Ther Adv Med Oncol

2020, Vol. 12: 1–9

DOI: 10.1177/1758835920923818

Tivozanib in renal cell carcinoma: a new approach to previously treated disease

Nicholas J. Salgia, Zeynep B. Zengin and Sumanta K. Pal

***Abstract*:** Targeted therapies have been a mainstay of the renal cell carcinoma (RCC) treatment paradigm for the better part of two decades. Multikinase inhibitors of the vascular endothelial growth factor receptor tyrosine kinases (VEGF-TKIs) comprise nearly all targeted therapies in RCC, having been prospectively tested through large, multi-institutional phase III trials. Tivozanib is a VEGF-TKI with high selectivity for VEGF receptors 1–3. Tivozanib has been under investigation for nearly 15 years, with a robust portfolio of preclinical and clinical data. This review seeks to characterize tivozanib within the context of RCC by highlighting preclinical and early clinical trials alongside the phase III trials in RCC, TIVO-1, and TIVO-3. We also aim to explore further trials of tivozanib, whether in combination with other agents and/or in differing disease settings, while providing insight into the utility of tivozanib as a clinical tool for the management of RCC.

Keywords: renal cell carcinoma, TIVO-1, TIVO-3, tivozanib, vascular endothelial growth factor receptor tyrosine kinase

Received: 30 January 2020; revised manuscript accepted: 9 April 2020.

Correspondence to:
Sumanta K. Pal
Department of Medical Oncology & Experimental Therapeutics, City of Hope Comprehensive Cancer Center, 1500 East Duarte Road, Duarte, CA 91010, USA
spal@coh.org

Nicholas J. Salgia
Zeynep B. Zengin
Department of Medical Oncology & Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA, USA

Introduction

The vascular endothelial growth factor receptor (VEGFR) family represents an important target for therapies in multiple diseases, including renal cell carcinoma (RCC). The receptor tyrosine-kinases, VEGFR1–3, are implicated in both tumor-mediated angiogenesis and lymphogenesis.[1–3] VEGF tyrosine kinase inhibitors (VEGF-TKIs) have shown substantial clinical efficacy in the treatment of advanced RCC over the past 15 years.[4–7] VEGF-TKIs are approved as first-line therapy and beyond for the treatment of RCC and National Comprehensive Cancer Network guidelines indicate the utility of VEGF-TKIs for a variety of clinical scenarios across all lines of therapy.[8]

In 2015, following the results of CheckMate-025, nivolumab, an anti-PD-1 immune checkpoint inhibitor, was approved for VEGF-TKI-refractory RCC, initiating the rise of immunotherapy in the treatment landscape.[9] This paradigm was furthered by the approval of a combination of nivolumab plus ipilimumab (an anti-CTLA-4 checkpoint inhibitor) as a first-line approach for metastatic RCC following the CheckMate-214 study.[10] Even as immune checkpoint inhibition proliferates in the RCC treatment algorithm following these studies, VEGF-TKIs still play an important role in both the front-line and refractory disease settings for locally advanced and metastatic RCC.

Tivozanib is a VEGF-TKI that has been extensively studied in the context of solid tumors and in advanced RCC through preclinical data and clinical trials. The current review aims to highlight important characteristics of the compound including its chemistry and pharmacokinetics, to summarize important clinical trial results and regulatory decisions regarding tivozanib, and finally provide a commentary on the role tivozanib may play in the clinical management of RCC.

Compound characteristics and preclinical data

Tivozanib ($C_{22}H_{19}ClN_4O_5$; molecular weight, 454.9 g/mol), also known as AV-951, KRN951, and tivozanib hydrochloride monohydrate, is an oral VEGF-TKI specific for VEGFR1–3.[11] Tivozanib maintains structural and functional similarity to

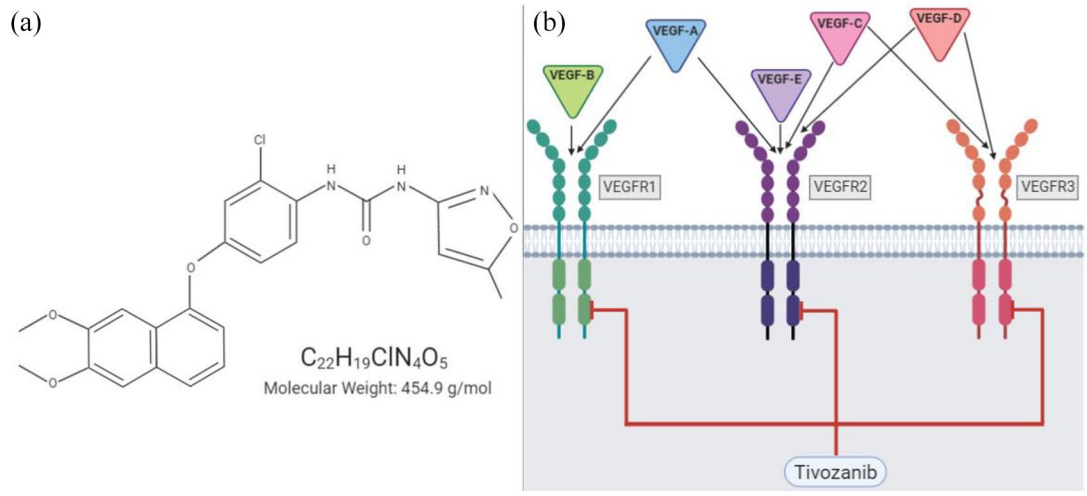

Figure 1. (a) Two-dimensional chemical structure of tivozanib; (b) mechanism of action for tivozanib.
VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

other VEGF-TKIs, implicating its role in mitigating angiogenesis and lymphogenesis (Figure 1). Importantly, as distinguished from other VEGF-TKIs, tivozanib has been shown to have inhibitory effects at nanomolar concentrations, with an IC_{50} (the concentration necessary to inhibit 50% of activity) of 30nM for VEGFR1, 6.5nM for VEGFR2, and 15nM for VEGFR3. The compound is unique in being highly specific for VEGFR1–3, with minimal residual effects on c-KIT and PDGFR-β. In preclinical human tumor xenografts of lung, breast, colon, ovarian, pancreas, and prostate cancer, tivozanib displayed antitumor activity. Delayed contrast MRI in rodent studies revealed reductions in tumor vascular hyperpermeability related to the antitumor effects of tivozanib.[12]

Further preclinical work utilized a peritoneal disseminated tumor rodent model to assess tivozanib's antitumor and antiangiogenic effects.[13] Treatment with tivozanib at 4 days post-tumor transplant inhibited tumor-induced angiogenesis and the development of tumor metastases while treatment at 14 days post-tumor transplant resulted in the regression of newly formed vasculature and malignant sites. Continuous treatment of tumor-burdened rats resulted in prolonged survival. The results of these studies led to the development of a phase I clinical trial to investigate the activity, safety, and efficacy of tivozanib in solid tumors.

Phase I clinical trial

A phase I study commenced in 2004 to investigate tivozanib in advanced solid tumors (Figure 2).[14] The primary outcome assessed in the study was safety through maximum tolerated dose and dose-limiting toxicities. Other outcomes of the study included the pharmacokinetics of single and multiple doses, biomarker analysis of tumor through contrast-enhanced MRI (CE-MRI), and tivozanib's antitumor activity. The study required that patients have an Eastern Cooperative Oncology Group (ECOG) performance status of ⩽2, estimated life expectancy of greater than 3 months, and a cytologically or histologically confirmed solid tumor. Patients were excluded if they had received systemic or radiotherapy within 28 days of the first scheduled dose of tivozanib or if they had significant comorbidities.

In total, 41 patients were enrolled on to the study. The most common malignancies in the study were colorectal cancer ($n = 10$), RCC ($n = 9$), and pancreatic cancer ($n = 6$). Other cancer types with more than one patient enrolled on trial were non-small cell lung cancer, esophageal cancer, melanoma, and hepatocellular carcinoma. Dosing of tivozanib was started at 2.0mg for 28 days followed by 14 days off. Seven patients received this dose, with dose-limiting toxicities in the first cycle including grade 3 proteinuria and grade 3 ataxia. A second cohort investigated dosing at 1.0mg, enrolling six patients with no dose-limiting toxicities. An intermediate cohort of 1.5mg was established, enrolling six patients. Uncontrollable hypertension was the only dose-limiting toxicity experienced in this cohort. Therefore, 1.5mg was defined as the maximum tolerated dose and an expansion cohort of 10 additional patients,

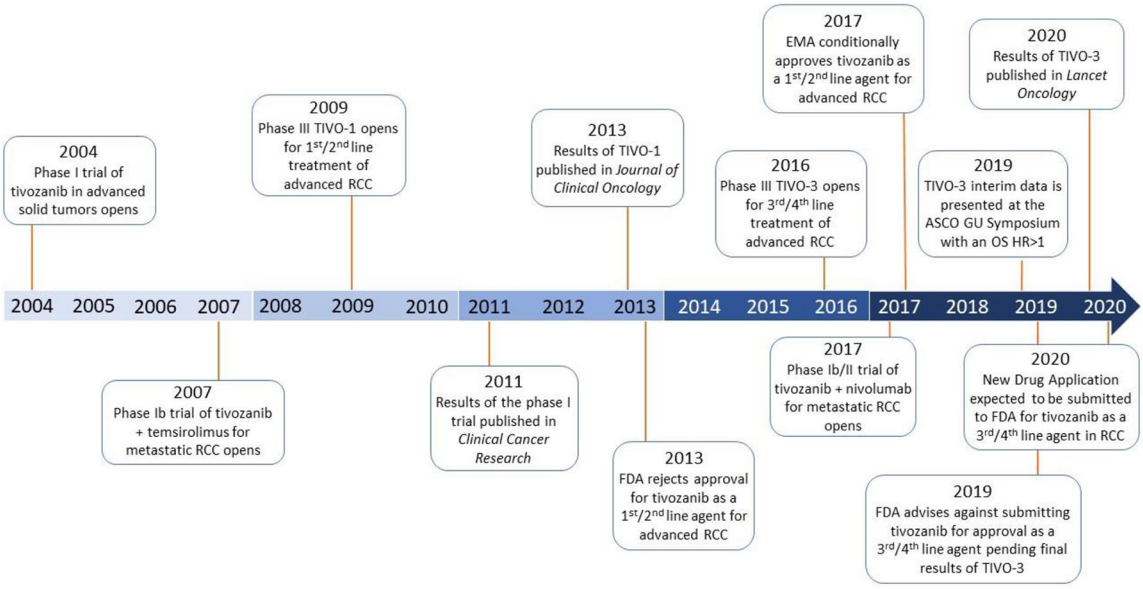

Figure 2. Timeline of clinical investigation and regulatory approvals for tivozanib in renal cell carcinoma.
ASCO GU, American Society of Clinical Oncology Genitourinary Cancers; EMA, European Medicines Agency; FDA, Food and Drug Administration; RCC, renal cell carcinoma.

followed by 12 more patients, were enrolled to further assess for safety. Adverse events (AEs) experienced in the expansion cohort included transaminase elevation, uncontrollable hypertension, fatigue, and dyspnea.

Pharmacokinetic analysis determined the mean half-life of tivozanib was 4.7 days and pharmacodynamic studies displayed an increase in serum VEGF-A and a decrease in serum VEGFR2, both in a dose-dependent manner. CE-MRI was limited to only eight study participants, but a trend toward decreased vascularization was identified, suggesting antiangiogenic effects. Two patients with RCC experienced a partial response to therapy (one confirmed, one unconfirmed), and nine patients across disease types maintained stable disease over at least three cycles. This early phase trial provided data supporting the safety and efficacy of tivozanib as a clinical agent, providing a rationale and foundation for subsequent phase III trials.

Phase III clinical trials and regulatory responses

TIVO-1

The first phase III clinical trial investigating tivozanib in RCC was TIVO-1 (NCT01030783) (Figure 3).[15] Opened in 2009, TIVO-1 was an open-label, randomized study comparing tivozanib with sorafenib in the context of metastatic or recurrent disease and 0–1 prior therapies. Tivozanib was administered 1.5 mg orally daily for 3 weeks on, 1 week off over continuous 4-week cycles. Sorafenib was administered at 400 mg orally twice daily. Key inclusion criteria included pathologically confirmed disease with a clear cell component, previous nephrectomy (partial or radical), and an ECOG performance status of 0–1. Key exclusion criteria included the previous receipt of any VEGF- or mTOR-directed agents, central nervous system (CNS) metastases, or other significant comorbidities. TIVO-1 was designed with a primary endpoint of progression-free survival (PFS). Secondary endpoints included overall survival (OS) and objective response rate (ORR). The study took place across 76 centers in 15 countries.

In total, 516 patients received at least one dose of treatment. A total of 259 patients were randomly assigned to receive tivozanib and 257 received sorafenib. The study met its primary endpoint with an improvement in PFS from 11.9 months with tivozanib compared with 9.1 months with sorafenib (HR, 0.797; CI 0.639–0.993; $p = 0.042$). Response rate, too, favored tivozanib with a confirmed ORR of 33.1% for tivozanib *versus* 23.3%

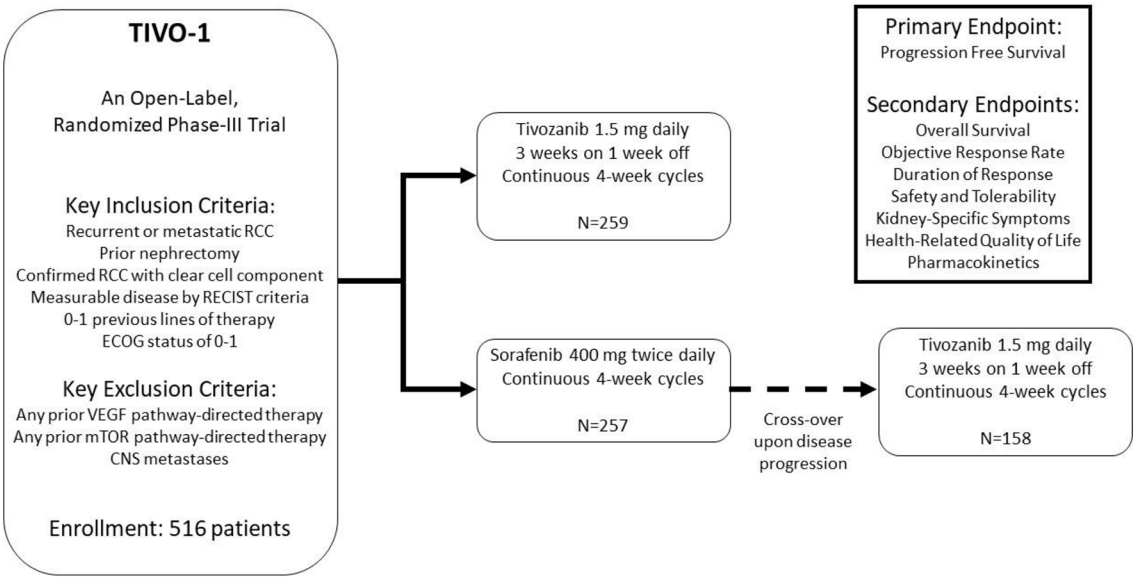

Figure 3. Study design schema for TIVO-1, including the cross-over protocol from sorafenib to tivozanib after disease progression.
CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; mTOR, mammalian target of rapamycin, RCC, renal cell carcinoma; RECIST, response evaluation criteria in solid tumors; VEGF, vascular endothelial growth factor.

for sorafenib ($p = 0.014$) based on blinded independent radiological review.

Survival, however, followed an opposing trend. In total, 242 deaths occurred by the data cut-off, with 118 deaths in the tivozanib arm and 101 in the sorafenib arm. Sorafenib demonstrated a longer OS with 29.3 months compared with 28.8 months on tivozanib (HR, 1.245; CI 0.954–1.624; $p = 0.105$). However, following initial disease progression, 63% of patients on the sorafenib arm received an additional targeted therapy compared with only 13% on the tivozanib arm. A total of 158 out of 162 (96%) patients who went on to receive a next-line therapy after sorafenib received tivozanib. This was due in part to the structure of the study, wherein patients who developed progressive disease on the sorafenib arm could cross-over to receive tivozanib as part of a separate protocol (NCT01076010). This design and differences in next-line use of targeted therapy agents confounded OS results in this study.

The safety profiles of the two agents were similar. Only 4% and 5% of patients discontinued therapy due to treatment-related AEs on the tivozanib and sorafenib arms, respectively. Dose reductions due to AEs occurred for 43% of patients receiving sorafenib and 14% of patients receiving tivozanib. Common AEs encountered more frequently with tivozanib compared with sorafenib included hypertension (44% *versus* 34%, respectively) and dysphonia (21% *versus* 5%, respectively). AEs more frequently implicated with sorafenib use compared with tivozanib included hand-foot syndrome (54% *versus* 14%, respectively) and diarrhea (33% *versus* 23%, respectively).

In response to the results of TIVO-1, the European Medicines Agency (EMA) approved tivozanib for the first-line treatment of advanced RCC given the study's ability to meet the primary endpoint of prolonged PFS. The EMA approved tivozanib in 2017 as a first- and second-line intervention for RCC under the context of additional monitoring for safety and efficacy.[16] The US Food and Drug Administration (FDA), however, was deterred by the OS results, and rejected tivozanib's front-line approval in 2013 following an overwhelming 13–1 vote in opposition from the FDA's advisory committee.[17]

TIVO-3

Following the FDA's decision to deny approval for tivozanib in the front-line setting, a new phase III trial was designed to investigate tivozanib's effects on metastatic RCC refractory to targeted therapy, immune checkpoint inhibitors, and/or other agents. TIVO-3 (NCT02627963) was an

open-label, randomized study comparing tivozanib with sorafenib in the third- and fourth-line settings for metastatic RCC.[18] Inclusion criteria for TIVO-3 included histologically or cytologically confirmed RCC with a clear cell component, an ECOG performance status of 0 or 1, and metastatic RCC that failed two or three prior regimens, including at least one VEGF-TKI other than tivozanib or sorafenib. Exclusion criteria included prior treatment with tivozanib or sorafenib, greater than three previous lines of therapy, or CNS metastases. The trial was designed with a primary endpoint of PFS and OS as a key secondary endpoint.

Through study recruitment, 350 patients were enrolled on to TIVO-3 with an equal distribution of 175 patients assigned to both the tivozanib and sorafenib arms. Patients were stratified for randomization by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk category (favorable, intermediate, or poor) and previous therapy. There were three categories for previous therapy: two anti-VEGF agents, one anti-VEGF agent and one immune checkpoint inhibitor (anti-PD-1/PD-L1), or one anti-VEGF agent and any other systemic therapy (such as anti-mTOR agents). For patients who had received three previous lines of therapy, only the two most recent agents were considered.

The primary endpoint of PFS was once again met, with tivozanib demonstrating a prolonged PFS of 5.6 months compared with sorafenib's 3.9 months (HR, 0.73; CI 0.56–0.94; $p=0.016$) by independent review. In a subgroup analysis, patients with good-risk disease by IMDC criteria experienced greater PFS with tivozanib (11.1 months) *versus* sorafenib (6.0 months) (HR, 0.46; CI 7.4–14.6; $p=0.01$), while for patients with IMDC poor-risk disease, the PFS of sorafenib (3.7 months) outperformed that of tivozanib (2.1 months) (HR, 1.15; CI 1.8–3.5). When stratified by previous therapeutic agents, patients who had received previous checkpoint inhibition had a greater PFS on tivozanib (7.3 months) than on sorafenib (5.1 months) (HR, 0.55; CI 0.23–0.94; $p=0.028$). A similar trend was seen in patients who had received two previous anti-VEGF agents, with PFS on tivozanib (5.5 months) outperforming sorafenib (3.7 months) (HR, 0.58).

As with TIVO-1, OS played a divisive role in the results of this study. Upon presentation of interim data at the 2019 American Society of Clinical Oncology Genitourinary Cancers Symposium (ASCO GU), a median OS of 16.4 months with tivozanib was outpaced by a median OS of 19.7 months with sorafenib (HR, 1.12; CI 0.84–1.51; $p=0.44$).[19] However, at the analysis of data 2 years after final patient enrollment, the OS survival trend was flipped in favor of tivozanib. The tivozanib arm reported a median OS of 16.4 months *versus* 19.6 months in the sorafenib arm (HR, 0.99; CI 0.76–1.29; $p=0.95$).[18] In addition, 20 patients on tivozanib remained progression free *versus* only two patients on sorafenib at the time of data cut-off and an ORR of 18% with tivozanib *versus* 8% with sorafenib ($p=0.017$) was reported.

Future directions

Combinations in RCC

Combination therapies of anti-VEGF molecules and immune checkpoint inhibitors have grown at a rapid rate in RCC. Most notably, the combinations of bevacizumab/atezolizumab, axitinib/pembrolizumab, and axitinib/avelumab have all recently been reported in the context of phase III clinical trials for advanced RCC, with the latter two receiving FDA approval for treatment-naïve patients in early 2019.[21–23] An ongoing trial is investigating the combination of axitinib/nivolumab in the VEGF-TKI-refractory setting (NCT03172754), while a planned phase III trial of cabozantinib/atezolizumab will study the role of combination therapy post-checkpoint inhibition. Tivozanib is currently being studied in combination with nivolumab, an anti-PD-1 immune checkpoint inhibitor, through a phase Ib/II study for the treatment of metastatic RCC (NCT03136627) in the first- or second-line setting (Table 1).[24] The initial phase of the study implemented a 3 + 3 dose-escalation design to determine the maximum tolerated dose. This was followed by an expansion cohort of up to 25 patients at the maximum tolerated dose to evaluate safety, tolerability, and antitumor efficacy of the combination. Data presented at the European Society for Medical Oncology (ESMO) Congress 2019 reported a PFS of 18.9 months, ORR of 56%, and a disease control rate of 96% in the maximum tolerated dose cohort for the combination of tivozanib + nivolumab. Plans for a phase III randomized study investigating this combination are being discussed following the results presented at ESMO 2019.

A phase Ib study was developed to test the combination of tivozanib with temsirolimus, an mTOR inhibitor, in an open-label, nonrandomized,

Table 1. Clinical trials using tivozanib as the investigatory agent (as monotherapy or in combination) in renal cell carcinoma.

Trial identifier	Trial phase	Enrollment	Line of therapy	Investigatory arm	Comparator arm	Results (investigatory *versus* comparator)	Hazard ratio	*p* value
NCT01030783 (TIVO-1)	III	516	First/ second	Tivozanib	Sorafenib	PFS: 11.9 months *versus* 9.1 months	0.797 (CI 0.639–0.993)	0.042
						OS: 28.8 months *versus* 29.3 months	1.245 (CI 0.954–1.624)	0.105
NCT02627963 (TIVO-3)	III	350	Third/ fourth	Tivozanib	Sorafenib	PFS: 5.6 months *versus* 3.9 months	0.73 (CI 0.56–0.94)	0.016
						OS: 16.4 months *versus* 19.6 months	0.99 (CI 0.76–1.29)	0.95
NCT03136627	Ib/II	25 (receiving maximum tolerated dose)	First/ second	Tivozanib + nivolumab	–	PFS: 18.9 months	–	–
						ORR: 56%	–	–
NCT00563147	Ib	27 (in all dose-escalation cohorts + expansion cohort)	Second line and beyond	Tivozanib + temsirolimus	–	Partial response: 23% of patients	–	–
						Stable disease: 68% of patients	–	–

CI, confidence interval; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

single group design (NCT00563147).[25] In this study, patients received tivozanib in one of three doses, 0.5 mg, 1.0 mg, or 1.5 mg daily (3 weeks on, 1 week off), and temsirolimus in an intravenous dosing of 15 mg or 25 mg weekly. The study was structured in a standard 3 + 3 dose-escalation design with a subsequent expansion cohort. Among the 27 patients treated on protocol, the combination of tivozanib and temsirolimus was relatively well tolerated, with AEs including fatigue and thrombocytopenia. Partial responses occurred in 23% of the cohort and stable disease in 68%. Even with the relative clinical success of the combination, pharmacokinetics did not support an interaction between the two therapies.

Tivozanib in other disease settings

Tivozanib may have potential for use in other cancers beyond RCC. Recent and ongoing trials have begun to investigate tivozanib in both hepatocellular carcinoma and ovarian cancer. The combination of tivozanib and durvalumab, an anti-PD-1 immunotherapy, is being studied in untreated, advanced hepatocellular carcinoma through a phase I/II dose-escalation and cohort expansion study (NCT03970616). Tivozanib is also being studied in a single-arm phase II trial in the context of recurrent, platinum-resistant ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (NCT01853644). In this study, 30 patients were treated, with a median PFS of 4 months and median OS of 8 months and limited AEs, demonstrating compound activity without substantial toxicities, while exploratory tumor analyses are still ongoing.[26] Tivozanib has also been clinically studied through phase I and II clinical trials as both monotherapy and in combinations in sarcoma, glioblastoma, breast cancer, and colorectal and other advanced gastrointestinal cancers.[27–32] The development of phase III clinical trials using tivozanib as an experimental regimen, either as monotherapy or in combination, is a necessary step in better understanding the compound's potential therapeutic role across cancer types.

Clinical insight

The clinical development of tivozanib in RCC is highly contingent on survival data from the most recent phase III evaluation of the drug (TIVO-3). If the hazard ratio of less than 1.0 is maintained, one can foresee utilization of tivozanib in patients with heavily pretreated disease. Current clinical trials largely address patients who are undergoing first- and second-line therapy. Combinations of VEGF and immunotherapy regimens are currently relevant only to the first-line setting, and although a handful of trials have emerged for second-line therapy, there are almost no studies available to patients (outside of phase I investigations) that address third- and fourth-line therapy. Tivozanib could potentially fill this void. The excellent tolerability profile of the agent makes it suitable for patients with heavily pretreated disease who may have some degree of clinical deterioration. At the authors' institution, the current standard of care reflects initial therapy with nivolumab and ipilimumab in most patients, followed by therapy with cabozantinib. After failure of these agents or similarly sequenced therapies, tivozanib would represent a very reasonable third-line agent.

If the data for the combination of tivozanib with immunotherapy continue to show the current balance of efficacy and safety, one could ultimately envision studies that move tivozanib to earlier therapeutic settings. Having said that, with multiple front-line studies already matured, the regimen may at best become confined to second-line treatment. In the relatively saturated landscape of first- and second-line therapy for advanced RCC, carving a niche will be quite challenging.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

SKP: Honoraria: Novartis, Medivation, and Astellas Pharma; Consulting or Advisory Role: Pfizer, Novartis, Aveo, Myriad Pharmaceuticals, Genentech, Exelixis, Bristol-Myers Squibb, and Astellas Pharma; Research Funding: Medivation.

Compliance with ethical standards

No external funding was used in the preparation of this manuscript.

References

1. Hicklin DJ and Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol* 2005; 23: 1011–1027.
2. Bjorndahl MA, Cao R, Burton JB, *et al.* Vascular endothelial growth factor-a promotes peritumoral lymphangiogenesis and lymphatic metastasis. *Cancer Res* 2005; 65: 9261–9268.

3. Plate KH, Breier G, Millauer B, *et al.* Up-regulation of vascular endothelial growth factor and its cognate receptors in a rat glioma model of tumor angiogenesis. *Cancer Res* 1993; 53: 5822–5827.

4. Motzer RJ, Hutson TE, Tomczak P, *et al.* Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007; 356: 115–124.

5. Escudier B, Eisen T, Stadler WM, *et al.* Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007; 356: 125–134.

6. Sternberg CN, Davis ID, Mardiak J, *et al.* Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2010; 28: 1061–1068.

7. Hutson TE, Al-Shukri S, Stus VP, *et al.* Axitinib versus sorafenib in first-line metastatic renal cell carcinoma: overall survival from a randomized phase III trial. *Clin Genitourin Cancer* 2017; 15: 72–76.

8. Motzer RJ, Jonasch E, Michaelson MD, *et al.* NCCN guidelines insights: kidney cancer, version 2.2020. *J Natl Compr Canc Netw* 2019; 17: 1278–1285.

9. Motzer RJ, Escudier B, McDermott DF, *et al.* Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015; 373: 1803–1813.

10. Motzer RJ, Tannir NM, McDermott DF, *et al.* Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 2018; 378: 1277–1290.

11. National Center for Biotechnology Information. Tivozanib. PubChem Database, CID=9911830, https://pubchem.ncbi.nlm.nih.gov/compound/Tivozanib (accessed 22 January 2020).

12. Nakamura K, Taguchi E, Miura T, *et al.* KRN951, a highly potent inhibitor of vascular endothelial growth factor receptor tyrosine kinases, has antitumor activities and affects functional vascular properties. *Cancer Res* 2006; 66: 9134–9142.

13. Taguchi E, Nakamura K, Miura T, *et al.* Antitumor activity and tumor vessel normalization by the vascular endothelial growth factor receptor tyrosine kinase inhibitor KRN951 in a rat peritoneal disseminated tumor model. *Cancer Sci* 2008; 99: 623–630.

14. Eskens FA, de Jonge MJ, Bhargava P, *et al.* Biologic and clinical activity of tivozanib (AV-951, KRN-951), a selective inhibitor of VEGF receptor-1, -2, and -3 tyrosine kinases, in a 4-week-on, 2-week-off schedule in patients with advanced solid tumors. *Clin Cancer Res* 2011; 17: 7156–7163.

15. Motzer RJ, Nosov D, Eisen T, *et al.* Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. *J Clin Oncol* 2013; 31: 3791–3799.

16. European Medicines Agency. Fotivda 2017, https://www.ema.europa.eu/en/medicines/human/EPAR/fotivda (Accessed on 23 January, 2020)

17. Smith M. *FDA rejects renal cancer drug Tivozanib*. MedPageToday, 2013, https://www.medpagetoday.com/hematologyoncology/renalcellcarcinoma/39736.

18. Rini BI, Pal SK, Escudier BJ, *et al.* Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomised, controlled, open-label study. *Lancet Oncol* 2020; 21: 95–104.

19. Rini BI, Pal SK, Escudier B, *et al.* TIVO-3: a phase III, randomized, controlled, multicenter, open-label study to compare tivozanib to sorafenib in subjects with refractory advanced renal cell carcinoma (RCC). *J Clin Oncol* 2019; 37: Abstract 541.

20. Dearment A. *AVEO Oncology puts off seeking FDA approval for kidney cancer drug until 1Q20*. MedCityNews, 2019, https://medcitynews.com/2019/11/aveo-oncology-puts-off-seeking-fda-approval-for-kidney-cancer-drug-until-1q20/.

21. Rini BI, Powles T, Atkins MB, *et al.* Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. *Lancet* 2019; 393: 2404–2415.

22. Rini BI, Plimack ER, Stus V, *et al.* Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019; 380: 1116–1127.

23. Motzer RJ, Penkov K, Haanen J, *et al.* Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019; 380: 1103–1115.

24. Barthelemy P, Escudier B, Negrier S, *et al.* TiNivo: tivozanib combined with nivolumab results in prolonged progression free survival in patients with metastatic renal cell carcinoma (mRCC): final results. *Ann Oncol* 2019; 30(Suppl. 5): v356–v402.

25. Fishman MN, Srinivas S, Hauke RJ, *et al.* Phase Ib study of tivozanib (AV-951) in combination with temsirolimus in patients with renal cell carcinoma. *Eur J Cancer* 2013; 49: 2841–2850.

26. Swetzig WM, Lurain JR, Berry E, *et al.* Efficacy and safety of tivozanib in recurrent, platinum-resistant ovarian, fallopian tube or primary peritoneal cancer. *J Clin Oncol* 2019; 37: Abstract 5538.

27. Agulnik M, Costa RLB, Milhem M, *et al.* A phase II study of tivozanib in patients with metastatic and nonresectable soft-tissue sarcomas. *Ann Oncol* 2017; 28: 121–127.

28. Kalpathy-Cramer J, Chandra V, Da X, *et al.* Phase II study of tivozanib, an oral VEGFR inhibitor, in patients with recurrent glioblastoma. *J Neurooncol* 2017; 131: 603–610.

29. Mayer EL, Scheulen ME, Beckman J, *et al.* A phase I dose-escalation study of the VEGFR inhibitor tivozanib hydrochloride with weekly paclitaxel in metastatic breast cancer. *Breast Cancer Res Treat* 2013; 140: 331–339.

30. Oldenhuis CN, Loos WJ, Esteves B, *et al.* A phase Ib study of the VEGF receptor tyrosine kinase inhibitor tivozanib and modified FOLFOX-6 in patients with advanced gastrointestinal malignancies. *Clin Colorectal Cancer* 2015; 14: 18–24.e1.

31. Benson AB III, Kiss I, Bridgewater J, *et al.* BATON-CRC: a phase II randomized trial comparing tivozanib plus mFOLFOX6 with bevacizumab plus mFOLFOX6 in stage IV metastatic colorectal cancer. *Clin Cancer Res* 2016; 22: 5058–5067.

32. Wolpin BM, Ng K, Zhu AX, *et al.* Multicenter phase II study of tivozanib (AV-951) and everolimus (RAD001) for patients with refractory, metastatic colorectal cancer. *Oncologist* 2013; 18: 377–378.