Development of Second-Generation VEGFR Tyrosine Kinase Inhibitors: Current Status

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Abstract The vascular endothelial growth factor (VEGF) signaling pathway appears to be the dominant pathway involved in tumor angiogenesis, providing a rationale for targeting the VEGF receptors (VEGFR-1, -2, and -3) in the treatment of cancers. In particular, VEGF signaling is thought to be important in renal cell carcinoma (RCC) because of the deregulation of the pathway through nearly uniform loss of the von Hippel Lindau protein. The tyrosine kinase inhibitors (TKIs) sorafenib, sunitinib, and pazopanib are approved by the US Food and Drug Administration for the treatment of advanced RCC; however, these multi-targeted agents inhibit a wide range of kinase targets in addition to the VEGFRs, resulting in a range of adverse effects unrelated to efficient VEGF blockade. This article reviews recent advances in the development of the second-generation VEGFR TKIs, including the more selective VEGFR TKIs tivozanib and axitinib, and focuses on the potential benefits of novel inhibitors with improved potency and selectivity.

Keywords Angiogenesis • Axitinib • Cediranib • Growth factors • Pazopanib • Renal cell carcinoma • Sorafenib • Sunitinib • Tivozanib • Tyrosine kinase inhibitors • Vascular endothelial growth factor

Introduction

Angiogenesis, the formation of new capillary blood vessels, is fundamental to normal development and critical for physiological processes in adults, such as reproduction and wound healing. Angiogenesis is also associated with pathologic conditions, such as rheumatoid arthritis, age-related macular degeneration, and diabetic retinopathy, and is also a crucial component of tumor growth and metastasis [1]. As a nascent tumor grows, the cell mass limits diffusion of oxygen, creating hypoxia, which in turn activates the hypoxia-inducible factor (HIF) transcription factors and thereby upregulates expression of the vascular endothelial growth factor (VEGF) family of proteins. When combined with appropriate proteolytic factors in the microenvironment, the VEGFs enable the recruitment and proliferation of nearby vessel structures to initiate and sustain tumor neovascularure [2]. Evidence suggests that acquisition of a blood supply is a rate-limiting step in the establishment of solid tumors. Thus, inhibition of angiogenesis has emerged as an important antitumor strategy for solid tumors [3].

While a number of angiogenesis inducers have been identified [1], the VEGF signaling pathway appears to be the dominant pathway involved in tumor angiogenesis [3]. The VEGF family consists of five structurally related proteins (VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor [PLGF]), and signaling through this pathway is mediated by the binding of these growth factors to three receptors (VEGF receptor [VEGFR]-1, VEGFR-2, and VEGFR-3). The ligands bind each receptor with distinct but overlapping specificity as well as distinct biological function, together acting to affect proliferation, migration, and morphogenesis of endothelial cells to form functional vasculature [4•, 5, 6, 7].
Although VEGF signaling is important for the growth of many different tumor types, advances in our understanding of tumor cell biology have indicated a particularly strong rationale for blocking VEGF as a treatment strategy in clear cell renal cell carcinoma (RCC). Functional defects in the von Hippel Lindau gene (VHL), which is a negative regulator of HIF1 and HIF2 and thus a tumor suppressor, are present in over 90% of clear cell RCC tumors [8]. VHL inactivation results in the stabilization of HIFs, particularly HIF2 [9, 10], and upregulation of the expression of a large set of hypoxia-induced genes, including VEGF-A and VEGF-C [8].

Therapeutic inhibition of the VEGF pathway may be achieved via monoclonal antibodies or receptor traps targeted to the various VEGF ligands (eg, bevacizumab binding to VEGF-A, TB-403 binding to PLGF, aflibercept binding to VEGFs), antibodies targeting the extracellular domain of various VEGFRs (IMC-1C11 binding to VEGFR-2), or via intracellular inhibition of VEGF signaling through use of small-molecule tyrosine kinase inhibitors (TKIs) that target the intracellular kinase domains of the three VEGFRs [11]. This article reviews recent advances in the development of second-generation VEGFR TKIs, focusing on the potential benefits of novel inhibitors with improved potency and selectivity.

Approved TKIs with Anti-VEGFR Activity

Over the past 4 years, three oral multitargeted TKIs, sorafenib [12••], sunitinib [13••, 14], and pazopanib [15••], have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency for the treatment of advanced RCC. In addition to the VEGFR tyrosine kinases, these agents potently inhibit a wide range of tyrosine kinases and other targets (such as platelet-derived growth factor receptor [PDGFR], stem cell factor receptor [c-kit], FMS-like tyrosine kinase-3 [Flt3], rearranged during transfection [RET], colony-stimulating factor 1 receptor [CSF1R], c-Raf, and Raf homolog B1 [B-Raf]), which disrupt multiple signaling pathways [12••, 13••, 14, 15••, 16]. This lack of specificity for the VEGFRs is manifested in the occurrence of several toxicities that are unrelated to blockage of the VEGF pathway, often termed “off-target” effects of multitargeted TKIs. These toxicities have not been observed with the monoclonal antibody bevacizumab, which is a selective VEGF pathway inhibitor available for human use.

A phase 3 randomized study [13••] comparing oral sunitinib (50 mg once daily for 4 weeks, followed by 2 weeks without treatment) with subcutaneously administered interferon (IFN)-α (9 million units 3 times weekly) as first-line treatment in 750 patients with metastatic RCC showed significant improvement in median progression-free survival (PFS; 11 months vs 5 months, respectively; \( P<0.001 \)) and objective response rate (ORR; 31% vs 6%, respectively; \( P<0.001 \)) with sunitinib. While IFN-α was associated with a higher incidence of grade 3 or 4 treatment-related fatigue (12% vs 7% with sunitinib; \( P<0.05 \)), sunitinib was associated with a higher incidence of grade 3 diarrhea (5% vs 0%), vomiting (4% vs 1%), hypertension (8% vs 1%), and hand-foot syndrome (5% vs 0%; \( P<0.05 \) for all comparisons). Sunitinib was also associated with a higher incidence of grade 3 or 4 neutropenia (12% vs 7%, respectively, including two cases of febrile neutropenia with sunitinib) and thrombocytopenia (8% vs 0%; \( P<0.05 \) for all comparisons). A total of 38% of patients in the sunitinib group required a dose reduction, and 32% required a dose interruption.

The pivotal phase 3, randomized, placebo-controlled study [12••] of sorafenib (TARGET) enrolled 903 patients with advanced clear cell RCC that was resistant to therapy with cytokines. Treatment with oral sorafenib 400 mg twice daily significantly prolonged PFS (5.5 months) compared with placebo (2.8 months; \( P<0.01 \)); overall survival (OS) was not significantly different between the treatment groups. Partial responses were reported for 10% of sorafenib-treated patients compared with 2% in the placebo group (\( P<0.001 \)). The most common grade 3 or 4 adverse events with sorafenib included hand-foot skin reactions (6%), fatigue (5%), dyspnea (4%), and diarrhea (2%); grade 3 or 4 hypertension and cardiac ischemia were rare serious adverse events occurring more often with sorafenib (4% and 3%, respectively) than with placebo (<1% for both).

The activity of pazopanib was assessed in a randomized, placebo-controlled, phase 3 study involving 435 patients with locally advanced or metastatic RCC (46% of whom were previously treated with cytokines) [15••]. Median PFS was significantly longer with pazopanib compared with placebo in the overall study population (9.2 months vs 4.2 months; \( P<0.0001 \)), as well as in the treatment-naive (11.1 months vs 2.8 months; \( P<0.0001 \)) and cytokine-pretreated subpopulations (7.4 months vs 4.2 months; \( P<0.001 \)). ORR was also significantly greater with pazopanib compared with placebo (3%; \( P<0.001 \)). The most common grade 3 and 4 adverse events associated with pazopanib included diarrhea (4%), hypertension (4%), lymphocytopenia (4%), and asthenia (3%). Abnormalities in hepatic function were more frequent in the pazopanib arm (alanine transaminase ≥ 3 times the upper limit of normal in 18% of patients), and were associated with two treatment-related deaths. In an expert review at the FDA Oncology Drug Advisory Committee meeting, hepatotoxicity with pazopanib was felt to be similar to that seen with sunitinib during their phase 3 trial [17].
Selectivity and Potency of VEGFR Inhibitors

Although multitargeted TKIs have demonstrated anti-tumor activity, they are associated with a variety of “off-VEGF target” effects related to their nonspecific nature [16]. For example, hand-foot skin reactions, fatigue, stomatitis, diarrhea, hair color changes, myelosuppression, and thyroid dysfunction are commonly associated with treatment with multitargeted TKIs. Low potency of currently available TKIs (Fig. 1a) requires administration of higher doses to obtain optimal VEGFR blockade and efficacy; however, higher doses are in turn associated with increased blockade of non-VEGF kinases due to low selectivity (Fig. 1b), leading to toxicities that often require dose reductions or interruptions. The off-target effects of multitargeted TKIs have also limited their use in combination regimens due to overlapping toxicities with chemotherapeutic drugs. These limitations of multitargeted TKIs have led to the development of more selective and potent anti-VEGFR TKIs (Table 1), with the objective of providing improved antitumor activity with fewer off-target toxicities at therapeutic doses.

Second-Generation VEGFR TKIs

Tivozanib

Tivozanib (AV-951) is an extremely potent and selective oral pan-VEGFR TKI with picomolar potency to each of the three VEGFRs (VEGFR-1, 0.21 nM; VEGFR-2, 0.16 nM; VEGFR-3, 0.24 nM), which results in a high selectivity for the VEGFRs relative to other kinases [18,
A phase 2 randomized discontinuation trial involving patients with locally advanced or metastatic RCC (83% of whom had clear cell RCC, and 73% of whom had undergone nephrectomy) evaluated 16 weeks of open-label treatment with tivozanib 1.5 mg/day, after which patients who had <25% tumor change were randomized to 12 weeks of treatment with tivozanib or placebo. Preliminary results indicate that among all treated patients (N=272), tivozanib was associated with an ORR of 27% and a median PFS of 11.8 months. Among those with clear cell RCC who had undergone nephrectomy (n=176), the ORR was 32% and the median PFS was 14.8 months [20]. Among those patients randomized to double-blind treatment, median PFS was longer among those randomized to receive tivozanib (n=58; 12.1 months) compared with placebo (n=53; 6.3 months), with a significantly greater proportion of patients progression free after 12 weeks of treatment on the tivozanib arm (P=0.003) [21]. Of the 29 patients with progressive disease while on placebo, 26 patients crossed back to open-label tivozanib and 24 experienced response or stable disease. The most common adverse events observed in >20% (any grade) were hypertension (50%) and dysphonia (22%); the incidences of gastrointestinal events, fatigue, and hand-foot syndrome were low. Grade 3 adverse events included hypertension (8%) and asthenia (2%); an additional 1% of patients experienced grade 4 hypertension [20]. As observed with agents approved in RCC, response to tivozanib and median PFS were higher among patients experiencing hypertension during treatment compared with those that did not [22]. An ongoing open-label phase 3 trial (TIVO-1) is comparing tivozanib versus sorafenib in treatment-naive or cytokine-pretreated patients with advanced clear cell RCC who have undergone a nephrectomy (ClinicalTrials.gov identifier: NCT01030783).

Preliminary results from an ongoing phase 1 study [23] evaluated the combination of tivozanib with temsirolimus, a mammalian target of rapamycin (mTOR) inhibitor, in patients with metastatic RCC. The combination was well tolerated at full doses of each agent (tivozanib 1.5 mg/day and temsirolimus 25 mg/week), with no dose-limiting toxicities observed and no evidence of pharmacokinetic interaction between tivozanib and temsirolimus. Clinical activity was encouraging, with 2 of 16 patients achieving confirmed partial responses and 8 patients achieving stable disease for >10 weeks as of the cutoff date. Grade 3 adverse events included thrombocytopenia, fatigue/asthenia, hypertension, and rash, each of which was reported by 1 patient (6%) [23]. Tivozanib is the first TKI to be safely combined with an mTOR inhibitor at full dose and schedule of both agents. A study evaluating the combination of tivozanib with everolimus is ongoing (ClinicalTrials.gov identifier: NCT01058655).

Tivozanib is also currently being evaluated in patients with other cancer types, including a phase 1 study of tivozanib monotherapy in patients with NSCLC (ClinicalTrials.gov identifier: NCT00826878), a phase 1 study of tivozanib in combination with paclitaxel in patients with advanced or metastatic breast cancer (ClinicalTrials.gov identifier: NCT00717340), and a phase 1 study of tivozanib in combination with FOLFOX6 in patients with advanced colorectal and other gastrointestinal cancers (ClinicalTrials.gov identifier: NCT00660153).

### Table 1 Clinical activity and tolerability of monotherapy with second-generation VEGFR TKIs in RCC

| Agent       | Study design                                      | Activity                                           | Grade ≥3 adverse events (active treatment arms)        |
|-------------|--------------------------------------------------|----------------------------------------------------|--------------------------------------------------------|
| Axitinib    | Phase 2, single-arm, 52 patients with clear cell mRCC [25] | ORR 44%; TTP 15.7 months; OS 29.9 months          | Hypertension (8%), diarrhea (5%), fatigue (4%), anorexia (1%), limb pain (2%), arthralgia (1%), myalgia (1%), stomatitis (1%) |
| Tivozanib   | Phase 2, single-arm, 62 patients with sorafenib-refractory clear cell mRCC [26] | ORR 23%; PFS 7.4 months; OS 13.6 months           | Hand-foot syndrome (16%), fatigue (16%), hypertension (16%), dyspnea (15%), diarrhea (15%), dehydration (8%), hypotension (7%) |
| Tivozanib   | Phase 2, randomized discontinuation study of 272 patients with locally advanced or mRCC (all histologies) [20] | ORR 27%; PFS 11.8 months                          | Hypertension (9%), asthenia (2%)                          |
| Cediranib   | Phase 2, randomized, placebo-controlled; 71 patients with advanced RCC [37] | Cediranib: tumor size −20%; ORR 34%; PFS 12.1 months; Placebo: tumor size +19%; PFS 2.7 months | Fatigue (19%), hypertension (19%), diarrhea (13%)          |

mRCC metastatic renal cell carcinoma; ORR objective response rate; TTP time to progression; OS overall survival; PFS progression-free survival; RCC renal cell carcinoma; TKI tyrosine kinase inhibitor; VEGFR vascular endothelial growth factor receptor.

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Axitinib

Axitinib (AG-013736) is a potent small-molecule inhibitor of all known VEGFRs, with lower potency against PDGFR and c-kit [24]. In a phase 2 study [25•] of 52 patients with metastatic clear cell RCC (94% of whom had undergone nephrectomy), axitinib was initiated at 5 mg twice daily. Dose escalation was possible in 6 patients (12%), and dose reductions were required in 42% of patients because of grade 2 (13%) and grade 3 (29%) adverse events. Axitinib was associated with an ORR of 44% (2 complete and 21 partial responses), with a median duration of response of 23 months. Median time to progression was 15.7 months, and median OS was 29.9 months; PFS was not reported. Adverse events observed in >20% of patients were diarrhea (60%), hypertension (58%), fatigue (52%), nausea (44%), dysphonia (37%), anorexia (35%), dry skin (33%), weight loss (27%), dyspepsia (23%), and vomiting (21%). Grade 3 or 4 treatment-related adverse events included hypertension (15%), diarrhea (5%), and fatigue (4%). Hypertension of any grade was reported in 30 (58%) patients but resolved with antihypertensive treatment in all but 8 patients (7 of whom had a previous history of hypertension) [25•]. In a second phase 2 study [26•] involving 62 patients with sorafenib-refractory metastatic RCC (95% with clear cell histology, all had undergone nephrectomy), axitinib 5 mg twice daily provided an ORR of 23%, with a median duration of response of 17.5 months. An additional 21 (34%) patients had stable disease. Median PFS was 7.4 months, and median OS was 13.6 months. The most common adverse events were fatigue (77%), diarrhea (61%), anorexia (48%), hypertension (45%), nausea (44%), and dyspnea (39%). Hand-foot syndrome (35%) and mucositis (34%) were also common. Grade 3 or 4 adverse events included hand-foot syndrome (16%), fatigue (16%), hypertension (16%), dyspepsia (15%), diarrhea (15%), dehydration (8%), and hypotension (7%). There appears to be an association between hypertension and efficacy of axitinib: a pooled analysis [27] of phase 2 data demonstrated that median OS for patients with at least one diastolic blood pressure measurement ≥90 mm Hg (n=59) during axitinib therapy was 130 weeks compared with 42 weeks for patients without elevated diastolic blood pressure (n=50; P<0.01). No apparent relationship between drug concentrations and maximum diastolic blood pressure was observed. Axitinib is currently being compared with sorafenib predominantly in the second-line setting in two phase 3 studies in patients with treatment refractory metastatic clear cell RCC (ClinicalTrials.gov identifiers: NCT00678392 and NCT00920816).

Axitinib has also demonstrated efficacy in patients with several other cancer types. As monotherapy, axitinib showed activity against thyroid cancers in a phase 2 study (n=60) [28•], yielding an ORR of 30% and a median PFS of 18.1 months. In a phase 2 study [29] of 32 patients with stage IV melanoma, treatment with axitinib resulted in an ORR of 16%, a median PFS of 2.3 months, and a median OS of 13.0 months in patients with diastolic blood pressure ≥90 mm Hg and 6.2 months for those without. In advanced non–small cell lung cancer (NSCLC), a disease control rate of 41%, median PFS of 4.9 months, and median OS of 14.8 months were achieved with axitinib in a phase 2 study (n=32) [30•].

Axitinib has also demonstrated activity in advanced NSCLC and other solid tumors in combination with chemotherapy in a phase 1 study (n=47) [31]: ORR was 29% when combined with paclitaxel plus carboplatin (platinum-naive and taxane-naive patients) and 26% when combined with gemcitabine plus cisplatin (pretreated patients). In a randomized phase 2 study (n=168) [32], axitinib combined with docetaxel showed promising activity in metastatic breast cancer, with a median time to progression of 8.2 months with the combination versus 7 months with docetaxel alone (P=0.052) and an ORR of 40% with the combination versus 23% with docetaxel alone (P=0.038). A phase 1 study [33] assessed the combination of axitinib with bevacizumab, a monoclonal antibody to the VEGF ligand, plus chemotherapy (FOLFOX) compared with axitinib plus chemotherapy (FOLFOX or FOLFIRI) in 30 patients with metastatic colorectal cancer and other solid tumors. Responses were observed with all treatment combinations, although patient numbers were too small for statistical comparisons [33]. In contrast to the other cancer types evaluated, the addition of axitinib to gemcitabine in pancreatic cancer has demonstrated only small nonsignificant clinical improvements compared with gemcitabine alone in phase 2 (n=103) [34] and phase 3 (n=632) [35] studies, and is not recommended for further evaluation.

Across all cancer types, the most common adverse events observed with axitinib treatment were hypertension, gastrointestinal events, fatigue, anorexia, and hematologic abnormalities [25•, 26•, 28•, 29, 30•, 31–35]. Notably, in a phase 1 study [33] of patients with colorectal and other cancers, the incidence of hypertension was 81% among patients receiving axitinib plus bevacizumab and chemotherapy versus 37% among those receiving axitinib plus chemotherapy without bevacizumab.

Several additional clinical studies are ongoing to evaluate axitinib therapy in patients with the above cancers as well as advanced gastric cancers, soft tissue sarcomas, and acute myeloid leukemia or myelodysplastic syndrome (ClinicalTrials.gov).

Cediranib

Cediranib (AZD2171) is an oral VEGFR TKI that has affinity for the VEGFRs, c-kit, PDGFRβ, fibroblast growth
factor receptor (FGFR)-1, and several other kinases [36]. In a phase 2 study [37], 71 patients with advanced or metastatic RCC were randomized to 12 weeks of treatment with cediranib 45 mg/day (n=53) or placebo (n=18). The mean change in tumor size from baseline was significantly greater among patients randomized to cediranib (20% reduction) versus placebo (19% increase; \( P<0.0001 \)), with partial responses observed in 34% of patients in the cediranib arm. Median PFS was also significantly greater with cediranib (12.1 months) versus placebo (2.7 months; \( P=0.017 \)). Common grade 3 or 4 adverse events included fatigue (19%), hypertension (19%), and diarrhea (13%); 58 (87%) patients required a dose reduction or interruption due to toxicities [37]. Preliminary results from another phase 2 study [38] of 43 patients with metastatic RCC have shown partial responses in 38% of patients and a median PFS of 8.7 months during treatment with cediranib 45 mg/day. Treatment-related grade 3 or 4 adverse events included hypertension (30%), fatigue (26%), joint pain (12%), dyspnea (12%), and abdominal pain (5%).

Cediranib monotherapy has also demonstrated promising efficacy in patients with a range of other cancers. In an open-label exploratory study [39] involving 19 patients with recurrent or metastatic head and neck cancer or NSCLC, 6 (35%) patients showed a reduction in tumor metabolic activity of \( \geq 25\% \) (assessed by fluorodeoxyglucose positron emission tomography) after 71 days of treatment with cediranib 30 mg/day. In a phase 2 study [40] of patients with recurrent glioblastoma, treatment with cediranib 45 mg/day resulted in radiographic partial response in 27% to 57% of patients, depending upon assessment methodology; the median PFS was 3.8 months, and median OS was 7.5 months. In another phase 2 study [41] involving 47 patients with recurrent epithelial ovarian, fallopian tube, or peritoneal cancer, treatment with cediranib provided clinical benefit (response or stable disease) in 14 (30%) patients; the original dose of cediranib was 45 mg/day, but was subsequently reduced to 30 mg/day because of toxicities in the first 11 patients (primarily fatigue [52%) and diarrhea [31%]). Preliminary results from a phase 2 study [42] in men with castration-resistant prostate cancer that had progressed on docetaxel therapy showed evidence of antitumor activity with cediranib 20 mg/day, with 19 of 34 patients achieving tumor regression, including 6 with partial responses.

Cediranib has also been investigated in a number of combination regimens in breast, colorectal, NSCLC, and small cell lung cancer. Studies of cediranib in combination with chemotherapy in patients with advanced lung cancers have produced inconsistent results, which typically did not demonstrate significant improvement with the addition of cediranib [43–46]. The ORR for patients with NSCLC ranged from 16% to 38% with cediranib and 16% to 18% without; median PFS ranged from 5.6 to 6.3 months with cediranib to 4.5 to 5.0 months without [43–45]. Further, addition of cediranib was associated with dose reduction/interruption and/or discontinuation due to toxicity in a majority of patients from each study [43, 44, 46]. Similar results have been observed for cediranib 20 mg/day in combination with FOLFOX chemotherapy versus bevacizumab plus chemotherapy as first-line therapy in patients with metastatic colorectal cancer [47], and for cediranib 45 mg/day in combination with fulvestrant (selective estrogen-receptor antagonist) in women with hormone-sensitive metastatic breast cancer [48].

Across cancer types, study results have shown that, although generally effective, cediranib at 45 mg/day was not well tolerated [41, 45, 46, 48], with one study in NSCLC indicating that the lower dose of 30 mg/day cediranib in combination with chemotherapy was not well tolerated either [44]. Overall, the most frequently reported toxicities with cediranib include hematologic abnormalities, fatigue, hypertension, anorexia, dysphonia, gastrointestinal events, and hepatobiliary abnormalities [37–39, 41, 44–46, 48].

Several ongoing clinical trials are evaluating cediranib in patients with the above cancer types as well as in patients

| All grades (grades 3–4) | Sunitinib [62] (n=375) | Sorafenib [63] (n=451) | Pazopanib [15*] (n=290) | Axitinib [25*] (n=52) | Tivozanib [20*] (n=272) |
|------------------------|------------------------|------------------------|-------------------------|------------------------|-------------------------|
| **Adverse events**      |                        |                        |                         |                        |                         |
| Mucositis/stomatitis   | 43% (10%)              | NA                     | NA                      | 9% (1%)                | 4% (<1%)                |
| Hand-foot syndrome     | 21% (5%)               | 30% (6%)               | 37% (6%)                | 19% (2%)               | 27% (4%)                |
| Rash/desquamation      | 27% (1%)               | 40% (1%)               | 37% (6%)                | 19% (2%)               | 27% (4%)                |
| Fatigue                | 58% (9%)               | 37% (6%)               | 19% (2%)                | 6% (0%)                | 27% (4%)                |
| Diarrhea               | 58% (6%)               | 43% (2%)               | 52% (4%)                | 31% (5%)               | 8% (2%)                 |
| Dose reduction         | 32%                    | 13%                    | 14%                     | 29%                    | 10%                     |
| Dose interruption      | 38%                    | 21%                    | 14%                     | NA                     | 4%                      |

*NA not available; RCC renal cell carcinoma; TKI tyrosine kinase inhibitor; VEGFR vascular endothelial growth factor receptor.*

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Other TKIs in Development with VEGFR Affinity

Several other TKIs with anti-VEGFR affinity are also in various stages of clinical development, although most are novel multitargeted TKIs. BIBF 1120 is a potent blocker of VEGFR, PDGFR, and FGFR kinase activity, which has shown antitumor activity and acceptable tolerability in preclinical models [49]. Results from a phase 2 study [50] suggest that maintenance therapy with BIBF 1120 at 250 mg twice daily could delay disease progression in ovarian cancer after previous response to chemotherapy [50]. BMS-690514 is a potent and reversible inhibitor of VEGFR, EGF, human epidermal growth factor (HER)-2, and HER-4 [51]. In a phase 1 study [51] of 30 patients with a variety of advanced or metastatic solid tumors, BMS-690514 at the maximum tolerated dose of 150 mg/day plus paclitaxel and carboplatin produced partial responses in 9 (30%) patients. Brivanib (BMS-582664) is a dual inhibitor of VEGFR-2 and FGFR-1 [52] that has shown evidence of activity against hepatocellular cancer in a phase 2 study (n=96) [53]. Dovitinib (TKI258), an inhibitor of FGFR, VEGFR, PDGFR, and other tyrosine kinases, has demonstrated clinical activity and acceptable toxicity in preliminary reports from a phase 1/2 study (n=181) in advanced NSCLC. A phase 1b study (n=26) [57] of motesanib demonstrated a good tolerability profile when combined with gemcitabine in the treatment of solid tumors. Vandetanib (ZD6474), a dual inhibitor of VEGFR and EGFR tyrosine kinases, has demonstrated efficacy in NSCLC and medullary thyroid cancer, while negative results have been observed in phase 2 studies in small cell lung cancer, metastatic breast cancer, and multiple myeloma [58]. The feasibility and tolerability of the dual VEGFR and PDGFR inhibitor telatinib (BAY 57-9352) has been demonstrated in a phase 2 study [59] in patients with advanced gastric and gastroesophageal cancers. A phase 1 study [60] in patients with advanced NSCLC (n=23) has demonstrated acceptable tolerability with regorafenib (BAY 73-4506), a multikinase inhibitor of all three VEGFRs, PDGFR, FGFR, c-kit, and several other receptors. Vatalanib (PTK787/ZK222584), an inhibitor of VEGFR-1, -2, and -3, has shown efficacy in stabilizing metastatic melanoma in a phase 2 study [61]. Studies of the above agents in a variety of cancer types are currently planned or ongoing (ClinicalTrials.gov).

Conclusions

Currently available multitargeted agents provide important clinical benefits for patients with VEGF-driven tumors, such as RCC. However, these agents are also associated with off-target toxicities that limit their effectiveness. The development of second-generation VEGFR TKIs with improved potency and selectivity has the potential to provide more effective and better tolerated treatment options, enabling rationally designed combination therapies. Available data from clinical studies suggest that second-generation TKIs are generally associated with lower off-target toxicities (Table 2). Ongoing and future studies will further evaluate the clinical effectiveness and tolerability of VEGFR TKIs in a variety of tumor types.

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Disclosure

Both authors are employees of AVEO Pharmaceuticals, Inc.

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