REVIEW

Tivozanib in the treatment of renal cell carcinoma

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Abstract: Renal cell carcinoma (RCC) is an aggressive malignancy compared to other urological malignancies and has been associated with poor responses to conventional cytotoxic chemotherapy. Interferon-α and interleukin-2 were previously utilized in a limited number of patients with good performance status due to toxicity and safety issues. Over the last decade, through advances in the understanding of the biology and pathology of RCC, the important role of vascular endothelial growth factor (VEGF) in RCC has been identified. Data from randomized trials have led to the approval of first-generation tyrosine kinase inhibitors (TKIs) sorafenib, sunitinib, and pazopanib; however, these agents inhibit a wide variety of kinase targets and are associated with a range of adverse effects. More recently, a new generation TKI, axitinib, has been approved by the US Food and Drug Administration. Tivozanib is a novel TKI, which is a potent inhibitor of VEGF-1, VEGF-2, VEGF-3, c-kit, and PDGR kinases, with a more restricted target spectrum. Phase II and III studies have demonstrated significant activity and a favorable safety profile as an initial targeted treatment for advanced RCC. This review examines the emerging data with tivozanib for the treatment of advanced RCC. Preclinical investigations as well as Phase I, II, and III data are examined; data on the comparative benefits of tivozanib are reviewed. Finally, we discuss the future potential of tivozanib in combination, biomarkers associated with tivozanib response, and acquisition of resistance and nonkidney cancer indications.

Keywords: targeted therapy, renal cell cancer, tyrosine kinase inhibitor, tivozanib

Introduction

Renal cell carcinoma (RCC) accounts for approximately 3% of adult malignancies and 90%–95% of all malignant kidney tumors. On January 1, 2009, in the United States, there were approximately 320,182 men and women alive who had a history of cancer of the kidney and renal pelvis. It is estimated that 64,770 men and women (40,250 men and 24,520 women) were diagnosed with, and 13,570 men and women died of cancer of the kidney and renal pelvis in 2012.[1,2]

RCC is an aggressive malignancy compared to other urological malignancies;[3] 20%–30% of patients present with metastatic disease due to the insidious nature of the disease and absence of a screening test.[4] Approximately 25% of patients with early-stage disease at diagnosis relapse after nephrectomy.[5] Patients with advanced disease have a 5-year survival rate of 10%, compared to 85% for patients with localized RCC. Therefore, advanced RCC has been associated with a poor prognosis and poor responses to conventional cytotoxic chemotherapy. Immunotherapy with high-dose interleukin (IL)-2 or interferon-alpha (INF-α) has been used as therapy in select patients with good performance status. The response rate with immunotherapy is relatively

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low (5%–30%), and toxicity and safety issues often limit their use.[6–8] The clinical efficacy of INF-α is limited; a meta-analysis reviewed data from 463 patients with advanced RCC who were administered INF-α as first-line systemic therapy and suggested that treatment with INF-α provides a median progression-free survival (PFS) of 4.7 months and a median overall survival (OS) of 13 months.[9] In the cytokine era, this result was proposed as a benchmark for the future targeted therapies.[9,10]

Advances in the understanding of the biology and pathology of RCC identified the important role of vascular endothelial growth factor (VEGF). This has led to development of numerous targeted agents, which have established a new benchmark for PFS and OS in Phase III trials compared with INF-α.[11–13] Data from randomized trials have led to the approval of seven agents over the last 5 years for advanced RCCs in first- or second-line treatment in metastatic RCC: sunitinib, sorafenib, bevacizumab (with or without INF-α), temsirolimus, everolimus, pazopanib, and axitinib.[14] Unfortunately, the existing treatment options have several restrictions: durable responses are rare; some cases show no response; the median prolongation in PFS is generally measured in months; and in some responding patients, toxicities can make long-term treatment difficult or necessitate dose reductions and interruptions. Because of these issues, additional therapies are still needed. Tivozanib (AV-951) is a novel agent that is a potent inhibitor of VEGF-1, VEGF-2, VEGF-3, c-kit, and PDGR kinases. Phase II and III studies have demonstrated significant activity and favorable safety profile as initial targeted treatment for advanced RCC.[15,16]

Molecular biology of RCC

The biology of hereditary renal neoplasms has led to a better understanding of the molecular basis of clear cell RCC. The Von Hippel–Lindau (VHL) tumor suppressor gene, located on chromosome 3p25, is mutated in patients with hereditary VHL syndrome, inducing cysts and tumors in the central nervous system and abdomen such as hemangioblastoma and pheochromocytoma. This condition also includes a predisposition to the development of clear cell RCC.[17] Interestingly, VHL gene inactivation has also been observed in 84% to 98% of sporadic RCCs based upon specific mutations or epigenetic gene silencing.[18–24] Thus, VHL abnormalities are key in the pathogenesis of clear cell RCC.

VHL protein regulates normal cellular responses to hypoxia by ubiquitin-mediated hypoxia-inducible factor 1 alpha (HIF1alpha). Using normal oxygen levels, oxygen content in the blood controls the formation of VHL protein complexes, by targeting HIF1alpha for deprivation by proteasomes. Low oxygen conditions lead to HIF1alpha accumulation and bind to HIF1beta, followed by formation of a complex that transcriptionally activates genes. Similarly, mutation or inactivation of the VHL protein disrupts the ability to degrade HIF1alpha, causing excessive accumulation even under normal oxygen conditions. This abnormal response activates the hypoxia response pathway and galvanizes numerous HIF-responsive genes, which leads to overproduction of proangiogenic factors, including growth factors such as VEGF, platelet-derived growth factor (PDGF), and transforming growth factor alpha/beta. HIF accumulation also takes place with activation of the mammalian target of rapamycin (mTOR) through cellular stimuli and the phosphoinositide 3-kinase/Akt (protein kinase) pathway.[25] Activated mTOR also leads to a cascade of events such as phosphorylation of 4E binding protein-1, leading to eukaryotic initiation factor-4 subunit E enhancing the translation of mRNAs that encode cell-cycle regulators such as cyclin D1 and c-myc.[26,27] Sulzbacher et al[28] documented PDGF expression in a large number of RCCs. PDGF receptor expression was correlated with higher in highly malignant tumors and adverse outcomes for patients with RCC. These pathways are involved in tumor proliferation,[29–32] as well as in promoting tumor-associated angiogenesis.[33]

VEGF primarily affects vascular endothelial cells by binding to and activating three structurally similar receptor tyrosine kinases:[30] VEGFR1 (also known as FLT1), VEGFR2 (also known as KDR), and VEGFR3 (also known as FLT4). Each VEGF ligand has a specific binding affinity for each of these tyrosine kinase receptors, which contributes to their diversity. Therefore, binding of each VEGFR tyrosine kinase activates a distinct downstream pathway that leads to diverse effects that leads to tumor proliferation and metastasis by mediating numerous changes within the tumor vasculature and promoting tumor angiogenesis.[18,33] Tumor angiogenesis is enhanced through increasing blood flow by promoting endothelial cell proliferation and survival; enhancing migration of endothelial cells; and increased permeability of existing cellular transport channels, developing an environment for endothelial cell migration through boosting chemotaxis of bone marrow derived endothelial cell precursors.[18,34–36]

Inhibition of VEGF in renal cell carcinoma

The inhibition of VEGF signaling may affect tumor growth through several mechanisms, such as antiangiogenic effects,

induction of endothelial cell apoptosis, and blockade of migration of hematopoietic and endothelial progenitor cells. The angiogenesis in RCC, in both the primary and metastatic sites of disease, is presumed to be highly VEGF-dependent due to the high-frequency inactivation of the VHL tumor suppressor gene. Therefore, VEGF has been an important target in development of therapeutic agents in RCC.

RCC is one of the most immunogenic tumors.[5,37] Programmed cell death 1 is one of these immunogenic mechanisms. BMS-936558, a monoclonal antibody directed at the programmed cell death 1 T-cell coinhibitory receptor, has been investigated in a Phase I study. In the RCC cohort, nine of 33 patients had an objective response.[38] Another monoclonal antibody, BMS-936559, targeting programmed cell death 1 ligand protein, is also being studied (ClinicalTrials.gov identifier: NCT01354431).[39] In the tumor microenvironment, VEGF weakens the host immune response by reducing dendritic cell differentiation and increasing secretion of immunosuppressive cytokines such as IL-10 and transforming growth factor beta.[34] Therefore, VEGF-inhibitors may also take part in modulation of the antitumor immunity.[40]

VEGF-targeted agents include bevacizumab, a humanized monoclonal antibody that inhibits VEGF A, and receptor tyrosine kinase inhibitors (TKIs) such as sorafenib, sunitinib, pazopanib, and axitinib.[29,41] These agents target the VEGF receptors, as do additional TKIs in ongoing clinical development. Amongst the three receptors for VEGF, VEGFR-2 on endothelial cells appears to be the key target.[42] This model initiated the development of novel agents with enhanced targeting of VEGFR2, such as tivozanib.

Preclinical investigations and tivozanib pharmacology

Tivozanib is a quinoline–urea derivative, a small molecule recently developed as a third-generation VEGF receptor TKI.[43] In preclinical studies, oral administration of tivozanib to athymic rats decreased the microvessel density within tumor xenografts and reduced VEGFR-2 phosphorylation levels in tumor endothelium, triggering inhibition of angiogenesis and vascular permeability. It also demonstrated antitumor activity in several human tumor xenografts, including lung, breast, colon, ovarian, pancreas, and prostate cancer. Preclinical activity for tivozanib in colorectal cancer was demonstrated by inhibition of progression in the peritoneal cavity in a colon cancer model with reduced tumor angiogenesis, ascites formation, and tumor spread, thereby prolonging survival.[44]

The activity of tivozanib has been assessed against several receptor tyrosine kinases using either cell-free kinase assays or the inhibition of ligand-induced phosphorylation of growth factor receptors. Tivozanib is a potent and selective VEGFR TKI with the highest potency for VEGFR-2, with similar levels for VEGFR-1 and VEGFR-3 (Table 1). Tivozanib showed relatively less inhibitory activity of c-kit, PDGF receptor (PDGFR)-b, Flt-3, fibroblast growth factor receptor-1, and c-met. Tivozanib has virtually no activity for EGFR and insulin-like growth factor-1. The specific potency of tivozanib on VEGFR-2 provides a theoretical distinction compared to earlier drugs used in RCC treatment such as sorafenib, sunitinib, and pazopanib.

Multitargeted TKIs may have a theoretical advantage of increased antitumor activity and delaying resistance; however, off-target effects may contribute to adverse events. Hand–foot syndrome, skin rash, fatigue, stomatitis, diarrhea, pigmentation changes, myelosuppression, and thyroid dysfunction are commonly associated with multitargeted TKI treatments.[10,45] Low potency of first-generation TKIs requires administration of higher doses to obtain optimal VEGFR inhibition. This usually leads to off-target toxicities at therapeutic doses. Compared with other US Food and Drug Administration-approved small-molecule TKIs, tivozanib is relatively specific for VEGFR-1, VEGFR-2, and VEGFR-3, although it still exhibits PDGFR-b inhibition. Although IC50 determination can be variable, depending on the cell system used, the IC50 concentrations for tivozanib inhibiting VEGFRs are the lowest in this group of agents (Table 1).

Phase I studies

Prior pharmacokinetic analysis in healthy volunteers demonstrated good oral bioavailability, slow absorption, predominantly fecal excretion, and long half-life. In this study, the half-life was 4.7 days, suggesting suitability for once-daily dosing.[46] Concentration–time profiles from the

Table 1 Receptor tyrosine kinase inhibitory activity at 50% of US Food and Drug Administration-approved TKIs in cell-free kinase assay (IC50)

TKI	Tivozanib	Axitinib	Sunitinib	Pazopanib	Sorafenib
VEGFR-1	30	ND	21	7	9
VEGFR-2	6.5	0.2	34	15	28
VEGFR-3	15	ND	3	2	7
PDGFR-B	49	1.6	75	215	1129
c-Kit	78	1.7	40	48	1862
FGFR-1	530	ND	437	80	64

Abbreviations: c-Kit, stem cell factor receptor; FGFR, fibroblast growth factor receptor; IC50, half-maximal inhibitory concentration; ND, not determined; PDGFR-B, platelet-derived growth factor receptor, beta; TKI, tyrosine kinase inhibitors; VEGFR, vascular endothelial growth factor.

majority of patients showed secondary peaks, indicating that tivozanib may undergo enterohepatic recirculation, which would likely be a contributing factor in the observed long $t_{1/2}$.

The first-in-human Phase I and pharmacologic study of tivozanib was conducted in 41 patients with advanced solid tumors,[47] including nine subjects with RCC. Tivozanib was administered at dose levels of 1.0 mg, 1.5 mg, and 2.0 mg per day for 28 days, followed by a 14-day break. The initial 2 mg dose produced dose-limiting toxicity, with grade 3 proteinuria, hypertension, and ataxia. At the 1.5 mg dose level of tivozanib, hypertension was the most common adverse event (62% grade 3, 0% grade 4). Among the other grade 1 or 2 adverse events, dysphonia was seen in 56% and diarrhea in 31% of patients. Laboratory abnormalities included a low percentage of grade 3/4 liver function abnormalities and the absence of proteinuria. This study suggested a similar side effect spectrum to other oral VEGFR inhibitors. In another Phase II study, investigators administered tivozanib 1.5 mg/day with a dosing schedule of 3 weeks on, 1 week off. Pharmacokinetic analysis and toxicity assessment was performed, and the results were consistent with those from previous tivozanib Phase I pharmacokinetic data in patients with advanced solid tumors and in healthy patients with no excess toxicity or drug accumulation.[16,48,49] On that basis, the schedule of tivozanib 1.5 mg daily for 3 weeks followed by a 1-week break was adopted and used in all studies since.

Plasma levels of VEGF-A and soluble VEGFR-2 showed dose-dependent increases and decreases, respectively. Partial response was observed in two of nine patients with RCC. Six patients had stable disease and one patient disease progression.[47] Subsequent evaluation of pharmacokinetic and toxicity in early studies suggested that a dosing regimen of 3 weeks on then 1 week off might be more optimal than 4 weeks on and 2 weeks off. Hence, this schedule was explored in the subsequent Phase II study.

Phase II study

The first Phase II trial of tivozanib enrolled 272 patients with a random discontinuation design for patients with stable disease; 83% had RCC with a clear cell component, 73% had undergone nephrectomy, and 46% had received prior therapy. Tivozanib was administered at a dose of 1.5 mg daily for 3 weeks, followed by a 1-week rest (3/1 week schedule). Median treatment duration was 8.5 months, while median PFS was 11.7 months (95% confidence interval [CI], 8.3 to 14.3 months) with an overall response rate of 24% (95% CI, 19%–30%). Subgroup analysis was also

conducted to explore the effect of prior therapy, but there was no significant difference in PFS between patients who had had received prior therapy and those who were treatment naïve. The adverse events related to tivozanib were similar to those observed in the Phase I trial: hypertension (45%) and dysphonia (21%).[16,48,50]

In the randomized discontinuation trial phase of the trial, 118 patients with stable disease were randomized to either tivozanib or a placebo. After 16 weeks of initial therapy, patients were allocated to further therapy based on the response. Patients with more than 25% tumor regression were continued on tivozanib, while patients with more than 25% tumor progression stopped therapy. Those patients judged to have stable disease were then randomized in a double-blind fashion to continue tivozanib or placebo for 12 weeks. In this group, the median PFS was longer for patients continuing tivozanib (n = 61; 10.3 months) compared to the placebo group (n = 57; 3.3 months). The data for all patients entered is summarized in Tables 2 and 3.

In summary, the results of this trial showed that tivozanib was active and well tolerated in patients with advanced RCC. The adverse event profile was acceptable and similar to those seen with other VEGFR inhibitors, including hypertension.[16]

Phase III trials

In TIVO-1, a Phase III randomized, open-label, multicenter trial, 517 patients with clear cell advanced RCC, with prior nephrectomy and Eastern Cooperative Oncology Group performance status 0 or 1, were enrolled. Patients were treatment naïve or received no more than one prior systemic therapy for metastatic disease; those who were previously treated with VEGF- or mTOR-targeted therapy were excluded. Patients were randomized 1:1 to tivozanib 1.5 mg

Table 2 Overall radiologic response to tivozanib among patient subgroups

Patient group	Patient number	Median PFS (months)	ORR (%)	Duration of response (months)
All patients	272	11.7 (95% CI, 8.3–14.3)	24 (95% CI, 19–30)	16.1 (95% CI, 9.3–19.6)
Clear cell RCC	226	12.5 (95% CI, 9.0–17.7)	26 (95% CI, 19–30)	17.8 (95% CI, 12.0–21.0)
Clear cell RCC and prior nephrectomy	176	14.8 (95% CI, 10.3–19.2)	30 (95% CI, 23–37)	16.1 (95% CI, 11.2–19.6)

Abbreviations: CI, confidence interval; ORR, objective response rate; PFS, progression-free survival; RCC, renal cell carcinoma.

Table 3 Adverse events and laboratory abnormalities

Adverse event	All grades (%)	Grade 1/2 (%)	Grade 3/4 (%)
Hypertension	45	31	12
Dysphonia	22	22	0
Asthenia	10	7	3
Diarrhea	12	10	2
Fatigue	8	6	2
Hand–foot syndrome	4	4	<1
Stomatitis	4	6	<1
ALT elevation	29	28	1
AST elevation	27	26	1
Direct bilirubin	24	22	2

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

once daily for 3 weeks on, 1 week off, or to sorafenib 400 mg twice daily continuously. Patients with protocol-defined progression on sorafenib were provided with tivozanib on an extension protocol; the design did not call for crossover from tivozanib to sorafenib as progression. Median PFS was 11.9 months for tivozanib, compared to 9.1 months for sorafenib (hazard ratio [HR], 0.797; 95% CI, 0.639–0.993; $P = 0.042$). In the treatment-naïve subgroup, the median PFS was 12.7 months for tivozanib and 9.1 months for sorafenib (HR, 0.756; 95% CI, 0.580–0.985; $P = 0.037$). OS trended in favor of sorafenib (stratified HR, 1.245; 95% CI, 0.954–1.624; $P = 0.105$). Tivozanib demonstrated significant improvement in PFS and ORR compared with sorafenib as initial targeted treatment for advanced RCC. The safety profile of tivozanib was favorable, with significantly less hand–foot syndrome (13% versus 54%), diarrhea (22% versus 32%), and alopecia (2% versus 21%) compared to sorafenib. Hypertension (44% versus 34%), back pain (14% versus 7%), and dysphonia (21% versus 5%) were significantly more common in the tivozanib arm.[15]

In the extension study, patients with progressive disease (PD) on sorafenib and patients with PD on tivozanib received subsequent treatment. Of the 257 patients on sorafenib, 155 (60.3%) were treated with next-line tivozanib at the time of the analysis. At the time of final OS analysis, which was 2 years after the last patient was enrolled, 118 deaths had occurred in the tivozanib arm (45.4%) compared to the sorafenib arm, where 101 deaths occurred (39.3%). There was no significant difference in OS between the two treatment arms (28.8 months for tivozanib versus 29.3 months for sorafenib). After discontinuation of initial therapy, 64% of patients in the tivozanib arm received no next-line therapy, compared with 26% of patients in the control arm. The authors suggested that the high rate of utilization of second-line tivozanib in patients following PD on sorafenib might

have affected the OS outcome.[51] The key additional factor in this trial was that patients, many of whom resided in Eastern Europe, initially received tivozanib but had limited access to additional targeted therapies with efficacy in metastatic RCC.[15] This meant that those initially given sorafenib received two drugs, compared to the one drug administered to those given tivozanib.

In the Phase II extension study of tivozanib for patients crossing over from sorafenib, RCC patients who were treated with tivozanib after progression on sorafenib were evaluated. Partial response (PR) was 7.9%; stable disease (SD) was 65.4%, and 71.3% of patients showed some degree of tumor shrinkage. Median duration of PR, SD, and PFS was 11.1 months (95% CI, 7.5–not reported [NR] months), 12.7 months (95% CI, 7.4–NR months), and 5.6 months (95% CI, 5.4–9.1 months), respectively. The preliminary data demonstrated that tivozanib has antitumor activity after PD on sorafenib. The adverse event profile of tivozanib after sorafenib was similar to that observed in TIVO-1.[52]

The subgroup analysis from TIVO-1 showed significant improvement in PFS by tivozanib compared to sorafenib. The PFS advantage was observed in those patients who were of Caucasian descent, had an Eastern Cooperative Oncology Group performance status of 0, who were diagnosed more than 1 year prior, who had received no prior treatment, who had more than 2 metastatic sites, whose baseline systolic blood pressure (BP) was greater than 140 mmHg, and whose baseline diastolic BP was less than 90 mmHg. Patients who developed hypertension during the study had significantly longer PFS than patients with normal BP. The improvement in PFS was more marked for tivozanib compared to sorafenib for the patients who developed hypertension.[53] Similar results were previously reported by Rini et al[54] in patients with metastatic RCC, whereby sunitinib-associated HTN is associated with improved clinical outcomes.

Health-related quality of life assessment was generally similar for tivozanib and sorafenib. The physical well-being assessment demonstrated more significant improvement with tivozanib compared to sorafenib.[55] The data for Phase III trials utilizing VEGF inhibitors or VEGF antibodies in advanced RCC are summarized in Tables 4 and 5.

Future aspects
Tivozanib will be compared to sunitinib in the TAURUS trial, a first-line randomized Phase II patient preference trial in metastatic RCC. In this trial design (modeled on the PISCES trial, which compared pazopanib and sunitinib), patients are randomized to either tivozanib or sunitinib for

Table 4 Phase III trials utilizing VEGF inhibitors or VEGF antibodies in advanced RCC survival and toxicity data

Trial	Arms	N	MSKCC prognostic risk:[76] Favorable Intermediate Poor	Toxicity all grades[†]		OS PFS ORR (CR + PR) CR
Motzer et al[15,51,77] Phase III	Tivozanib Sorafenib	260 257	27% versus 34% 67% versus 62% 7% versus 4%	Diarrhea Fatigue HFS HTN	22% 18% 13% 44%	28.8 versus 29.3 months 11.9 versus 9.1 months 33% versus 23% 1% versus 1%
Escudier et al[78] Phase III	Sorafenib Placebo	451 452	NR 48% versus 49% 52% versus 50%	Diarrhea Fatigue HFS HTN	43% 37% 30% 2%	19.3 versus 15.9 months 5.5 versus 2.8 months* 11% versus 2%* <1% versus 0%
Motzer et al[11] Phase III	Sunitinib INF-α	375 375	38% versus 34% 56% versus 59% 6% versus 7%	Diarrhea Fatigue HFS HTN	53% 51% 20% 24%	26.4 versus 21.8 months 11 versus 5 months* 47% versus 12%* 0% versus 0%
Escudier et al[79] Phase III	Bevacizumab + INF-α Placebo + INF	327 322	27% versus 29% 56% versus 56% 9% versus 8%	Diarrhea Fatigue HFS HTN	20% 33% NR 26%	23.3 versus 21.3 months 10.2 versus 5.4 months* 31% versus 13%* 1% versus 2%
Rini et al[80] Phase III	Bevacizumab + INF-α INF	369 363	26% versus 26% 64% versus 64% 10% versus 10%	Diarrhea Fatigue HFS HTN	NR 93% NR 28%	18.3 versus 17.4 months 8.5 versus 5.2 months* 13% versus 9% <1% versus <1%
Sternberg et al[81] Phase III	Pazopanib Placebo	290 145	39% versus 39% 55% versus 53% 3% versus 3%	Diarrhea Fatigue HFS HTN	52% 40% <10% 40%	22.9 versus 20.5 months 9.2 versus 4.2 months* 30% versus 3%* <1% versus 0%
Rini et al[82] Phase III	Axitinib Sorafenib	361 362	28% versus 28% 37% versus 36% 33% versus 33%	Diarrhea Fatigue HFS HTN	55% 39% 27% 40%	Not reported 6.7 versus 4.7 months* 19% versus 9%* 0% versus 0%

Notes: *Not significant; [†]toxicity for agent in the intervention arm.
Abbreviations: CR, complete response; HFS, hand–foot syndrome; HTN, hypertension; INF, interferon; MSKCC, Memorial Sloan-Kettering Cancer Center; N, number; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor.

12 weeks, followed by a restaging and toxicity assessment and crossover to the other drug for 12 weeks. Patients are then reassessed and state a preference for either drug.

Combination therapies in RCC

Currently approved targeted therapy improved PFS and OS in advanced RCC; however, durable responses are infrequent, and resistance is commonly seen after a median of 6–15 months.[56] Despite maximal inhibition of VEGF/VEGFR and PDGF/PDGFR pathways, resistance reliably develops due to a process known as "reactive resistance." There are two major models that explain the resistance to VEGF inhibitors, which are adaptive and intrinsic. The adaptive mechanism of resistance hypothesizes that tumors elude the VEGF inhibitor effects and salvage their functionality through an escape mechanism.[57] In preclinical models, HIF1alpha and HIF2alpha are major mediators of this process.[58,59] In a xenograft model, it was shown that increased IL-8 was consistent with escape from antiangiogenic agents. Administration of IL-8 neutralizing antibody successfully sensitized tumors to sunitinib, which supported this hypothesis.[60] Increased placental growth factor levels, angiopoietin pathway, and PDGFR have been associated with emergence of alternative proangiogenic mechanisms that would lead to resistance.[61–64] Intrinsic resistance defines the types of tumors that would not respond to VEGF inhibitors under any circumstances. This mechanism has been only shown in animal models.[65] Tumors that are driven by this pathway develop progressive disease soon after VEGF inhibitor treatment has been started. However, given that pathways other than VEGF or mTOR play a role in tumorigenesis,[57] other pathways may also be related to resistance to VEGF or mTOR-targeted therapy in RCC. For instance, basic fibroblast growth factor, hepatocyte growth factor, and IL-6 have recently been shown to increase

Table 5 Phase III trials utilizing VEGF inhibitors or VEGF antibodies in advanced RCC discontinuation data

| Trial | Arms | N | Reasons to discontinue therapy | | | | | |
| | | | PD or death | | Toxicity | | Patient choice | |
			N	%	N	%	N	%
Motzer et al[15,77]	Tivozanib	260	189	72	4	1	NR	NR
Phase III	Sorafenib	257	226	87	5	2	NR	NR
Escudier et al[78]	Sorafenib	451	246	55	18	4	7	2
Phase III	Placebo	452	300	66	17	4	11	2
Motzer et al[11]	Sunitinib	375	92	25	30	8	4	1
Phase III	INF-α	375	170	45	47	13	16	4
Escudier et al[79]	Bevacizumab + INF-α	327	151	46	86	26	10	10
Phase III	Placebo + INF-α	322	224	70	32	10	11	11
Rini et al[80]	Bevacizumab + INF-α	369	200	54	85	23	40	11
Phase III	INF-α	363	218	60	66	18	33	3
Sternberg et al[81]	Pazopanib	290	158	54	41	14	18	6
Phase III	Placebo	145	121	83	5	3	4	4
Rini et al[82]	Axitinib	361	172	48	22	6	10	3
Phase III	Sorafenib	362	193	53	33	9	7	2

Abbreviations: INF, interferon; N, number; NR, not reported; PD, progressive disease; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor.

or remain high immediately before progression in patients being treated with sunitinib.[66]

Because the activation of multiple parallel pathways leads to VEGF resistance, investigators have postulated that adding inhibitors of other pathways might mitigate resistance and improve outcome.

Given significant activity in RCC, mTOR inhibitors and VEGF inhibitors are an obvious potential combination to provide targeted inhibition tumor cell growth via parallel and overlapping pathways in the context of different side effect profiles.[41] Previously tested combinations of mTOR inhibitors with sunitinib or sorafenib were either not tolerated or tolerated at attenuated doses due to adverse event profile.[67,68] More recently, the TORAVA randomized Phase II trial assessing the safety profile and efficacy of bevacizumab and temsirolimus demonstrated a worse toxicity profile and poorer disease control than sunitinib.[69] In contrast, a Phase I study of the combination of everolimus and sorafenib at submaximal doses produced acceptable toxicity and evidence of antitumor activity in previously untreated patients with metastatic RCC.[70]

Tivozanib was combined with temsirolimus in a Phase IB study. In contrast to other combinations, the authors reported that full doses of tivozanib (1.5 mg/day) and temsirolimus (25 mg/week) were tolerable, with no dose-limiting toxicities. Activity in terms of prolonged stable disease and partial response was reported in subjects on the trial. These results are promising, since tivozanib was the first selective VEGFR TKI to be successfully combined with an mTOR inhibitor at the full recommended dose and schedule of both agents.[71,72]

A recent study has demonstrated activity of tivozanib after treatment with VEGF inhibitors, specifically sorafenib.[52] Additional studies are warranted to determine whether tivozanib, alone or in combination, may be effective after resistance to other VEGF-targeted drugs develops.

Nonkidney cancer clinical development directions with tivozanib

Tivozanib is also currently being evaluated in patients with other cancer types and demonstrated promising results. Phase I studies showed that tivozanib can be safely combined at full doses and schedule with paclitaxel in metastatic breast cancer and FOLFOX6 in advanced gastrointestinal tumors.[49,73] A study evaluating the combination of tivozanib with everolimus in metastatic colorectal cancer is ongoing (ClinicalTrials.gov identifier: NCT01058655). In another open-label trial, tivozanib is being investigated in patients with nonsmall cell lung cancer (ClinicalTrials.gov identifier: NCT00826878).

Biomarkers associated with tivozanib response

Tumor-associated macrophages enhance immunosuppression and angiogenesis by secreting VEGF, cytokines, and other angiogenesis factors. These tumor-associated macrophages are regulated by myeloid-derived suppressor cells. Myeloid-derived suppressor cells and their secreted alternative ligands are associated in the development of resistance to bevacizumab and VEGF receptor TKI therapy.[40]

Myeloid cells have also been investigated as a predictor of tivozanib efficacy. In a preclinical study to identify biomarkers associated with tivozanib response, a population-based tumor model comprising more than 100 genetically developed breast HER2 tumors was used to test the efficacy of tivozanib. IHC analysis of infiltrating myeloid cells in 21 patient samples demonstrated a significant correlation between the percent myeloid cell composition in the tumors and maximum tumor shrinkage by RECIST (Response Evaluation Criteria In Solid Tumors) criteria. The data demonstrated the presence of tivozanib sensitive and insensitive angiogenesis mechanisms in both murine and human solid tumors. These findings provided evidence for a potential biomarker that could be utilized to predict tivozanib response.[36]

The Phase II BATON trial was designed to further validate a tivozanib-resistance biomarker, as well as to determine the biomarkers that may predict clinical activity and/or toxicity with tivozanib. Investigators identified a 42-gene resistance signature defining a specific tumor infiltrating myeloid population by using a novel, coherence-based bioinformatics analysis of pretreatment tumor microarray data. They analyzed 21 samples from patients treated with tivozanib in a Phase II RCC trial. The data demonstrated that the percent of myeloid cell composition in the tumors and clinical antitumor activity of tivozanib was significantly correlated (ClinicalTrial.gov identifier: NCT01297244).[74]

In a more recent study, investigators characterized molecularly annotated datasets that were available from a Phase III TIVO-1 trial to further characterize molecular RCC subtypes and evaluate relationships between subtypes and VEGF TKI activity. Based on their analysis, the hypoxia signature was significantly associated with better PFS on tivozanib. The study demonstrated a distinct molecular profile, which can be classified by a low hypoxia signature and may help identify tivozanib responders.[75]

Conclusion

In conclusion, tivozanib is a novel TKI with relative selectivity for VEGF receptors compared to earlier drugs. Tivozanib demonstrated better response rates and PFS in a Phase III study in a composite group of patients who were therapy naïve or who had had one line of therapy, typically with cytokines. The safety profile of tivozanib differed from sorafenib with less hand–foot skin reactions and diarrhea, and more hypertension. Phase I data suggests that tivozanib and temsirolimus can be given together in full therapeutic doses, while other trials investigating combinations are ongoing. The TAURUS clinical trial is currently investigating the efficacy of tivozanib versus sunitinib in a first-line setting (ClinicalTrials.gov identifier: NCT01673386). However, given the target and toxicity profile of tivozanib, the setting in which this agent may be used to greatest advantage in the current RCC landscape is in first-line therapy for metastatic disease. A first-line Phase III trial of tivozanib compared to pazopanib is in its planning phase. Tivozanib will also be explored in other cancers including colorectal, lung, breast, and hepatobiliary cancers.

Disclosure

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