# Activity of Tivozanib (AV-951) in Patients With Renal Cell Carcinoma (RCC): Subgroup Analysis From a Phase 2 Randomized Discontinuation Trial (RDT)

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## 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 is the most common RCC subtype and generally appears to be more responsive to systemic therapies than non–clear cell subtypes[3]
- Nephrectomy is a known prognostic marker in RCC[4-6]

## Objectives

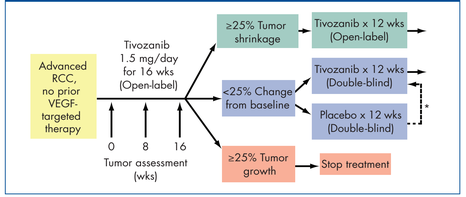
- To explore the effect of RCC subtype, nephrectomy, and prior therapy on the efficacy of tivozanib in patients with RCC
- To evaluate the safety and tolerability of tivozanib

## 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.**




RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor.
*Patients with progression during the double-blind phase were un-blinded; those on placebo were allowed to restart tivozanib.
All patients were un-blinded after 12 weeks of double-blind treatment.

### Subgroup Analyses

- Retrospective subgroup analyses evaluated efficacy by RCC histology subtype, nephrectomy status, and prior treatment status at study enrollment
- Efficacy (ie, objective response rate [ORR] 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)

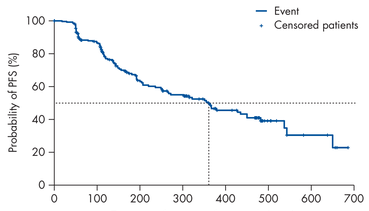
**Table 1. Patient Demographics**

| 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) |
| Non–clear cell RCC | 46 (16.9) |
| 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; MSKCC, Memorial Sloan-Kettering Cancer Center.

### Intent-to-treat Analysis

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



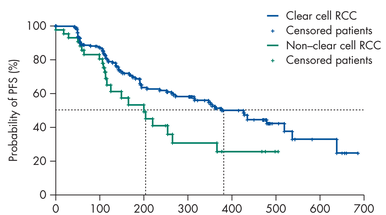

| | N | Median PFS | 95% CI |
|---|---|---|---|
| ITT population | 272 | 11.8 months (360 days) | 253-450 days |

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

### Effect of RCC Subtype and Prior Nephrectomy

- PFS was significantly higher among patients with clear cell RCC (**Figure 3** and **Table 2**) and those who had undergone nephrectomy (**Figure 4** and **Table 2**)
- ORR was also higher among both patient subgroups, although the difference was not significant for patients with clear cell RCC (**Table 2**)
- Median PFS was highest among patients with clear cell RCC who had undergone nephrectomy (14.8 months; **Figure 5**)

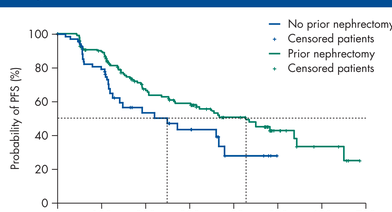
**Figure 3. Subgroup analysis of PFS by RCC subtype in all patients (N = 272), IRR.**




| | n | Median PFS | 95% CI |
|---|---|---|---|
| Clear cell RCC | 226 | 12.5 months (379 days) | 302-537 days |
| Non–clear cell RCC | 46 | 6.7 months (204 days) | 125-366 days |

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

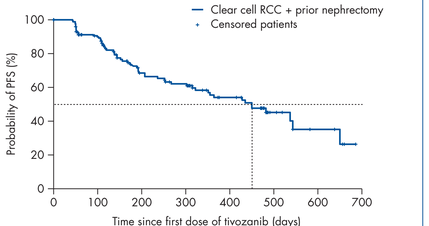
**Figure 4. Subgroup analysis of PFS by nephrectomy status in all patients (N = 272), IRR.**




| | 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 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.

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

| | PFS | | | ORR | |
|---|---|---|---|---|---|
| Subgroup[a] | n | Months | *P* value | n (%) | *P* value |
| All patients | 272 | 11.8 | | 73 (27) | |
| RCC subtype | | | | | |
| Clear cell RCC | 226 | 12.5 | 0.04 | 65 (29) | 0.11 |
| Non–clear cell RCC | 46 | 6.7 | | 8 (17) | |
| Nephrectomy status | | | | | |
| No prior 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.

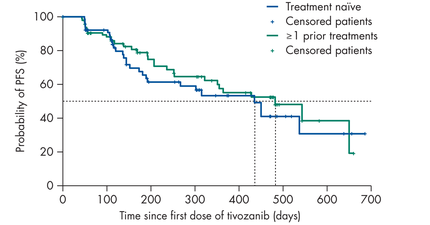
### Effect of Prior Treatment

- Within the subgroup of patients with clear cell RCC who had undergone prior nephrectomy, PFS was similar between treatment-naïve patients and those who had failed prior therapy with cytokines and/or chemotherapy (**Table 2** and **Figure 6**)

### Safety and Tolerability

- Hypertension (50.0%) and dysphonia (hoarseness of voice; 21.7%) were the most commonly reported treatment-related adverse events of any grade (**Figure 7**)
- There was a low incidence of diarrhea (12.1%), fatigue (8.1%), stomatitis (4.4%), and hand-foot syndrome (3.7%)
- Dose reductions due to adverse events were required by 10.3% of patients, and treatment interruptions due to adverse events were required by 3.7% of patients

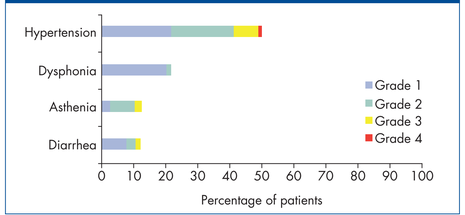
**Figure 6. Subgroup analysis of PFS by prior treatment status among patients with clear cell RCC who had undergone nephrectomy (n = 176), IRR.**




| | n | Median PFS | 95% CI |
|---|---|---|---|
| Treatment naïve | 77 | 14.3 months (435 days) | 192 days-NA |
| ≥1 prior treatments | 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.

**Figure 7. Treatment-related adverse events observed in ≥10% of patients.[a]**




[a]The incidences of mucositis/stomatitis and hand-foot syndrome were <5%.

## Conclusions

- **In this retrospective exploratory analysis, the median PFS of patients with clear cell RCC who had undergone nephrectomy was 14.8 months**
- **Median PFS and ORR were highest for the subgroup of patients with clear cell RCC who had undergone prior nephrectomy**
- **Median PFS was similar between treatment-naïve and previously treated patients with clear cell RCC who had undergone nephrectomy**
- **The adverse event profile of tivozanib was consistent with that of a selective VEGFR inhibitor with minimal "off-target" toxicities**

**References**

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