# Multikinase Inhibitors and Renal Cell Cancer: How They Work and the Promise They Hold

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**In Brief**
Today antiangiogenic therapy is being used to treat patients with a variety of cancers. Renal cell carcinoma (RCC) is one cancer that is seeing some success with newer targeted therapies. Advances in understanding the disease process of RCC at the molecular level have led to the emergence of multikinase inhibitors (MKIs). A new and promising class of drugs, MKIs inhibit the cellular action of growth factors, significantly changing the prognosis and quality of life for patients with RCC.

The United States saw an estimated 38,890 new cases of kidney cancer (renal cell and renal pelvis) in 2006, with kidney cancer accounting for about 12,840 deaths.[1] About 90 percent of all kidney cancers are attributed to RCC, with approximately 80 percent being the sub-type clear-cell RCC.

The principle treatment for RCC is surgical resection; however, approximately 30 percent of patients with localized disease undergoing surgery with curative intent have disease relapse. An additional 30 percent of these patients are initially diagnosed with metastatic disease.[2] RCC is essentially refractory to chemotherapy (response rates range from 4 to 6 percent in the metastatic setting)[3], and radiotherapy use is largely limited to symptom palliation.

Until recently, the clinical management of RCC has been limited to cytokine immunotherapy (with agents such as interleukin-2, or IL-2), which historically has yielded limited patient benefit. Approximately 10 to 20 percent of patients respond to these agents, although toxicities can be severe and few patients have long-term benefit.[4-8] Thus, new treatment approaches are needed for patients with RCC.

## Deconstructing RCC

Ongoing research efforts are aimed at clarifying the genetic events in RCC that characterize tumorigenesis and advanced disease. The development of RCC likely involves abnormal cellular signals and communication between cancer cells and resident vascular endothelial cells, which results in aggressive and highly vascularized tumors.

Research has linked several hereditary syndromes to kidney cancer. In particular, study of von Hippel-Lindau Syndrome has led to clues about the molecular underpinnings of RCC. The von Hippel-Lindau gene (VHL) is a tumor suppressor gene that normally helps protect cells from becoming cancerous. A mutation in the VHL gene associated with von Hippel-Lindau Syndrome has been linked to RCC. However, researchers have found that even those RCC patients without the inherited familial syndrome may have mutations in the VHL gene. And, in fact, loss in function of the VHL gene occurs in about 60 percent of sporadic (non-hereditary) cases of clear-cell RCC.[9] On the molecular level, these VHL gene mutations initiate an irregular conversation between tumor cells and the surrounding tissue.

In some RCC cases where no VHL mutation can be found, an increase in the methylation status of the VHL promoter (the part of a gene that contains information to turn the gene on or off) can also eliminate expression of the VHL gene.[10] In both instances, the loss of normal VHL protein levels in tumor cells leads to inappropriate activation of genes, such as the hypoxia-inducible factors (HIFs), that support cell survival in low oxygen conditions. This activation, in turn, favors tumor growth.[11]

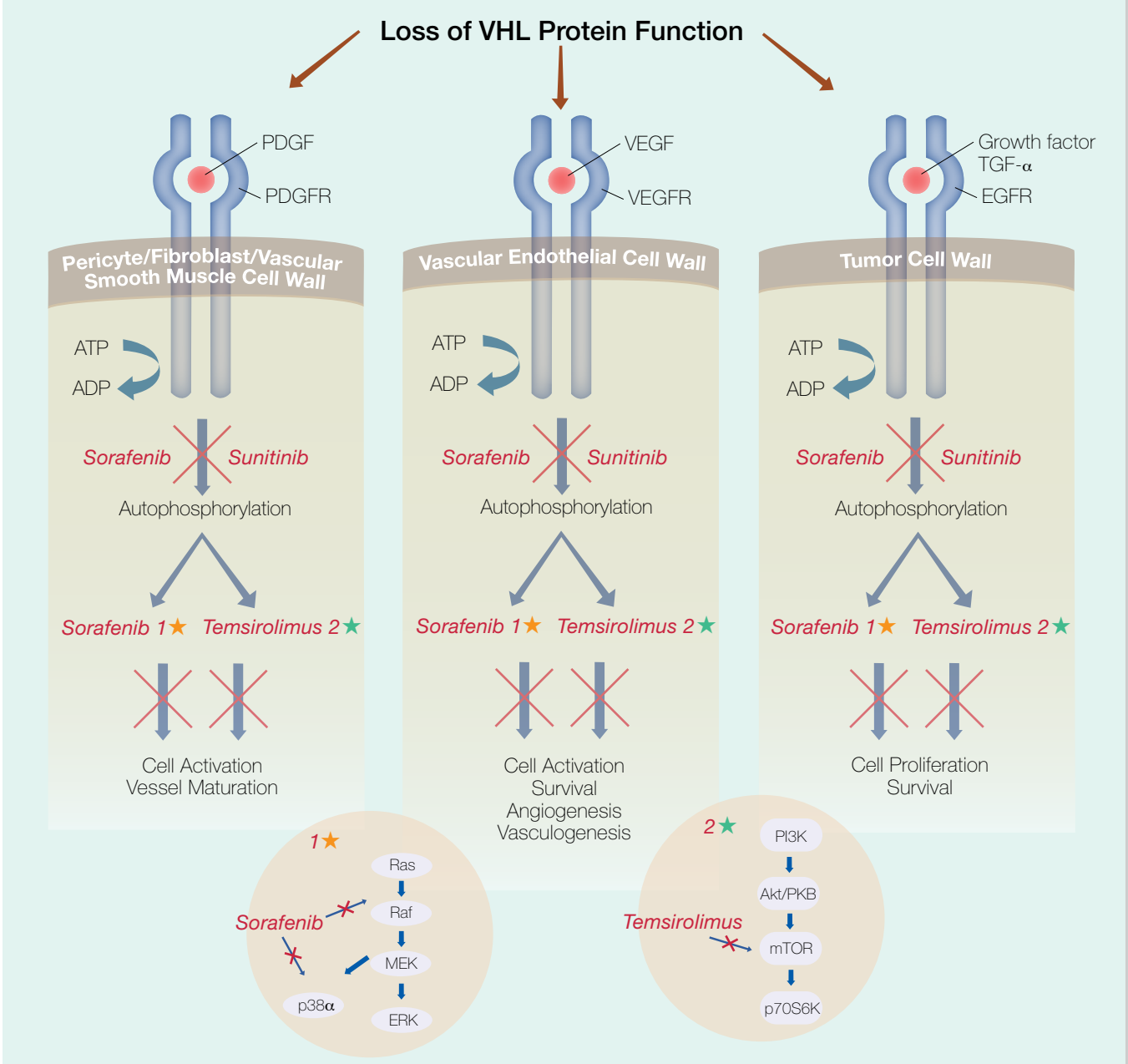
## Cellular Communication Gone Wrong

In normal cells living in an abundance of oxygen, VHL maintains low levels of HIF proteins by binding to them and targeting them for degradation.[12-13] In tumor cells without functional VHL, communication goes awry. HIF proteins build up in the tumor cells' nuclei. This massing of HIF proteins signals expression of pro-angiogenic growth factors, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), and the cell growth/survival factor, transforming growth factor-α (TGF-α).

In turn, tumor cells secrete increased levels of VEGF and PDGF into the microenvironment. These bind to their respective receptors (VEGFR and PDGFR) on the surface of resident endothelial cells and pericytes (connective tissue cells that wrap around a capillary). This binding event encourages angiogenesis. In other words, the intracellular signaling that takes place downstream of VEGFR and PDGFR activation ends in the increased expression of genes associated with angiogenesis and endothelial cell stabilization (see Figure 1). The transforming growth factor-α (TGF-α) binds to the epidermal growth factor receptor (EGFR) expressed on the same tumor cell and begins EGFR-mediated signaling that results in increased expression of proteins related to cell survival and proliferation.

The end effect, characteristic of the development of RCC, is an aberrant escalation in growth factor receptor signaling in tumor cells, endothelial cells, and pericytes. The outcome: increased angiogenesis and tumor cell survival and proliferation.

## Figure 1: Mechanisms of Action in Renal Cell Carcinoma




Schematic depicting the signaling events that characterize renal cell carcinoma. The pericyte/fibroblast/vascular smooth muscle cell wall, the vascular endothelial cell, and the tumor cell wall are simultaneously targeted by sorafenib, sunitinib, and temsirolimus. Sorafenib and sunitinib both exhibit binding specificity for tyrosine kinases, inhibiting the autophosphorylation of VEGFR (-1 and -2), PDGFR (α and β), FLT-3 and c-KIT. Further (1★) sorafenib can also inhibit the kinase activity of serine/threonine kinases that function at more distant positions in the cascade, such as c-Raf, BRaf, and p38MAPK. (2★) Temsirolimus is a specific inhibitor of the serine/threonine kinase mTOR, which is activated downstream of growth factor receptor signaling.

### MKIs at Work

Multikinase inhibitors are a new class of antiangiogenic therapeutics that inhibit the cellular action of growth factors, and recent trial data have demonstrated the efficacy of MKIs in the treatment of RCC. Based on these positive clinical trial results, two of these new oral drugs—sorafenib (Nexavar®) and sunitinib (Sutent®)—have gained regulatory approval for use in metastatic RCC. Temsirolimus, which has an FDA orphan drug designation, is another MKI that has demonstrated significant anti-tumor activity in "poor-risk" RCC patients with significantly improved patient survival compared to interferon-α (IFNα).

MKIs specifically inactivate the kinases (i.e., enzymes

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# Clinical Trials for MKIs in Renal Cell Carcinoma

Recent trial data demonstrates the efficacy of MKIs in the treatment of RCC.

## Sorafenib

In a Phase II trial, a total of 202 metastatic RCC patients were randomly assigned to receive 12 weeks of sorafenib treatment or placebo.[1] At 12 weeks, patients were assessed with imaging. Based on change in tumor volume, patients were categorized as responders, stable, or progressors. Patients in the stable group only (n=65) were then randomized either to continue on sorafenib or to receive a placebo. At follow-up 12 weeks later, 50 percent of sorafenib patients were progression-free compared with 18 percent of placebo patients.[1] Final results indicated that sorafenib-treated patients had four times longer progression-free survival than control patients (24 vs. 6 weeks).[1] In treated patients, 71 percent demonstrated a response or had stabilized disease.

TARGETs, a large, randomized Phase III trial, enrolled 903 patients with recurrent or metastatic, largely cytokine-refractory RCC.[2] In sorafenib-treated patients (n=451, 400 mg BID continuous dosing), the investigator-assessed objective response rate was 10 percent (43 of 451), 74 percent (333 of 451) of patients had stable disease, and only 12 percent (56 of 451) progressed.[3] The reported median progression-free survival was 24 weeks in sorafenib-treated patients compared with 12 weeks in the placebo group. Quality-of-life analysis showed no deterioration in the sorafenib group relative to placebo.[4] CT scans demonstrated some degree of tumor shrinkage in 74 percent of sorafenib-treated patients versus 20 percent of placebo patients.[5]

## Sunitinib

Analysis of two single-arm Phase II trials of sunitinib as second-line therapy in patients who had prior cytokine failure revealed substantial anti-tumor activity in this setting.[6,7] Patients (total=169) were treated with 50 mg daily oral sunitinib for 4 weeks with 2 weeks off, repeated in 6-week cycles. A combined objective response rate of approximately 40 percent and disease stabilization rate of 25 percent were reported, with an associated progression-free survival of 8.2 months.[6,7]

A randomized, Phase III trial that compared sunitinib to IFNα in the first-line setting demonstrated superiority for sunitinib in patients with advanced disease.[8] An objective response rate of 31 percent vs. 6 percent was observed for sunitinib versus IFNα-treated patients. An improvement in clinical outcome was also seen in terms of progression-free survival, with sunitinib-treated patients remaining free of progression for 6 months longer than those treated with IFNα (11 months vs. 5 months).[8]

## Temsirolimus

A randomized Phase II trial investigated the efficacy of temsirolimus over a range of doses administered on a weekly schedule (25 mg, 75 mg, or 250 mg) in refractory, advanced RCC.[9] An overall response ( ≥ 50 percent reduction in tumor measurements by World Health Organization criteria) rate of 7 percent (n=111) and minor response ( ≥ 25 percent but < 50 percent reduction in tumor measurements) rate of 26 percent were observed. The median survival was 15 months, and median time to progression was 5.8 months.

Interestingly, in a Phase III trial in which poor-risk metastatic RCC patients were randomized between three arms, IFNα (18 MU SC 3x/week), temsirolimus (25 mg IV/week), or temsirolimus (15 mg IV/week) plus IFNα (6 MU SC 3x/week), temsirolimus alone conferred an overall survival benefit compared with temsirolimus + IFNα and IFNα alone.[10] However, both the temsirolimus + IFNα group and the temsirolimus group performed similarly in terms of progression-free survival, suggesting that temsirolimus elongates the time to progression and overall survival, while IFNα may produce disease stabilization that does not translate to an overall survival benefit in this group of patients.

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that change other proteins through phosphorylation) that make up the signaling cascades downstream of growth-factor receptor and ligand binding, ultimately resulting in anti-tumor activity. MKIs bind to kinases so that the protein domain responsible for kinase activity (and message relaying) is inhibited. In brief, here is how the three MKIs work.

***Sorafenib*** is capable of inhibiting the two main classes of kinases in the protein–those that phosphorylate tyrosine kinases and serine/threonine kinases.[14] In the research setting, biochemical experiments have demonstrated that sorafenib inhibits the earliest signaling events requiring that receptor tyrosine kinases [VEGFR (-1 and -2), PDGFR (α and β), FLT-3, c-KIT, and RET] phosphorylate and activate themselves.[15] Further, sorafenib can silence the kinase activity of serine/threonine kinases that function at more distant positions in the cascade, such as c-Raf, BRaf, and p38MAPK. These actions suggest sorafenib as a potential inhibitor of tumorigenic signaling in both endothelial cells and tumor cells.

***Sunitinib*** exhibits binding specificity for tyrosine kinases only, inhibiting the autophosphorylation of VEGFR (-1 and -2), PDGFR (α and β), FLT-3, and c-KIT.

***Temsirolimus*** differs from both sorafenib and sunitinib in that it does not inhibit tyrosine kinases, but rather is a specific inhibitor of the serine/threonine kinase mTOR, which is activated downstream of growth factor receptor signaling. Upon treatment with temsirolimus, mTOR function is inhibited and protein synthesis slows considerably.[16] Subsequently, the cell cycle stops and proliferation is suppressed, thus curbing pathologic angiogenesis.[17,18]

## From Bench to Bedside

Development of new targeted therapies such as MKIs has raised issues in terms of criteria for measuring an agent's anti-tumor activity and resulting patient benefit. The RECIST (Response Evaluation Criteria in Solid Tumors) criteria measure tumor response using imaging, including X-ray, computed tomography (CT), and magnetic-resonance imaging (MRI). These criteria were developed by an international committee and have been in use since 2000. However, the RECIST criteria are unable to address the activity of MKIs and angiogenesis inhibitors. A growing trend is emerging toward using other methods to demonstrate an agent's anti-tumor activity and the resulting patient benefit.[19,20] Measures of drug efficacy have included evidence of response using tumor regression by CT scans and changes in biomarker levels that suggest physiologic drug activity.

Sunitinib's activity in inhibiting VEGFR-dependent signaling, for example, was used as an indicator of its anti-angiogenic and anti-tumor activity in a Phase II trial in the metastatic RCC setting (see page 24).[21]

Similarly, in the TARGETs (Treatment Approaches in Renal Cancer Global Evaluation Trial) trial, sorafenib-treated patients had a rise in plasma VEGF and a fall in circulating soluble VEGF receptor levels (see page 24).[22]

## A Look to the Future

Multi-kinase inhibitors have demonstrated efficacy in the treatment of RCC, and are actively being pursued as therapeutic options in other disease settings. Sorafenib, sunitinib, and temsirolimus theoretically function mainly through inhibiting VEGFR- and PDGFR-mediated signals that promote angiogenesis. Other mechanisms of action may be elucidated; however, their demonstrated ability to decrease tumor vascularization suggests that inhibition of angiogenesis plays a major role in their efficacy. Further studies with MKIs aim at defining combination regimens that may affect multiple tiers of signaling cascades simultaneously.

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