Effect of Hypertension, Nephrectomy, and Prior Treatment on the Efficacy of Tivozanib (AV-951) in a Phase 2 Randomized Discontinuation Trial in Patients With Renal Cell Carcinoma

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Introduction

- Tivozanib (AV-951) is a potent and selective small-molecule pan-VEGFR inhibitor with activity against the VEGFR-1, -2, and -3 kinases at subnanomolar concentrations
- This 272-patient phase 2 study of tivozanib included patients with renal cell carcinoma (RCC) of non–clear cell histology (17%), as well as patients without a nephrectomy (27%)[1]
  - Tivozanib has a median progression-free survival (PFS) of 11.8 months in this difficult-to-treat population
  - Phase 3 registration studies for sunitinib,[2] sorafenib,[3] and pazopanib[4] were performed predominantly in patients who had clear cell RCC and had undergone nephrectomy
- Nephrectomy is a known prognostic marker in RCC
- Hypertension has been proposed as a biomarker of clinical effect among agents that target the VEGFR tyrosine kinases in RCC[5]
  - VEGF signaling can modulate vascular contractility and blood pressure in humans, supporting an on-mechanism role for VEGFR inhibitors in the development of hypertension[6]

Objective

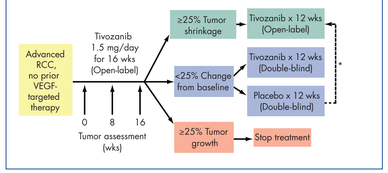
- To retrospectively explore the effect of nephrectomy, prior therapy, and hypertension on the efficacy of tivozanib in patients with RCC

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.

Retrospective Subgroup Analyses

- Efficacy (ie, PFS and objective response rate [ORR]) was evaluated by nephrectomy status, prior treatment status, and hypertension status
  - 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
- Nephrectomy status and prior treatment status were recorded at study enrollment
- Blood pressure (BP) was measured in the clinic on Days 1 and 15 for the first 4 cycles and on Day 1 of each subsequent cycle
- Hypertension was defined as systolic BP >140 mmHg and/or diastolic BP >90 mmHg; standard anti-hypertensive medications were used to manage hypertension

Results

Patients

- A total of 272 patients with locally advanced or metastatic RCC were enrolled in the study and received at least 1 dose of study medication (**Table 1**)

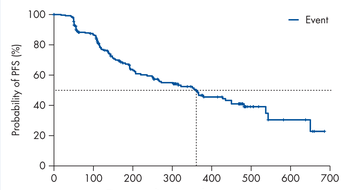
Table 1. Patient Demographics

Characteristic	N = 272
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)
Prior nephrectomy, n (%)	199 (73.2)
Histology, n (%)	
Clear cell RCC	226 (83.1)
Other	46 (16.9)
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; MSKCC, Memorial Sloan-Kettering Cancer Center.

Intent-to-treat Analysis

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



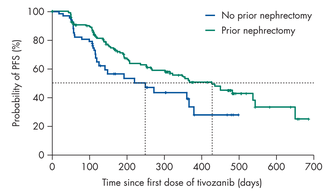
	N	Median PFS	95% CI
ITT population	272	11.8 months (360 days)	253-450 days

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

Effect of Prior Nephrectomy

- Both PFS and ORR were significantly higher among patients who had undergone nephrectomy (**Figures 3** and **4**; **Table 2**)

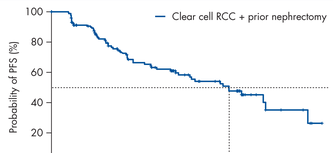
Figure 3. Subgroup analysis of PFS by nephrectomy status in all patients (N = 272), IRR.



	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 4. Subgroup analysis of PFS among patients with clear cell RCC who had undergone nephrectomy (n = 176), IRR.



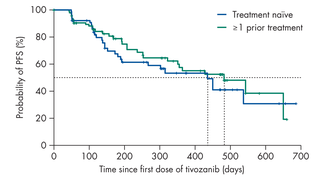
	n	Median PFS	95% CI
Clear cell RCC + prior nephrectomy	176	14.8 months (450 days)	322-650 days

PFS, progression-free survival; RCC, renal cell carcinoma; IRR, independent radiology review; CI, confidence interval.

Effect of Prior Treatment

- Within the subgroup of patients with clear cell RCC who had undergone nephrectomy, PFS was similar between treatment-naïve patients and those who had failed prior therapy with cytokines and/or chemotherapy (**Table 2** and **Figure 5**)

Figure 5. Subgroup analysis of PFS by prior treatment status among patients with clear cell RCC who had undergone nephrectomy (n = 176), IRR.



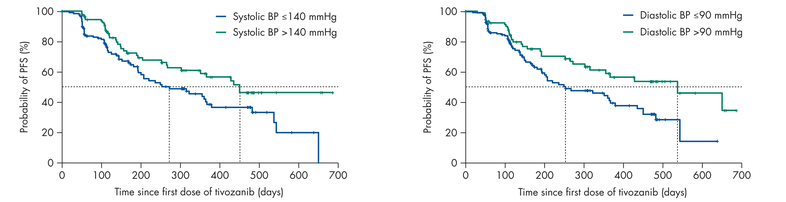
	n	Median PFS	95% CI
Treatment naïve	77	14.3 months (435 days)	192 days-NA
≥1 prior treatment	99	15.8 months (482 days)	322-650 days

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

Effect of Hypertension

- Hypertension was the most commonly reported treatment-related adverse event, reported by 50% of patients
- Development of hypertension at any time during therapy was associated with improved PFS among patients in the overall intent-to-treat population (**Figure 6** and **Table 3**) and in the subset of patients with clear cell RCC who had undergone nephrectomy (**Figure 7** and **Table 3**)
- Although the proportion of patients achieving ORR was also higher among those who developed hypertension, the difference was not significant (**Table 3**)

Figure 6. Subgroup analysis of PFS by hypertension status in all patients (N = 272), IRR.



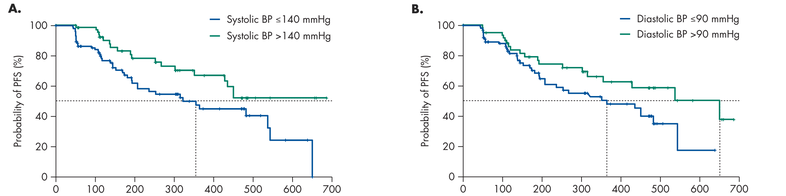
	n	Median PFS	95% CI
Systolic BP ≤140 mmHg	159	8.9 months (272 days)	200-367 days
Systolic BP >140 mmHg	113	14.8 months (450 days)	302 days-NA

PFS, progression-free survival; IRR, independent radiology review; CI, confidence interval; BP, blood pressure; NA, not available.

	n	Median PFS	95% CI
Diastolic BP ≤90 mmHg	177	8.3 months (253 days)	200-379 days
Diastolic BP >90 mmHg	95	17.7 months (537 days)	315 days-NA

PFS, progression-free survival; IRR, independent radiology review; CI, confidence interval; BP, blood pressure; NA, not available.

Figure 7. Subgroup analysis of PFS by hypertension status among patients with clear cell RCC who had undergone nephrectomy (n = 176), IRR.



	n	Median PFS	95% CI
Systolic BP ≤140 mmHg	105	11.7 months (355 days)	207-543 days
Systolic BP >140 mmHg	71	NA	428 days-NA

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

	n	Median PFS	95% CI
Diastolic BP ≤90 mmHg	113	12.0 months (364 days)	207-543 days
Diastolic BP >90 mmHg	63	21.4 months (650 days)	355 days-NA

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

Table 2. Subgroup Analysis of Efficacy Response by Baseline Characteristics, IRR

		PFS		ORR[a]	
Subgroup	n	Months	*P* value	n (%)	*P* value
All patients	272	11.8		73 (27)	
Nephrectomy status					
No nephrectomy	73	8.2	0.02	13 (18)	0.04
Prior nephrectomy	199	14.1		60 (30)	
Clear cell RCC + prior nephrectomy	176	14.8		56 (32)	
Prior treatment status (clear cell RCC + prior nephrectomy)					
Treatment naïve	77	14.3	0.43	33 (43)	0.006
≥1 prior treatments	99	15.8		23 (23)	

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

Table 3. Subgroup Analysis of Efficacy Response by Hypertension Status, IRR

		PFS		ORR[a]	
Subgroup	n	Months	*P* value	n (%)	*P* value
All patients					
Systolic BP >140 mmHg	113	14.8	0.01	34 (30)	0.31
Systolic BP ≤140 mmHg	159	8.9		39 (25)	
Diastolic BP >90 mmHg	95	17.6	0.01	32 (34)	0.06
Diastolic BP ≤90 mmHg	177	8.3		41 (23)	
Clear cell RCC + prior nephrectomy					
Systolic BP >140 mmHg	71	NA	0.02	25 (35)	0.43
Systolic BP ≤140 mmHg	105	11.7		31 (30)	
Diastolic BP >90 mmHg	63	21.4	0.06	24 (38)	0.18
Diastolic BP ≤90 mmHg	113	12.0		32 (28)	

IRR, independent radiology review; PFS, progression-free survival; ORR, objective response rate; BP, blood pressure; RCC, renal cell carcinoma; NA, not available; RECIST, Response Evaluation Criteria In Solid Tumors.
[a]Using standard RECIST criteria. ORR = complete + partial responses.

Conclusions

- **In this retrospective exploratory analysis, the median PFS of patients with clear cell RCC who had undergone nephrectomy was 14.8 months**
- **Both median PFS and ORR were higher for the subgroup of patients with clear cell RCC who had undergone nephrectomy than for the overall patient population**
- **Response was similar between treatment-naïve and previously treated patients with clear cell RCC who had undergone nephrectomy**
- **Presence of hypertension appears to be associated with improved clinical outcomes, both in the overall patient population and among the subset of patients with clear cell RCC who had undergone nephrectomy**

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