TIVO-3: Subgroup analysis of progression-free survival of tivozanib compared to sorafenib in subjects with refractory advanced renal cell carcinoma (RCC)

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Introduction

- Tivozanib is a novel, biochemically potent, and highly selective vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) approved by the European Medicines Agency for first-line treatment of adult patients with RCC[1]
- Tivozanib was developed to optimize the VEGFR blockade while minimizing off-target toxicities, ultimately leading to tolerable combinations with other therapies[2,3]
- TIVO-1, the first-line phase 3 RCC study, demonstrated superior progression-free survival (PFS) for tivozanib versus sorafenib (11.9 months vs. 9.1 months; hazard ratio [HR] 0.80; *P*=0.04), as well as a higher objective response rate (33% vs. 23%)[4]
- The TIVO-3 study is assessing tivozanib versus sorafenib in patients with third- and fourth-line metastatic RCC
  - Significantly longer PFS was reported for tivozanib than sorafenib (5.6 months vs. 3.9 months; HR 0.73; 95% confidence interval [CI]: 0.56, 0.94; *P*=0.017)[5]
  - Overall survival (OS) data are immature

Objective

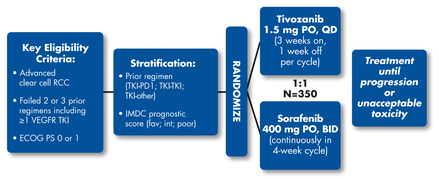
- To assess PFS among pre-specified patient subgroups in TIVO-3 including the type of prior treatment, International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk prognostic groups, and baseline patient characteristics

Methods

Study Design

- TIVO-3 (NCT02627963) is a phase III, open-label, randomized study comparing tivozanib with sorafenib in patients with refractory metastatic RCC (**Figure 1**)

Figure 1. Study design



BID=twice daily; ECOG=Eastern Cooperative Oncology Group; fav=favorable; IMDC=International Metastatic RCC Database Consortium; int=intermediate; PO=oral administration; PD1=programmed cell death 1; PS=performance status; QD=once daily; RCC=renal cell carcinoma; TKI=tyrosine kinase inhibitor; VEGFR=vascular endothelial growth factor receptor.

- Patients were randomized 1:1 to receive tivozanib 1.5 mg orally once daily in 4-week cycles (ie, 21 days on treatment followed by 7 days off treatment), or sorafenib 400 mg orally twice daily continuously
- Randomization was stratified by IMDC risk category (favorable; intermediate; poor) and prior therapy (two prior VEGFR TKIs; a prior checkpoint inhibitor [PD1 or PD1 ligand inhibitor] plus a prior VEGFR TKI; a prior VEGFR TKI plus any other systemic agent)

Study Endpoints

- The primary endpoint was PFS, defined as the time from randomization to first documentation of objective tumor progression and assessed by blinded independent radiological review
- Secondary endpoints included OS, objective response rate, duration of response, and safety

Results

- Baseline patient demographic and disease characteristics were balanced and typical of those seen in a patient population with advanced RCC (**Table**)

Table. Key Baseline Patient Characteristics

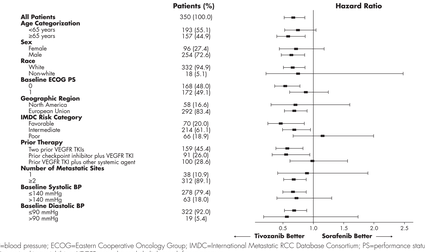
	Tivozanib (n=175)	Sorafenib (n=175)
Median age, years (range)	62 (34–88)	64 (30–90)
Male, %	72	73
ECOG PS, %		
0	49	47
1	50	48
IMDC risk category, %		
Favorable	19	21
Intermediate	62	60
Poor	18	19
Prior therapies, %		
Two VEGFR TKIs	45	46
Checkpoint inhibitor plus VEGFR TKI	27	25
VEGFR TKI plus another systemic agent	28	29

ECOG=Eastern Cooperative Oncology Group; IMDC=International Metastatic RCC Database Consortium; PS=performance status; TKI=tyrosine kinase inhibitor; VEGFR=vascular endothelial growth factor receptor.

PFS Overview

- In a Cox proportional hazards model, tivozanib demonstrated a PFS benefit for all patients (5.6 months vs. 3.9 months; HR 0.73; 95% CI: 0.56, 0.94; P=0.017) as well as a PFS benefit across patient subgroups (**Figure 2**)
  - Notably, patients enrolled in North America had a similar HR to those in Europe (0.71 vs. 0.69)
  - Patients with ECOG performance status (PS) of 0 had a lower HR (0.54) than patients with ECOG PS of 1 (0.87)
  - Patients with better IMDC risk scores benefited more from tivozanib treatment: favorable IMDC risk (0.46), intermediate IMDC risk (0.69), and poor IMDC risk (1.15)

Figure 2. Forest Plot for PFS

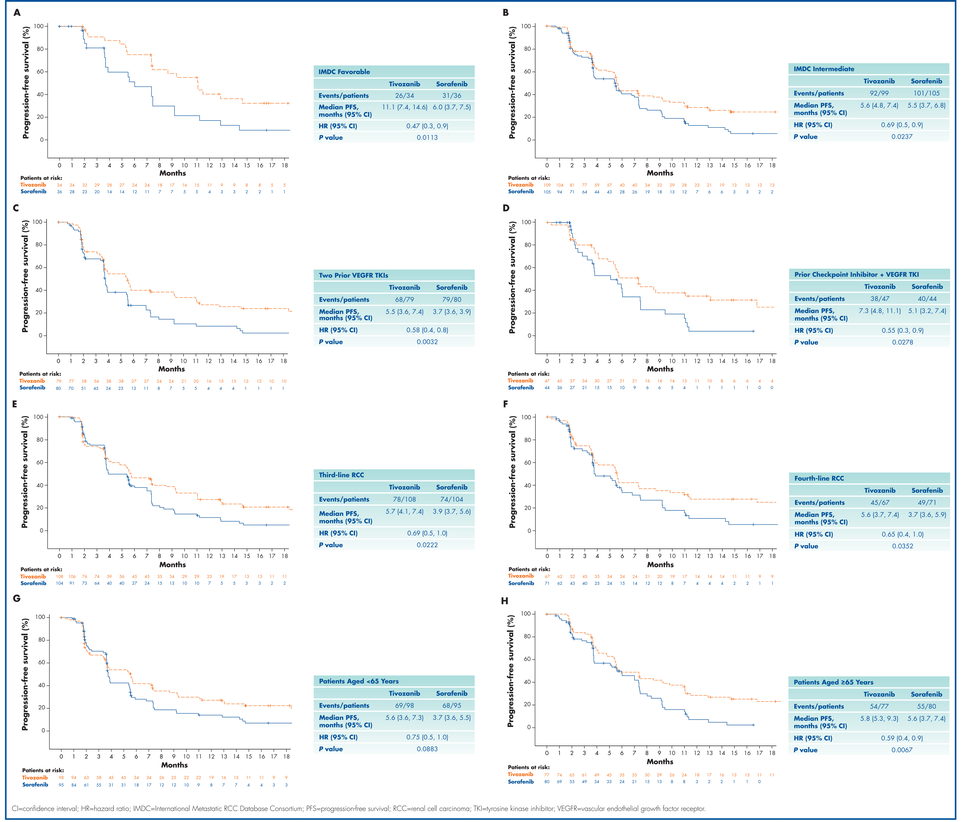


BP=blood pressure; ECOG=Eastern Cooperative Oncology Group; IMDC=International Metastatic RCC Database Consortium; PS=performance status; TKI=tyrosine kinase inhibitor; VEGFR=vascular endothelial growth factor receptor.

Stratified PFS Analyses

- PFS favored tivozanib over sorafenib in most patient subgroups, including IMDC favorable (**Figure 3A**), IMDC intermediate (**Figure 3B**), two prior VEGFR TKIs (**Figure 3C**), prior checkpoint inhibitor and VEGFR TKI (**Figure 3D**), third-line (**Figure 3E**) and fourth-line (**Figure 3F**) RCC, patients aged <65 years (**Figure 3G**), and patients aged ≥65 years (**Figure 3H**)

Figure 3. Stratified PFS Analyses by Patient Subgroups in TIVO-3



CI=confidence interval; HR=hazard ratio; IMDC=International Metastatic RCC Database Consortium; PFS=progression-free survival; RCC=renal cell carcinoma; TKI=tyrosine kinase inhibitor; VEGFR=vascular endothelial growth factor receptor.

Summary

- In the TIVO-3 trial, tivozanib significantly improved PFS compared with sorafenib in patients with treatment-refractory advanced RCC across several patient subgroups
  - Patients with favorable and intermediate IMDC risk seemed to derive the most benefit from tivozanib (HR 0.46 and 0.69, respectively)
  - Patients treated with a prior checkpoint inhibitor had a statistically significant benefit from treatment with tivozanib (HR=0.55)
    - 1- and 2-year PFS rates were higher in the tivozanib group than in the sorafenib group (35% vs. 4% and 25% vs. 0%, respectively)
  - Patients treated with two VEGFR TKIs had a statistically significant benefit from treatment with tivozanib (HR=0.57)
    - 1- and 2-year PFS rates were 27% and 18% in the tivozanib group and 8% and 0% in the sorafenib group, respectively

Conclusions

- Collectively, these data demonstrate a profound ability of tivozanib to treat patients with refractory advanced RCC, including those with PD1-refractory advanced RCC and those with disease refractory to two prior VEGFR TKIs
- These phase 3 study results are the first to demonstrate superiority of the primary endpoint (PFS) in patients with RCC treated in the third-line setting and beyond, and the first prospective randomized study to demonstrate PFS superiority versus another VEGFR TKI following PD1 treatment

References

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