Abstract: The landscape of treatment for metastatic renal cell carcinoma (mRCC) continues to evolve. Although several new drugs have been approved for the treatment of this disease in recent years, mRCC remains incurable. Thus, the search continues for new effective therapies. One such novel compound is axitinib (Inlyta, Pfizer), a potent vascular endothelial growth factor receptor tyrosine kinase inhibitor. Following phase I testing in advanced solid tumors (where hypertension, stomatitis, and diarrhea were the dose-limiting toxicities), use of axitinib has been further developed through phase II testing in thyroid, breast, lung, and renal cancers. Recently, the phase III AXIS (Axitinib [AG 013736] as Second Line Therapy for Metastatic Renal Cell Cancer) trial demonstrated an improvement in progression-free survival for patients with mRCC who were treated with axitinib versus sorafenib (Nexavar, Bayer) as second-line therapy. This article describes the preclinical and clinical evolution of axitinib, with an emphasis on its development and role in mRCC.

Introduction

Approximately 60,920 new cases of kidney cancer were diagnosed in the United States in 2011, and there were 37,120 deaths attributable to the disease. About 30% of patients are diagnosed with metastatic disease at the time of presentation, and the prognosis for these patients remains poor. Treatment options used to be limited to cytokine-based therapy, with either interleukin-2 or interferon-a. However, there have been many new advances in the treatment of metastatic renal cell carcinoma (mRCC), with 7 new drugs approved in recent years on the basis of pivotal phase III trials. These agents generally fall into 2 broad mechanistic categories: vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs), and inhibitors of the mammalian target of rapamycin (mTOR). The most recently approved agent, axitinib (Inlyta, Pfizer), falls into the former category. Axitinib distinguishes itself from other approved VEGFR-TKIs for mRCC (ie, pazopanib [Votrient, GlaxoSmithKline], sorafenib [Nexavar, Bayer], and sunitinib [Sutent, Pfizer]) with a unique receptor-targeting profile. The
agent has gone through a complex evolution, with phase II and III evaluations across a multitude of malignancies. Herein, the preclinical and clinical development of axitinib is discussed, with a particular focus on its current application in mRCC.

**Preclinical and Phase I Data**

In cellular models with endogenous or induced expression of receptor tyrosine kinases (RTKs), axitinib appeared to have high affinity for VEGFR2 (IC\textsubscript{50}=0.2 nM) and VEGFR3 (IC\textsubscript{50}=0.1-0.3 nM).\textsuperscript{12} As noted in Table 1, this affinity appears to compare favorably to other approved agents, such as sunitinib (VEGFR2 IC\textsubscript{50}=10 nM), sorafenib (IC\textsubscript{50}=10 nM), and pazopanib (IC\textsubscript{50}=30 nM).\textsuperscript{13,14} The selectivity of axitinib also distinguishes it from other VEGFR-TKIs. For example, the affinity ratio of axitinib for platelet-derived growth factor receptor-\(\beta\) (PDGFR-\(\beta\)), KIT, and Flt-3 versus VEGFR2 (ie, [RTK IC\textsubscript{50}]/[VEGFR2 IC\textsubscript{50}]) was 8.0, 8.5, and 5,000.0, respectively, compared with 0.5, 0.8, and 2.00 for sunitinib (Figure 1).\textsuperscript{12} Higher and more selective affinity for VEGFR2 has significant implications for the role of axitinib in mRCC. Approximately 50% of patients with sporadic mRCC have somatic von Hippel Lindau (VHL) gene mutations, and an additional 10–20% of patients demonstrate VHL hypermethylation.\textsuperscript{15} Dysregulation of VHL leads to increased expression of hypoxia-inducible factor-\(\alpha\) (HIF-\(\alpha\)), which in turn causes increased transcription of VEGF.

Murine xenografts bearing human tumors (M24met [melanoma], HCT-116 [colorectal], and SN12C [RCC]) were used to assess the antitumor activity of axitinib.\textsuperscript{12} In each model, axitinib monotherapy led to a dose-dependent reduction in tumor growth. The extent of tumor inhibition appeared to correlate with a reduction in microvessel density (characterized via CD31 staining) and Ki-67. There was also apparent synergy between axitinib

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**Table 1. Structure, VEGFR2 IC\textsubscript{50}, and Description of Phase III Evaluation for VEGFR-TKIs Currently Approved for Use in Patients With mRCC**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Structure</th>
<th>VEGFR2 IC\textsubscript{50}</th>
<th>Phase III Evaluation in mRCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib</td>
<td><img src="image1" alt="Structure" /></td>
<td>0.1 nM</td>
<td>Compared to sorafenib in patients with 1 prior systemic therapy (either a cytokine, sunitinib, bevacizumab, or temsirolimus)</td>
</tr>
<tr>
<td>Pazopanib</td>
<td><img src="image2" alt="Structure" /></td>
<td>30 nM</td>
<td>Compared to placebo in patients with either treatment-naïve disease or cytokine-refractory disease</td>
</tr>
<tr>
<td>Sorafenib</td>
<td><img src="image3" alt="Structure" /></td>
<td>10 nM</td>
<td>Compared to placebo in patients who were primarily cytokine-refractory</td>
</tr>
<tr>
<td>Sunitinib</td>
<td><img src="image4" alt="Structure" /></td>
<td>10 nM</td>
<td>Compared to IFN-a in patients who were treatment naïve</td>
</tr>
</tbody>
</table>

IFN-a=interferon-a; mRCC=metastatic renal cell carcinoma; TKI=tyrosine kinase inhibitor; VEGFR=vascular endothelial growth factor receptor.

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and cytotoxic agents. In a separate series of experiments, axitinib was dosed with the following: 1. docetaxel in mice-bearing LLC tumors; 2. carboplatin in mice-bearing ovarian tumors; and 3. gemcitabine (Gemzar, Eli Lilly) in mice-bearing pancreatic tumors. In the majority of models, it appeared that combination axitinib and chemotherapy delayed tumor growth when compared with either treatment alone. These data provide preclinical support for the combinations of axitinib with chemotherapy.

Given the encouraging laboratory data, a phase I trial of axitinib was pursued in patients with advanced solid tumors. A total of 36 patients were enrolled. Patients received doses of axitinib ranging from 5–30 mg orally twice daily. Median age in the cohort was 57 years (range, 41–76 years), and the most common tumor types were breast (n=13; 36%), RCC (n=6; 17%), and thyroid (n=5; 14%). Pharmacokinetic data suggested that peak plasma concentrations of axitinib were reached within 2–6 hours of administration, and a terminal plasma half-life of 2–5 hours was noted. The primary dose-limiting toxicity (DLT) observed with axitinib monotherapy was hypertension. Other DLTs included increased liver function tests, seizures, apnea, stomatitis, pancreatitis, and thromboembolism. The dose of 20 mg orally twice daily was thought to exceed the maximum tolerated dose (MTD), and DLTs also occurred in the first 2 cohorts treated at a dose of 10 mg orally twice daily. Ultimately, the recommended phase II dose of the agent was 5 mg orally

Figure 1. Relative affinity of axitinib for platelet-derived growth factor receptor-b (PDGFR-b), Flt-3, and KIT, as compared to vascular endothelial growth factor receptor 2 (VEGFR2).
Phase II Data

Thyroid Cancer

Promising preclinical data led to the development of several phase II clinical trials. One phase II trial was designed to evaluate the objective response rate (ORR) to axitinib in advanced thyroid cancer patients. Eligibility for participation in the study included a diagnosis of thyroid cancer of any histologic subtype (papillary, follicular, anaplastic, or medullary) that was resistant to or not appropriate for iodine-131 treatment. Sixty patients were enrolled, with a starting dose of axitinib 5 mg twice daily, titrated upward for patients without hypertension or intolerability. The primary endpoint of the study was met, with an ORR of 30% (95% confidence interval [CI], 18.9–43.2). No association between ORR and histology was observed. Median progression-free survival (PFS) was 18.1 months (95% CI, 12.1–NR). The most common treatment-related adverse events (AEs) of grade 3 or higher were hypertension (12%), fatigue (5%), and proteinuria (5%).

Breast Cancer

Building on preclinical data suggesting potential synergy with cytotoxic agents, a randomized, placebo-controlled phase II study evaluating axitinib was conducted in patients with metastatic breast cancer (MBC). A total of 168 treatment-naive patients with MBC were assigned 2:1 to receive docetaxel at a dose of 80 mg/m² intravenously (IV) once every 3 weeks with either axitinib 5 mg orally twice daily or placebo. Over 70% of subjects had estrogen receptor positive disease, and more than half had received prior adjuvant therapy. Stomatitis, fatigue, diarrhea, and mucositis were the most common treatment-related AEs of grade 3 or higher, and were more frequently observed with combination therapy compared to docetaxel alone. The rate of febrile neutropenia was higher in patients receiving axitinib (15.3% vs 7.1%), although additional hematologic toxicities were similar between the 2 treatment arms. Dose reductions in docetaxel were required in 55.4% of patients receiving both drugs, but in only 17.9% of patients receiving docetaxel alone.

Although the ORR was almost doubled in the combination group versus placebo (41.1% vs 23.6%, respectively; \( P = .011 \)), no significant improvement was observed in time to progression (TTP), the primary endpoint of the study. However, in a predefined subset analysis, a greater difference in both median TTP (9.2 months vs 7.0 months; \( P = .04 \)) and ORR (46.8% vs 13.3%; one-sided \( P = .001 \)) was noted in patients who had received prior adjuvant chemotherapy, which favored the combination of docetaxel with axitinib. Although hypothesis-generating, these data warrant further prospective assessment.

Lung Cancer

Single-agent axitinib has been shown to induce tumor necrosis in an animal lung carcinoma model with dose-dependent inhibition. An open-label, phase II study in advanced NSCLC evaluated axitinib at 5 mg twice daily, with dose escalation to a maximum of 10 mg twice daily if no AEs were noted. Thirty-two patients were evaluated for a mean duration of 3.5 months. Dose reductions were required in almost half of all patients, although one-fourth were escalated to 6–8 mg twice daily. All patients discontinued therapy, either due to progression (72%), nonfatal AEs (22%), or death (2 patients). The investigator-assessed ORR was 9%, and 3 patients achieved a PR. At a median follow-up of approximately 20 months, the median overall survival (OS) was 14.8 months, and the median PFS was 4.9 months (95% CI, 3.6–7.0). In patients with no prior therapy for metastatic disease, PFS was 9.2 months (95% CI, 5.8–16.3).

RCC

Two phase II trials of axitinib in mRCC have suggested potent antitumor activity. The first trial enrolled 52 patients with cytokine-refractory mRCC, with axitinib administered at a starting dose of 5 mg orally twice daily. Fifty-one of the 52 patients had clear cell RCC. Exclusion criteria included prior anti-angiogenic therapy and pre-existing uncontrolled hypertension. In this study, the observed ORR was 44.2% (95% CI, 30.5–58.7), including 2 patients with complete responses. These data are akin to results from a phase II study that evaluated sunitinib in cytokine-refractory mRCC patients, where an ORR of 40% was observed. Median TTP was 15.7 months (range, 8.4–23.4), and median OS was 29.9 months (range, 20.3–NR). The most common treatment-related AEs of grade 3 or higher were hypertension, fatigue, and nausea. No myelosuppression of grade 3 or higher was observed during this study.

In a second single-arm phase II trial, Rini and associates assessed axitinib monotherapy in 62 patients with sorafenib-refractory mRCC. Once again, clear cell mRCC was more prevalent (n=59) than any other histologic subtype. It must also be noted that 16 patients (25.8%) had received only 1 prior therapy, whereas 46 patients (74.2%) had been exposed to at least 2 prior treatment arms.
therapies. The most common prior regimens included cytokine-based therapy (61.3%), sunitinib (22.6%), cytotoxic chemotherapy (19.4%), and other therapy regimens not specified (29%). The starting dose of axitinib was 5 mg orally twice daily, with up to 53.2% of patients titrating up to 10 mg orally twice daily. The ORR was 22.6% (95% CI, 12.9–35), with a median PFS and OS of 7.4 months (95% CI, 6.7–11) and 13.6 months (95% CI, 8.4–18.8), respectively. The toxicity profile was consistent with other phase II evaluations, with hypertension (16.1%), fatigue (16.1%), hand-foot syndrome (16.1%), and diarrhea (14.5%) representing the most common AEs of at least grade 3. These promising data led to the evaluation of axitinib in the phase III trial setting.

**Phase III Data**

**Pancreatic Cancer**

Based on encouraging phase II data showing a survival advantage with gemcitabine plus axitinib when compared with gemcitabine plus placebo, a randomized phase III study was undertaken to evaluate axitinib in combination with gemcitabine. The study included 632 patients with either metastatic pancreatic cancer or locally advanced disease not amenable to curative surgical resection. Patients received gemcitabine at a dose of 1,000 mg/m² IV on days 1, 8, and 15 of a 28-day treatment cycle, and were randomized to receive additional therapy with either axitinib 5 mg orally twice daily or placebo. The dose of axitinib was increased to 10 mg orally twice daily in the absence of toxicity. At a planned interim analysis, the study was closed for futility by an independent data monitoring committee. With a median follow-up of approximately 27 weeks in both study arms, the median OS was found to be no different in patients receiving gemcitabine with axitinib versus gemcitabine with placebo (8.5 months vs 8.3 months, respectively; \( P = .54 \)).

Toxicity was generally higher with combination therapy; nausea, diarrhea, anorexia, dysphonia, hypertension, and stomatitis occurred more frequently among patients in the combination therapy arm. No significant difference in quality of life (QOL) was observed between the 2 groups.

**RCC**

The phase III AXIS (Axitinib [AG 013736] as Second Line Therapy for Metastatic Renal Cell Cancer) trial was designed to evaluate axitinib in the second-line therapy setting. In AXIS, 723 patients with clear cell mRCC who had failed only 1 previous line of therapy with either sunitinib-, bevacizumab-, temsirolimus-, or cytokine-based therapy (54%, 8%, 3%, and 35%, respectively) were enrolled. The median age of the study population was 61 years (range, 20–82 years), and the majority of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. By Memorial Sloan-Kettering Cancer Center criteria, 28%, 37%, and 33% of patients were favorable-, intermediate-, and poor-risk, respectively. By the more recently established Heng criteria, a similar distribution was observed. Patients were randomized 1:1 to either sorafenib 400 mg twice daily or axitinib, with starting doses of 5 mg twice daily, increasing to 7 mg twice daily, and ultimately 10 mg twice daily, as tolerated. The primary measured endpoint was PFS, defined as the time from randomization to either disease progression or death.

Patients were evaluated closely, with tumor assessments performed at screening, 6 weeks, 12 weeks, and then every 8 weeks thereafter. Patient-reported QOL assessments using the Functional Assessment of Cancer Therapy Kidney Symptom Index (FSKI-15) and FSKI Disease-Related Symptoms (FSKI-15) were performed at screening, every 4 weeks while on therapy, at the end of study treatment, and 28 days after the last study dose.

Results demonstrated a PFS of 6.7 months for axitinib versus 4.7 months for sorafenib, by independent review committee assessment (hazard ratio [HR], 0.665; \( P < .0001 \)). These data (which satisfied the primary endpoint of the trial) led to the approval of axitinib by the US Food and Drug Administration (FDA) on February 27, 2012. PFS favored axitinib in both the prior cytokine (12.1 months vs 6.5 months; \( P < .0001 \)) and sunitinib (4.8 months vs 3.4 months; \( P = .0107 \)) therapy subgroups. Of note, the PFS associated with sorafenib in cytokine-refractory patients enrolled in the AXIS study compared somewhat favorably to the PFS associated with sorafenib in the phase III trial known as TARGET (Treatment Approaches in Renal Cancer Global Evaluation Trial; 5.5 months).

In AXIS, PFS was numerically higher with sorafenib in patients with prior bevacizumab therapy (4.2 months vs 4.7 months; \( P = .63 \)), but the limited number of patients in this subgroup (n=59) challenge any further interpretation of these results. Notably, ORR was higher with axitinib compared with sorafenib (19.4% vs 9.4%; \( P = .0001 \)).

Results from the AXIS trial demonstrate a relatively safe toxicity profile for axitinib. The most common treatment-related AEs of grade 3 or higher in both arms were fatigue (11% with axitinib vs 5% with sorafenib) and gastrointestinal symptoms, including diarrhea (11% with axitinib vs 7% with sorafenib). Grade 3 or higher AEs observed more frequently in the sorafenib arm included hand-foot syndrome (5% with axitinib vs 16% with sorafenib) and rash (<1% with axitinib vs 4% with sorafenib). The most common AEs noticed in the axitinib arm were hypertension (grade 3 or higher: 16% with axitinib vs 7% with sorafenib) and hypothyroidism (all grades: 19% with axitinib vs 8% with sorafenib). There were few laboratory abnormalities of significance observed in either treatment arm.
Dose interruptions for any reason were similar in the 2 arms (77% with axitinib vs 80% with sorafenib).\textsuperscript{9} However, more patients in the sorafenib arm interrupted their dose due to AEs (63%) versus those in the axitinib arm (54%). Over one-third of patients were able to tolerate a dose increase on axitinib. Although some patients did require dose reductions, they were more common with sorafenib (52%) than axitinib (30%). Median relative dose intensity remained above 90% in both arms. Treatment discontinuations due to investigator-assessed AEs were observed in 8.2% of patients with sorafenib versus 3.9% of patients with axitinib.

As noted earlier, QOL assessments were paired with other clinical assessments in AXIS.\textsuperscript{26} The 2 patient-reported QOL assessment tools, FKSI-15 and FKSI-DRS, focused on 15 specific areas related to kidney cancer symptoms, including hematuria, pain, fatigue, ability to work, and weight loss. Completion rates for QOL assessments during treatment were over 90% in both arms. No significant differences or QOL decreases were observed. This finding is in accordance with previous research in patients treated with axitinib using different QOL assessment tools.\textsuperscript{28} However, the AXIS composite time to deterioration (TTD) endpoint (combination of death/progression/worsening in FKSI-15 or FKSI-DRS scores and therefore decreased QOL) showed a 25% risk reduction for axitinib versus sorafenib ($P=.0001$ for both comparisons).

**Positioning Axitinib Among Available Therapies for mRCC**

Thus far, the clinical development plan for axitinib has culminated in its FDA approval for use in patients with advanced RCC after failure of 1 prior systemic therapy, leading some to hail it as a “reference standard in second-line treatment of advanced RCC.”\textsuperscript{27,29} However, axitinib is not the only agent available in the post-TKI setting. On March 30, 2009, the FDA approved everolimus (Afinitor, Novartis) for patients with advanced RCC after treatment with sunitinib or sorafenib. The approval was based on results of the phase III RECORD-1 (Renal Cell Cancer Treatment With Oral RAD001 Given Daily) study.\textsuperscript{7,30} A total of 410 patients with mRCC were randomized in a 2:1 fashion to either everolimus monotherapy or placebo. Importantly, patients had received either sunitinib and/or sorafenib, and over half of the patients had received prior cytokine therapy. Thus, RECORD-1 assessed a heavily refractory population. Overall, PFS associated with everolimus therapy was 4 months compared with 1.9 months with placebo (HR, 0.30; $P<.0001$). A more recent subgroup analysis of these data suggested that PFS in patients who had been exposed to only 1 VEGFR-TKI was 5.42 months (95% CI, 4.30–5.82).\textsuperscript{31} With the caveats of cross-trial comparisons in mind, these results do appear to compare favorably to the PFS of 4.8 months seen in patients treated with prior sunitinib in the AXIS trial (95% CI, 4.5–6.4). Furthermore, the toxicity of everolimus therapy appeared to be more modest; no AEs of grade 3 or higher occurred in excess of 5% of patients receiving everolimus therapy. Thus, in the absence of comparative trials that juxtapose axitinib and everolimus, it is challenging to select the optimal therapy in the TKI-refractory space. The completed (but not yet reported) phase III 404 trial, which compared temsirolimus (Torisel, Pfizer) and sorafenib in patients with mRCC who have received prior sunitinib, may shed some light on the choice between mTOR and VEGF inhibition as a secondary approach. However, the agents assessed in this study (temsirolimus and sorafenib) are less than ideal for this comparison, as neither has been validated as post-TKI therapy in phase III studies.

Ideally, biomarkers could assist in the selection of appropriate therapies for TKI-refractory disease. Aside from representing one of the most frequent AEs associated with axitinib, hypertension may be a clinical biomarker of axitinib efficacy. Using pooled data from the phase II evaluations of axitinib in cytokine- and sorafenib-refractory populations, Rixe and associates demonstrated a median OS of 18.5 months in patients who achieved a diastolic blood pressure (DBP) of at least 90 mmHg during axitinib therapy (59 patients), compared to 6 months in patients who did not meet this benchmark (50 patients; $P<.01$).\textsuperscript{32,33} These compelling data have sparked a randomized phase II study that is enrolling approximately 200 patients with treatment-naïve mRCC.\textsuperscript{34} After 4 weeks of therapy at a dose of 5 mg orally twice daily, 70 patients will be randomized 1:1 to either axitinib at 5 mg orally twice daily with an axitinib dose titration or axitinib at 5 mg orally twice daily with a placebo dose titration. Dose titration will be performed in patients who do not experience a DBP of at least 90 mmHg at the standard starting dose. The primary endpoint of the study is ORR between the 2 titration arms. Notably, the improved clinical outcome with axitinib therapy in the context of hypertension has been observed in a broad spectrum of tumor types. In a pooled analysis of 230 patients with NSCLC, melanoma, pancreatic cancer, and mRCC, the occurrence of a DBP of at least 90 mmHg was associated with an improvement in median OS (25.8 months vs 14.9 months) and median PFS (10.2 months vs 7.1 months).\textsuperscript{35}

A Japanese study implicates soluble VEGFR2 (sVEGFR2) as a potential biomarker of axitinib response. In a series of 64 patients treated with axitinib, patients who had a greater decline in sVEGFR2 had a prolonged PFS (12.9 months vs 9.2 months; $P=.01$) and a higher
ORR (64.5% vs 37.5%; \( P = .045 \)).36 These results support similar data from a phase I study that included 12 patients with advanced solid tumors who were treated with axitinib.37 Moieties along the VEGF signaling axis have been explored as potential biomarkers of response with other currently approved agents for mRCC. For instance, changes in VEGF, sVEGFR2, and sVEGFR3 appear to correlate with response to sunitinib therapy.38 At present, none of these markers have had sufficient prospective validation to allow for meaningful clinical use.

To accompany molecular and clinical biomarkers, novel imaging techniques might also serve to predict axitinib efficacy. In mice-bearing BT474 tumors, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) allowed for detection of subtle microvascular changes that were reflected on subsequent histologic examination.39,40 It is not yet certain whether DCE-MRI findings in patients will correlate with clinical outcome in the context of axitinib therapy. To date, correlative studies examining similar imaging approaches with other VEGFR-TKIs (eg, sunitinib) are encouraging.41

### Conclusions

The clinical path of axitinib has thus far spanned across several disease types. Although the phase III efforts to confirm efficacy in advanced pancreatic cancer were unsuccessful, phase III evaluation in mRCC did show clinical benefit (when compared with sorafenib) in patients who had received 1 prior line of therapy. Since the FDA approval of axitinib in mRCC, one of the principal struggles for practicing oncologists has been to decipher the most appropriate placement of this agent in an increasingly crowded therapeutic landscape. As noted previously, when attempting to interpret the data in the context of specific subsets of patients with mRCC (ie, VEGFR-TKI refractory disease), there is a certain degree of ambiguity. In the future, comparative trials may help to resolve this ambiguity to some extent (although no direct comparison of axitinib and everolimus is currently planned or ongoing). In the meantime, the investigative community must look toward other means of identifying optimal candidates for axitinib therapy; such strategies may include the use of the clinical, radiographic, or molecular biomarkers described herein.

At present, there are over 20 clinical trials incorporating axitinib that are currently recruiting patients. Some of the ongoing studies seek to expand the current indication of axitinib therapy (Table 2). For example, there is an ongoing phase III study comparing axitinib and sorafenib in treatment-naïve patients with mRCC. The primary endpoint of this study is PFS, and a total of 447 patients are anticipated to accrue by April 2014.42 Other studies are attempting to characterize the safety and efficacy of combinations of axitinib with other approved agents for mRCC (ie, everolimus and temsirolimus).43,44 Outside of mRCC, there are ongoing efforts to determine the activity of axitinib in malignancies like hepatocellular carcinoma, glioblastoma multiforme, prostate and carcinoid tumors, and others.45-47 It will undoubtedly be interesting to witness the further development of axitinib.

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References