

Effect of hypertension, nephrectomy and prior treatment on the efficacy of tivozanib (AV-951) in a phase 2 randomized discontinuation trial (RDT) in patients with renal cell carcinoma (RCC)

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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 pazopanib⁴ were performed predominantly in patients who had clear cell RCC and had undergone a prior nephrectomy
- Nephrectomy is a known prognostic marker in RCC
- Hypertension has been proposed as a biomarker of clinical effect of agents that target the VEGFR tyrosine kinases in RCC⁵
 - VEGF signaling can modulate vascular contractility and blood pressure in humans, supporting an on-mechanism role for VEGFR inhibitors in the development of hypertension⁶

Objective

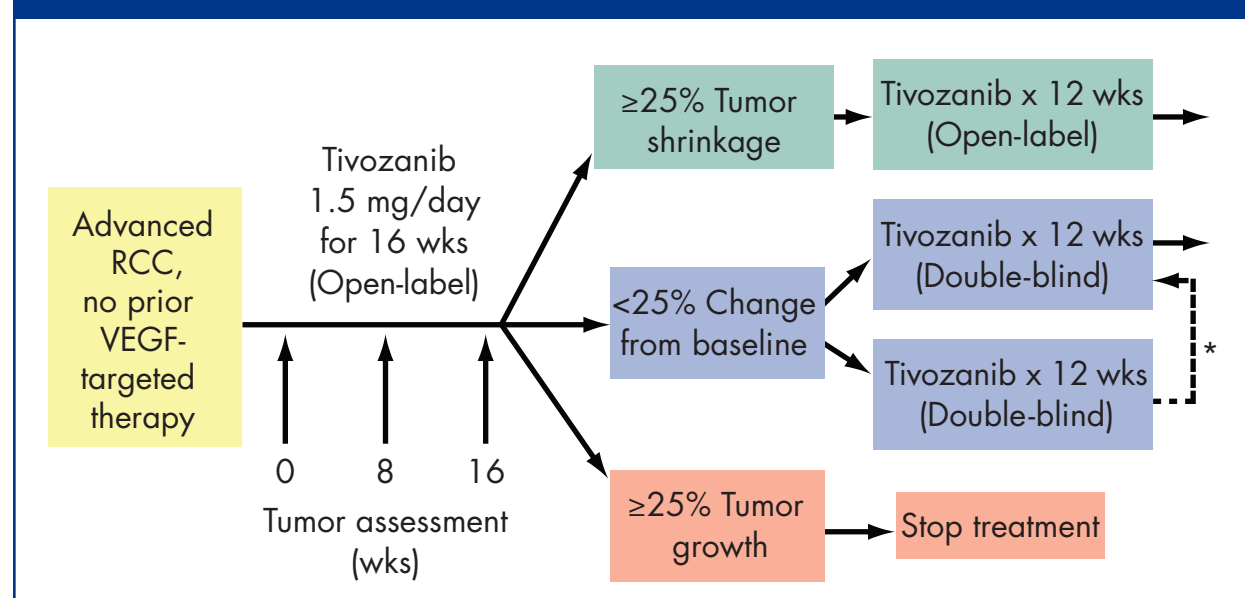
- To retrospectively explore the effect of nephrectomy, prior therapy, and hypertension on the efficacy of tivozanib in patients with RCC

Methods

Study Design

- Phase 2 randomized discontinuation trial
- 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.



*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
 - 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)

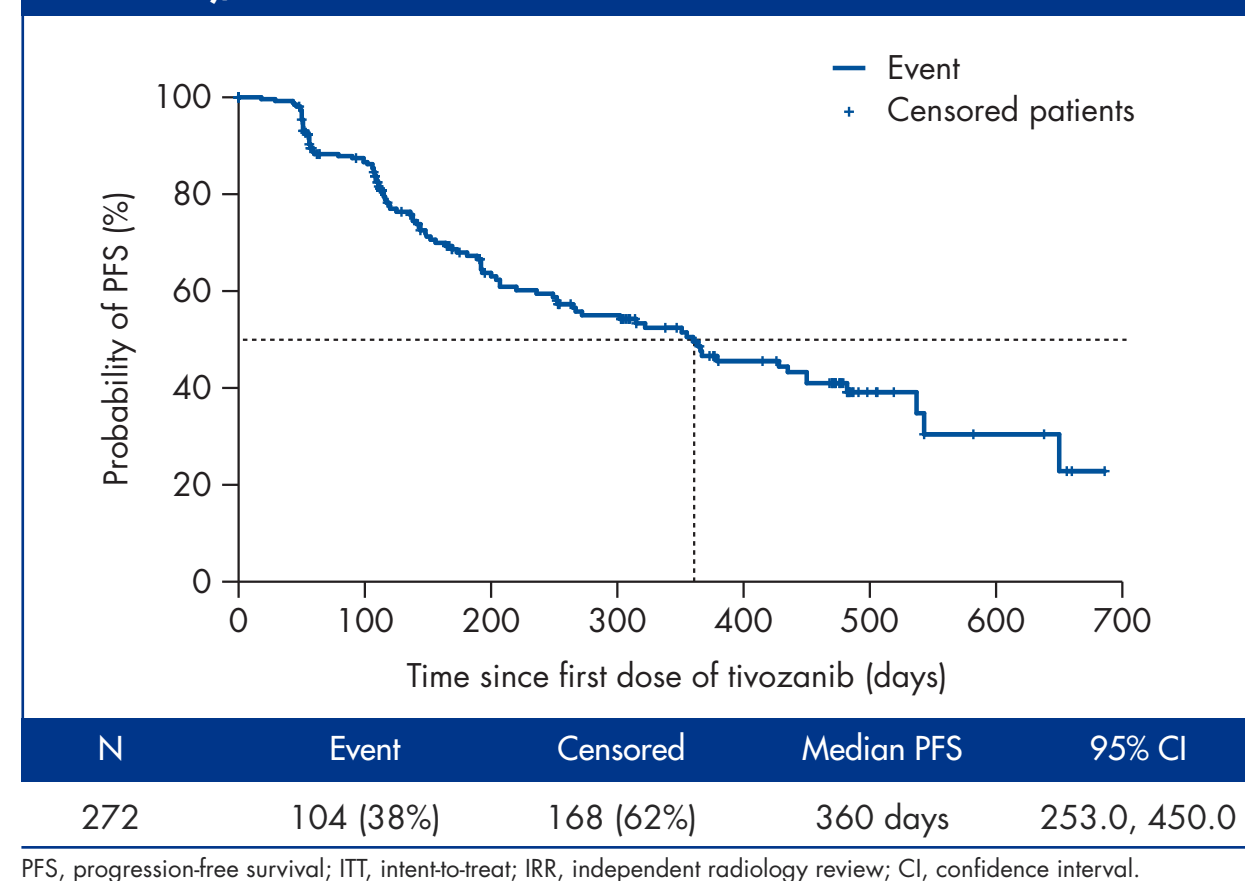
Table 1. Patient Demographics

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 (18.5)
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.

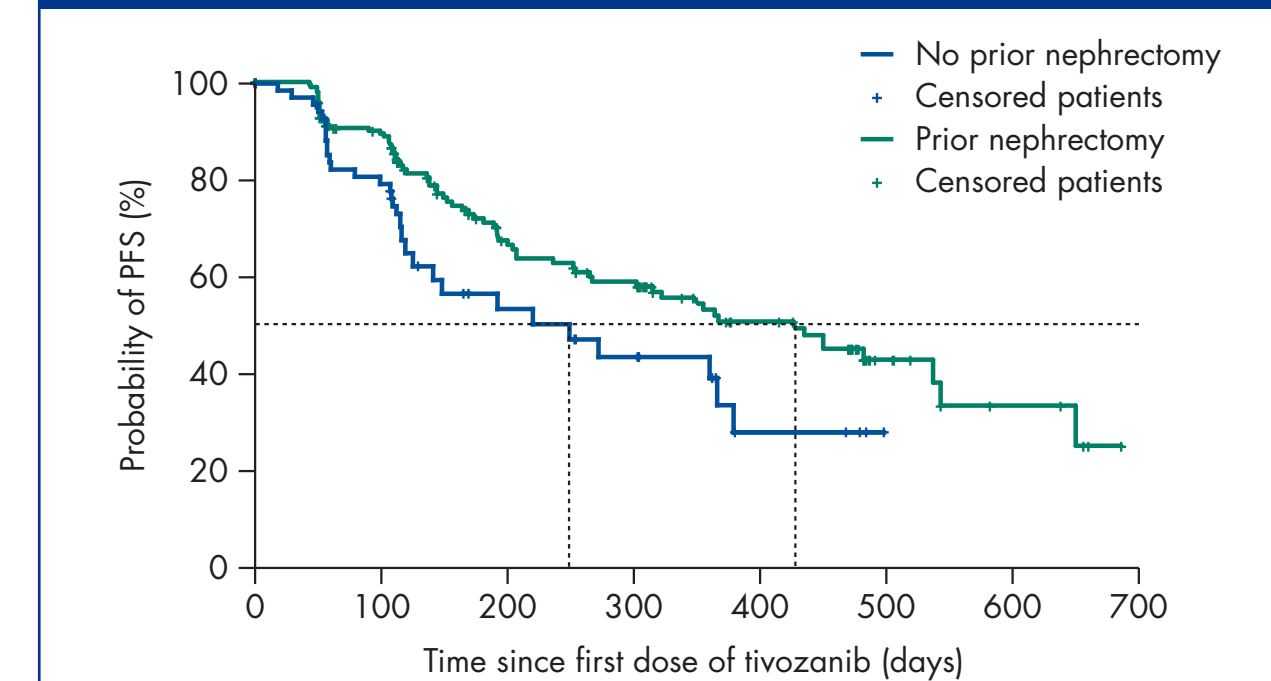


PFS, progression-free survival; ITT, intent-to-treat; IRR, independent radiology review; CI, confidence interval.

Effect of Prior Nephrectomy

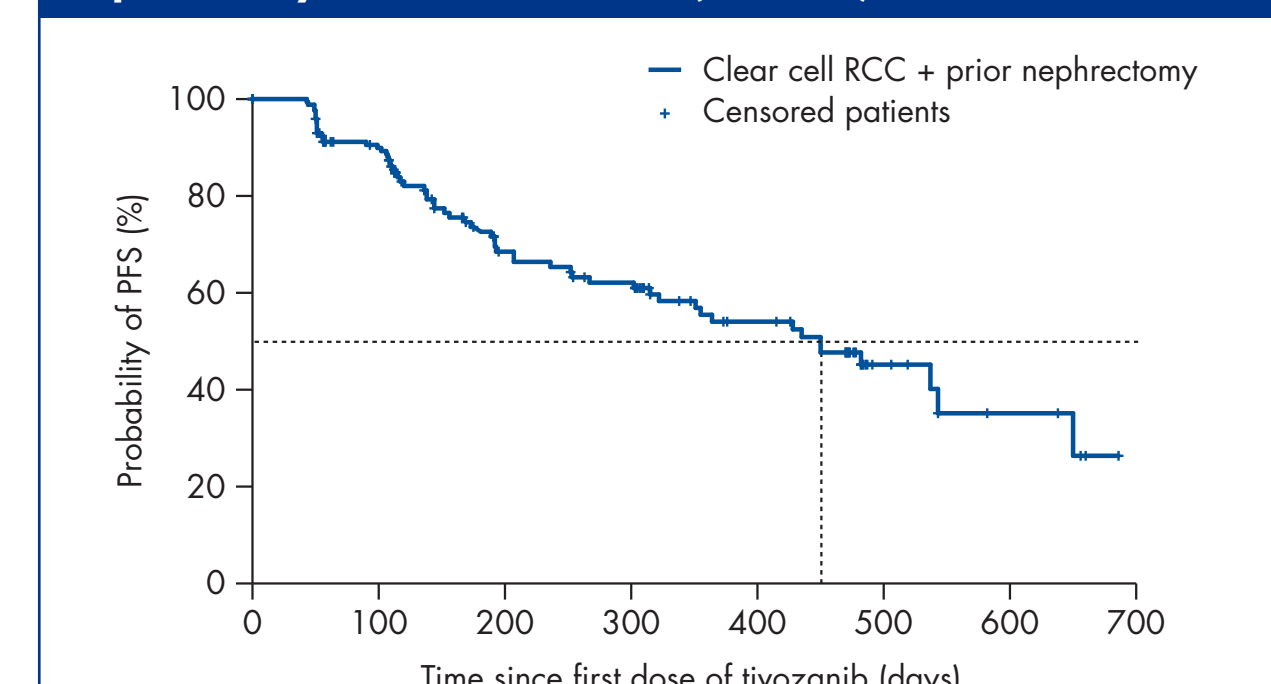
- Both PFS and ORR were significantly higher among patients with prior nephrectomy (Figures 3 and 4; Table 2)

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



PFS, progression-free survival; CI, confidence interval.

Figure 4. Subgroup analysis of PFS among patients with prior nephrectomy and clear cell RCC (n = 176).



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

Table 2. Subgroup Analysis of Efficacy Response by Baseline Characteristics

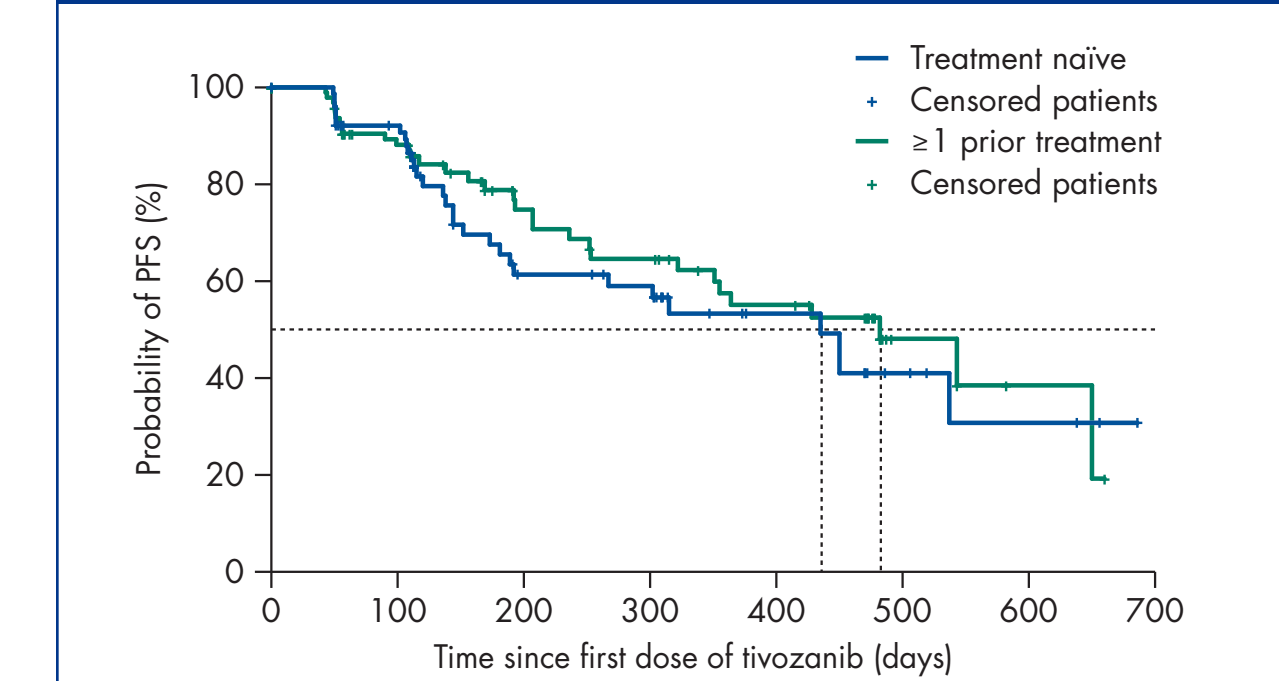
Response ^a	n	PFS		ORR	
		Months	P value	n (%)	P value
All patients	272	11.8		73 (27)	
Nephrectomy status			0.02		0.04
No nephrectomy	73	8.2		13 (18)	
Prior nephrectomy	199	14.1		60 (30)	
Prior nephrectomy + clear cell RCC	176	14.8		31 (30)	
Prior treatment status (prior nephrectomy + clear cell RCC subset)			0.43		0.006
Treatment naïve	77	14.3		33 (43)	
≥1 prior treatments	99	15.8		23 (23)	

PFS, progression-free survival; ORR, objective response rate; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors.
^aUsing standard RECIST criteria. ORR = complete + partial responses.

Effect of Prior Treatment

- After balancing other prognostic variables, 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 prior nephrectomy and clear cell RCC (n = 176).



PFS, progression-free survival; RCC, renal cell carcinoma; CI, confidence interval; NR, not yet reached.

Effect of Hypertension

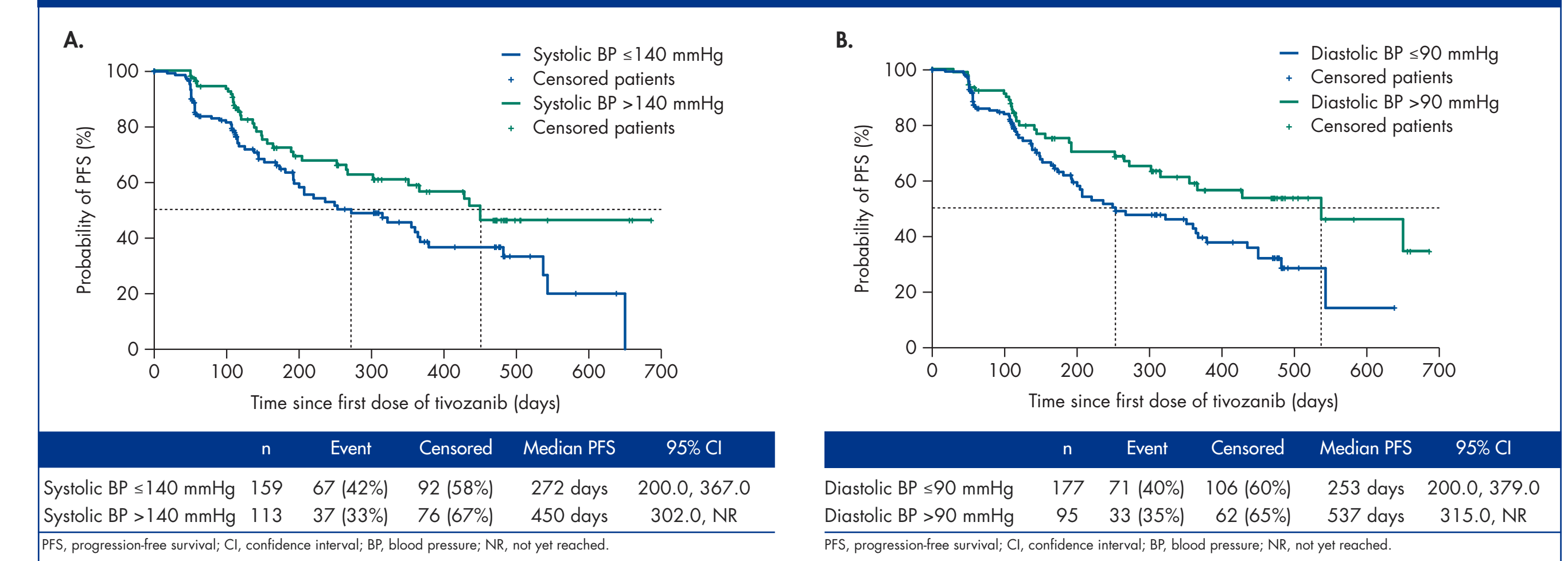
- Hypertension was the most commonly reported treatment-related adverse event, reported by 54% of patients
- Development of hypertension at any time during therapy was associated with improved PFS among patients in the overall intent-to-treat population (Figure 6 and Table 3) and in the subset of patients with clear cell RCC and prior 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)

Table 3. Subgroup Analysis of Efficacy Response by Hypertension Status

Response ^a	n	PFS		ORR	
		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)	
Prior nephrectomy + clear cell RCC subset					
Systolic BP >140 mmHg	71	NR	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)	

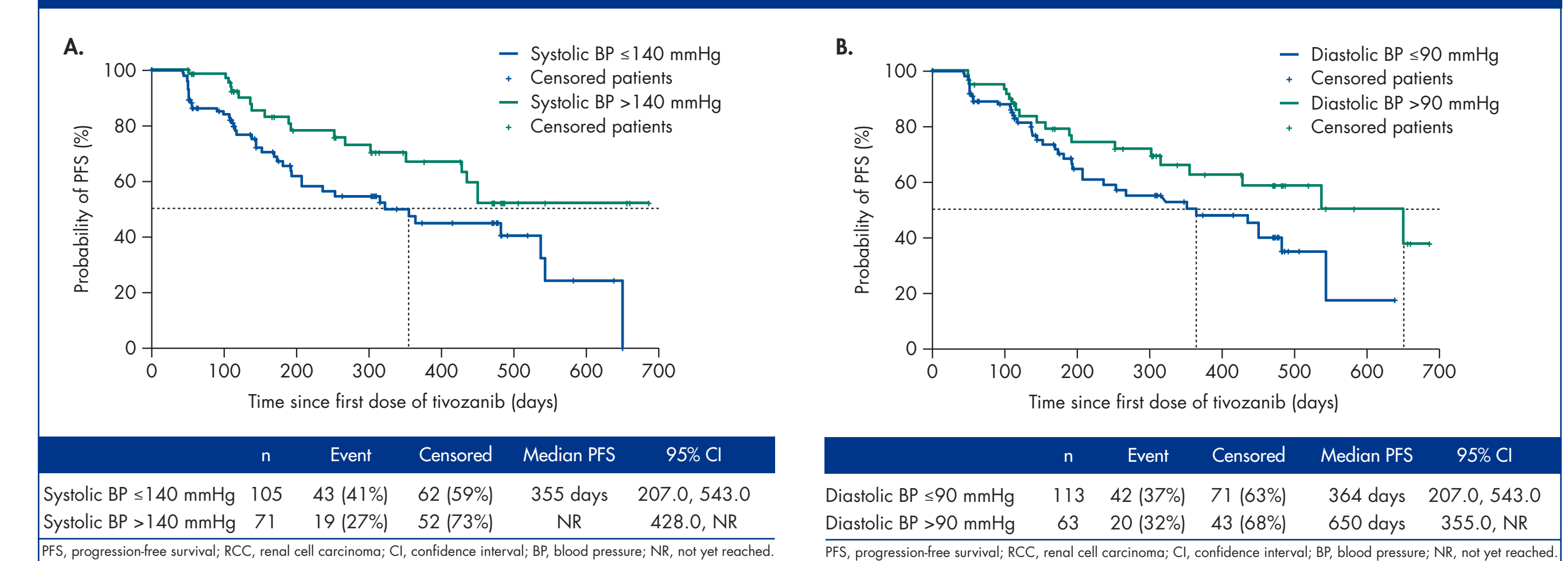
PFS, progression-free survival; ORR, objective response rate; BP, blood pressure; RCC, renal cell carcinoma; NR, not yet reached; RECIST, Response Evaluation Criteria in Solid Tumors.
^aUsing standard RECIST criteria. ORR = complete + partial responses.

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



PFS, progression-free survival; CI, confidence interval; BP, blood pressure; NR, not yet reached.

Figure 7. Subgroup analysis of PFS by hypertension status among patients with prior nephrectomy and clear cell RCC (n = 176).



PFS, progression-free survival; RCC, renal cell carcinoma; CI, confidence interval; BP, blood pressure; NR, not yet reached.

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 prior nephrectomy and clear cell RCC than for the overall patient population
- Response was similar between treatment-naïve and previously treated patients with prior nephrectomy and clear cell RCC
- Presence of hypertension appears to be associated with improved clinical outcomes, both in the overall patient population and among the subset of patients with prior nephrectomy and clear cell RCC

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