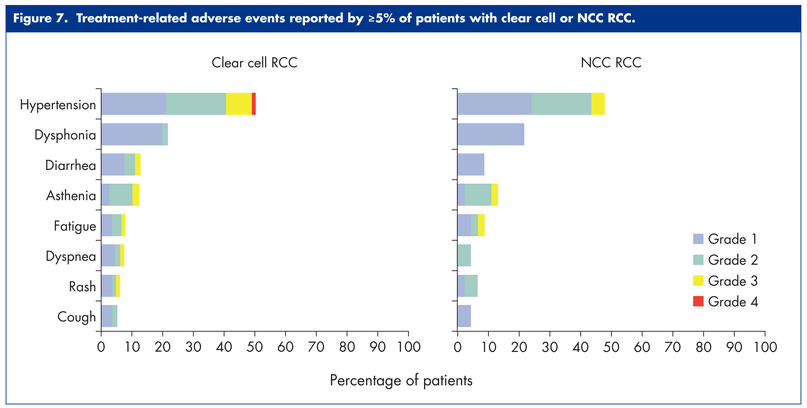
	n	Median PFS	95% CI
No prior nephrectomy	23	7.2 months (220 days)	116 days-NA
Prior nephrectomy	23	6.6 months (200 days)	149-367 days

PFS, progression-free survival; NCC, non–clear cell; RCC, renal cell carcinoma; IRR, independent radiology review; CI, confidence interval; NA, not available.

Safety and Tolerability

- The most commonly reported treatment-related adverse events of any grade were hypertension (clear cell, 49.1%; NCC, 47.8%) and dysphonia (clear cell, 21.7%; NCC, 21.7%; **Figure 7**)
- The most common grade ≥3 drug-related adverse events were hypertension (clear cell, 9.7%; NCC, 4.3%) and asthenia (clear cell, 2.2%; NCC, 2.2%)
- For both clear cell and NCC RCC, respectively, there were low incidence rates of stomatitis (4.9% and 2.2%), hand-foot syndrome (3.5% and 4.3%), and proteinuria (4.9% and 0%)

Figure 7. Treatment-related adverse events reported by ≥5% of patients with clear cell or NCC RCC.



NCC, non–clear cell; RCC, renal cell carcinoma.

Conclusions

- **In this retrospective exploratory analysis, disease control was observed for patients with all RCC histologic subtypes**
- **Patients with clear cell RCC who had undergone nephrectomy appear to experience the greatest benefit from tivozanib**
- **Among patients with NCC RCC, those with papillary (chromophil) RCC appear to experience the greatest benefit**
- **The rate of adverse events was similar among patients with clear cell and NCC RCC and was consistent with that of a selective VEGFR inhibitor with minimal "off-target" toxicities**

References

1. Eskens FALM, et al. In: *Proceedings of the 99th Annual Meeting of the AACR*. Philadelphia, PA: American Association of Cancer Research; 2008. Abstract #LB-201.
2. Bhargava P, et al. Poster presented at: Annual Meeting of the American Society of Clinical Oncology; May 29-June 2, 2009; Orlando, FL. Abstract #5032.
3. Rini BI. *J Clin Oncol*. 2009;27(19):3225-3234.
4. Motzer RJ, et al. *J Clin Oncol*. 1999;17(8):2530-2540.
5. Neves RJ, et al. *J Urol*. 1988;139(6):1173-1176.
6. Uygur MC, et al. *Int Urol Nephrol*. 1998;30(6):681-687.

Acknowledgments

Study supported by AVEO Pharmaceuticals, Inc., Cambridge, MA. Wilson Joe, PhD, of MedErgy provided editorial assistance.

POSTER PRESENTED AT THE NINTH INTERNATIONAL KIDNEY CANCER SYMPOSIUM (IKCS), OCTOBER 1-2, 2010, CHICAGO, ILLINOIS.

Activity of Tivozanib (AV-951) in Patients With Different Histologic Subtypes of Renal Cell Carcinoma

P. Bhargava,[1] B. Esteves,[1] M. Al-Adhami,[1] D. A. Nosov,[2] O. N. Lipatov,[3] A. A. Lyulko,[4] A. A. Anischenko,[5] R. T. Chacko,[6] D. C. Doval,[7] W. Slichenmyer[1]

[1]AVEO Pharmaceuticals, Inc., Cambridge, MA, USA; [2]Blokhin Oncology Research Center, Moscow, Russian Federation; [3]Bashkortostan Clinical Oncology Center, Ufa, Russian Federation; [4]Zaporizhya Medical Academy of Postgrad. Education, Zaporizhya, Ukraine; [5]Donetsk Regional Antitumor Center, Donetsk, Ukraine; [6]Christian Medical College, Vellore, India; [7]Rajiv Gandhi Cancer Institute, New Delhi, India.

POSTER PRESENTED AT THE NINTH INTERNATIONAL KIDNEY CANCER SYMPOSIUM (IKCS), OCTOBER 1-2, 2010, CHICAGO, ILLINOIS.