

# Novel Agents for the Treatment of Advanced Kidney Cancer

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## Abstract

Advanced kidney cancer accounts for over 12,000 deaths in the United States each year. Immunotherapy, typically interleukin-2 or interferon- $\alpha$ , have been the mainstay of treatment. Response rates are low for these immune-based treatments, and most patients with advanced kidney cancer succumb to their disease. There are several novel agents currently in clinical trials that show promise in this refractory disease. These compounds include antiangiogenic agents, raf kinase pathway inhibitors, and novel antimicrotubule agents. This review discusses some of the agents currently being explored for the treatment of advanced kidney cancer.

## Background

There are approximately 30,000 new cases of kidney cancer in the United States annually, resulting in almost 12,000 deaths.<sup>1</sup> Kidney cancer accounts for 3% of all adult tumors and usually occurs in patients 50–70 years old. There has been a 40% increase in kidney cancer over the last 25 years.<sup>2</sup> Kidney cancer is usually sporadic, although defined hereditary carcinoma syndromes exist.<sup>3–5</sup> Proposed risk factors for the development of kidney cancer include tobacco use, hemodialysis, and obesity, among others.<sup>6–8</sup>

There are 5 main histological types of kidney cancer. Clear cell carcinomas account for 85% and papillary carcinomas approximately 10%, with the remainder being chromophobe, collecting duct, and miscellaneous subtypes.<sup>9</sup> Sarcomatoid variants can occur with any subtype and are associated with a worse prognosis.<sup>10</sup> Well differentiated clear cell carcinomas typically have a more indolent course compared with poorly differentiated clear cell tumors.

Common presentations of kidney cancer include hematuria, abdominal mass, pain, weight loss, and anemia.<sup>11</sup> At initial diagnosis, approximately 30% of patients will have metastatic disease and another 25% of patients will have locally advanced disease. Sites of metastases include the lung, soft tissue, bone, liver, and central nervous system.<sup>12</sup>

Factors that are associated with a worse prognosis in advanced kidney cancer include poor performance status, elevated serum lactate dehydrogenase, anemia, hypercalcemia, and absence of prior nephrectomy.<sup>13,14</sup> The factors that are associated with a favorable response to therapy include prior nephrectomy, female gender, bone metastasis, and absence of liver metastasis.<sup>15</sup> For advanced kidney cancer, the 5-year survival rates range from 0% to 20%, and these rates have not changed significantly over the last 30 years.<sup>16,17</sup>

Immunotherapy has been the focus of treatment for advanced kidney cancer over the last 2 decades. The mechanism of immune modulation in kidney cancer is not clear. Interleukin-2 (IL-2) is a 15-kilodalton glycoprotein that is primarily produced by a CD4+ subset of mature T cells.<sup>18</sup> IL-2 functions by binding to the IL-2 receptor, promoting clonal T-cell expansion and cytotoxic activity of lymphocytes.<sup>19</sup> Response rates for IL-2 are usually reported in the 10–20% range, with few long-term survivors.<sup>20–23</sup> There are a variety of dose schedules and methods of administration of IL-2. A small subset of patients may benefit from high-dose

## Keywords

Erlotinib, revlimid, BMS-247550, bevacizumab, SU011248, BAY 43-9006

**Table 1.** Summary of Novel Agents Being Evaluated in Advanced Kidney Cancer<sup>3</sup>

Name	Mechanism of Action	Stage of Development	Comment	Reference
Erlotinib	EGFR Inhibitor	Phase II	Bevacizumab + Erlotinib 25% PR	47
Revlimid	Antiangiogenic	Phase II	Novel thalidomide analog	55
BMS-247550	Antimitotic	Phase II	10% PR in phase II trial	81
Bevacizumab	VEGF Inhibitor	Phase III	Prolonged TTP vs placebo	45
SU011248	VEGF, PDGF, Flt-3, and c-kit inhibitor	Phase III	33% PR in phase II trial	49
BAY 43-9006	Raf-kinase inhibitor	Phase III	38% PR phase I-I trials	72

EGFR=epidermal growth factor receptor; VEGF=vascular endothelial growth factor; PR=partial response; TTP=time to progression.

IL-2 at the expense of considerable toxicity.<sup>24</sup> This high-dose regimen is the only treatment for advanced kidney cancer approved by the US Food and Drug Administration.

Interferons are cytokine glycoproteins that have antiproliferative, immunomodulatory, and antiviral effects. The anticancer effects of interferon may arise from an antiangiogenic effect via inhibition of platelet-derived growth factor (PDGF), affecting the immune system, inhibition of protein synthesis, and altering gene regulation.<sup>25-27</sup> The response rates of patients treated with interferon alpha-2a range from 10% to 20%, with a small subset of patients achieving long-term survival.<sup>28-29</sup> Phase III trials have demonstrated that interferon therapy improves survival compared with progesterone therapy or vinblastine.<sup>30-32</sup> The combination of IL-2 with interferon in metastatic kidney cancer has not demonstrated a survival benefit over either single agent alone.<sup>33-36</sup>

Two phase III trials, European Organization for the Research and Treatment of Cancer (EORTC) 30947 and Southwest Oncology Group (SWOG) 8949, have demonstrated a survival benefit of nephrectomy followed by interferon versus interferon alone in patients with advanced kidney cancer.<sup>37,38</sup> Unfortunately, even with this aggressive approach most patients will eventually die from their disease.

There have been numerous small trials evaluating cytotoxic chemotherapy, with or without immunotherapy, in advanced kidney cancer. These agents include 5-fluorouracil, capecitabine, gemcitabine, and cisplatin, among others. Although response rates are generally reported in the 5–15% range, these studies have not demonstrated a survival benefit. The role of traditional cytotoxic chemotherapy in this advanced solid tumor is unclear.

Until recently, the mainstay of treatment for advanced kidney cancer was immunotherapy, with interferon or IL-2, with or without a cytoreductive nephrectomy. Although there are a few patients with long-term survival, the overall prognosis is poor. Novel targeting agents are now being tested in all phases

of clinical development for advanced kidney cancer. This article is a brief review of some of these agents that may lead to new treatment strategies for this highly refractory disease.

### Angiogenesis Inhibition

Over 30 years ago, Dr. Judah Folkman proposed that tumors lay dormant in situ for months to years, rarely growing beyond 2–3 mm in size until the development of neovascularization.<sup>39</sup> When a subgroup of tumor cells switches to an “angiogenic” phenotype there is a marked increase in tumor growth, cell invasion, and ultimately dissemination.<sup>40</sup> A variety of endogenous and exogenous factors have been identified that promote angiogenesis. These include platelet-derived growth factor (PDGF)- $\beta$ , transforming growth factor (TGF)- $\alpha$ , tumor necrosis factor (TNF), and vascular endothelial growth factor (VEGF).<sup>38,41</sup>

George and Kaelin<sup>42</sup> provided an excellent review of the von Hippel-Lindau (VHL) protein and its role in clear cell kidney cancer. The loss of the VHL tumor suppressor gene from either parent causes VHL disease. This disease causes a predisposition to form highly vascular tumors, namely hemangioblastomas and clear cell kidney cancer. When there is a mutation of the remaining normal VHL allele, the production of the VHL gene product, pVHL, is lost. The loss of both VHL alleles, one from each parent, is also commonly seen in sporadic clear cell kidney cancer.

In the presence of oxygen, pVHL binds to hypoxia-inducible factor (HIF)- $\alpha$ . This pVHL–HIF- $\alpha$  complex is then destroyed via a proteasome-mediated pathway. In a hypoxic setting, or in the absence of pVHL, HIF- $\alpha$  accumulates. HIF- $\alpha$  forms a heterodimer with HIF- $\beta$  and activates a large number of hypoxia-inducible genes. These hypoxia-inducible gene products include VEGF, PDGF- $\beta$ , TGF- $\alpha$ , and erythropoietin. The mechanism or mechanisms that promote clear cell kidney cancer in the presence of an overabundance of VEGF, PDGF- $\beta$ , TGF- $\alpha$ , and erythropoietin are unknown. The ability to target these gene products

by novel, molecularly targeted agents provides a rational anticancer strategy that is the basis for many of the new therapeutic drugs.

### Bevacizumab

Bevacizumab (Avastin, Genentech) is a humanized monoclonal antibody against VEGF. It was created from a murine antibody with 93% human and 7% murine amino acid sequence.<sup>43</sup> Gordon et al<sup>44</sup> reported a phase I trial of bevacizumab given on days 0, 28, 35, and 42 in patients with advanced cancer. There was no drug-related grade 3 or 4 toxicity, and bevacizumab was dose-escalated to 10 mg/kg. Grade I and II toxicities that were most likely related to the drug included asthenia, headache, and nausea.

Margolin and colleagues<sup>45</sup> reported a phase Ib trial of bevacizumab alone and in combination with doxorubicin, carboplatin plus paclitaxel, and fluorouracil plus leucovorin. There were no cumulative or late toxicities with any of the regimens.

A randomized phase II trial of bevacizumab in metastatic clear cell renal cancer has been published.<sup>46</sup> This trial was a double-blind, phase II trial that randomized patients to bevacizumab at doses of 3 mg/kg or 10 mg/kg given every 2 weeks versus placebo. The primary endpoints were time to progression and response rates. Patients with progressive disease on the placebo arm were allowed to cross-over to receive bevacizumab.

One hundred sixteen patients with advanced kidney cancer were randomized equally among all 3 arms. Grade 3 toxicity related to bevacizumab included epistaxis, hypertension, hematuria, and proteinuria. There were no grade 4 or 5 toxicities. There was a significant prolongation of the time to progression in the high-dose bevacizumab arm versus placebo (hazard ratio 2.55;  $P < 0.001$ ). The probability of being progression-free at 4 months for the high-dose, low-dose, and placebo arms were 64%, 39%, and 20%, respectively. There were no significant differences for survival between the 3 groups perhaps because the patients receiving placebo were allowed to cross-over to bevacizumab at the time of disease progression.

A large, randomized phase III trial from the Cancer and Leukemia Group B, Study 90206, has been initiated. This trial will randomize 700 patients with advanced kidney cancer to subcutaneous low-dose interferon- $\alpha$  versus low-dose interferon- $\alpha$  plus bevacizumab. The primary endpoint will be overall survival. This trial is open and currently enrolling patients.

### Gefitinib and Erlotinib

Epidermal growth factor receptor (EGFR) is overexpressed on the majority of kidney cancers. Gefitinib (Iressa, Astra-Zeneca) is an oral tyrosine kinase inhibitor of the EGFR. Two clinical trials using single-agent gefitinib have been reported. Drucker et al<sup>47</sup> presented their data on 18 patients with advanced kidney cancer given 500 mg of gefitinib daily. There were no tumor responses seen and the median time

to progression was 3.7 months. A second trial of gefitinib in advanced kidney cancer was presented at the 2003 annual meeting of the American Society of Clinical Oncology (ASCO).<sup>48</sup> In this trial, 21 patients were enrolled, and there were no complete or partial responses observed. The median progression-free survival was 2.7 months. These trials were disappointing in the lack of efficacy for a single-agent EGFR inhibitor in advanced renal cell cancer.

Erlotinib (Tarceva, Genentech) is another oral novel tyrosine kinase that inhibits the EGFR.<sup>49</sup> Hainsworth et al<sup>50</sup> presented the results of a phase II trial of bevacizumab given 10 mg/kg every 2 weeks plus erlotinib 150 mg given daily. Fifty-seven patients with metastatic kidney cancer were enrolled in the study. The combination was well tolerated and grade 3/4 toxicities included hypertension, diarrhea, rash, nausea and vomiting, and pruritus. There was a 25% partial response rate, 15% minor response rate, and stable disease in 47% of patients. The actuarial progression-free survival at 6 months was 71%. This combination of erlotinib plus bevacizumab demonstrates substantial clinical activity. Further confirmatory trials are ongoing.

### SU011248

SU011248 is an orally administered small molecule tyrosine kinase inhibitor of VEGF, PDGF, c-kit, and FLT3. This compound has good oral bioavailability with a prolonged half-life of approximately 40 hours and approximately 80 hours for its active metabolite, SU12662.<sup>51</sup> The dose-limiting toxicity for this phase I trial in advanced malignancies was fatigue/asthenia, and the recommended phase II dose was 50 mg daily for 4 weeks with a 2-week rest period.

Motzer and colleagues<sup>52</sup> reported at the 2004 ASCO meeting the results of a large phase II trial of SU011248 in advanced kidney cancer. This was a multi-institutional trial for patients with performance status 0–1 who had failed 1 prior cytokine-based therapy. The primary objective was overall response rate. Patients were eligible if they had normal cardiac, pancreatic, and adrenal function.

Sixty-three patients were enrolled. Clear cell histology was observed in 86% of patients, and 92% had a prior nephrectomy. The majority of patients (87%) had 2 or more metastatic sites of disease. Overall, SU011248 was well tolerated, and the toxicities were reversible by stopping the drug. The grade 3/4 toxicities observed included lymphopenia (32%), hyperlipasemia (21%), neutropenia (12%), anemia (8%), and fatigue (8%). There were no associated cases of pancreatitis with the hyperlipasemia. Two patients were taken off study for a decrease in left ventricular ejection fraction of >20%.

The median duration of therapy was 9 months (range <1 month to >16 months). At the time of the presentation at the 2004 ASCO meeting, 21 patients (33%) had a partial response (95% confidence interval [CI], 22–46%), 23 patients (37%) had stable disease greater than 3 months, and 19 patients (30%) had progressive disease. The median

time to progression was 8.3 months (95% CI, 6.6–10.8 months). The 33% overall response rate, and 8.3 months median time to progression, were the highest ever reported for second-line treatment of advanced kidney cancer. A large, international phase III trial is currently underway to compare SU011248 versus interferon- $\alpha$  in the first-line treatment of metastatic kidney cancer. The primary objective of this trial is overall survival.

### CC-5013

Thalidomide, in preclinical models, has been shown to inhibit angiogenesis.<sup>53</sup> There have been numerous clinical trials of thalidomide, alone and in combination with chemotherapy or immunotherapy, in advanced kidney cancer. The response rates of single-agent thalidomide in metastatic kidney cancer are low.<sup>54</sup> There is currently a large randomized phase III trial of interferon- $\alpha$  with or without thalidomide open and accruing patients. Results from this trial have not yet been reported.

CC-5013 (Revlimid, Celgene) is a novel oral thalidomide analogue. This “second-generation” thalidomide compound is thought to have both immune-modulatory and antiangiogenic activity. Preclinical testing, both in vitro and in vivo, has demonstrated that CC-5013 has more potent antiangiogenic properties than thalidomide.<sup>55,56</sup>

The toxicities reported for CC-5013 in the early phase I trials have been mild. These side effects have included nausea and vomiting, diarrhea, rashes, dizziness, peripheral neuropathy, fatigue, and bone marrow suppression.<sup>57</sup> The maximum tolerated dose of CC-5013 is 25 mg/day.<sup>58</sup> A pharmacokinetic trial of CC-5013, given daily between 5 mg/day and 50 mg/day, has been reported. The plasma half-life ranged between 2.8 hours and 6.1 hours, and no plasma accumulation was observed after repeated daily doses.<sup>59</sup> A phase II trial of CC-5013 in advanced kidney cancer is currently underway. Over 20 patients have been enrolled, and there have been no grade 3 or 4 toxicities. Data regarding the efficacy of CC-5013 in advanced kidney cancer have not yet been reported.<sup>60</sup>

### BAY 43-9006

BAY 43-9006 (sorafenib, Bayer) is a novel oral small-molecule tyrosine kinase inhibitor of the raf-1 protein kinase that is in early phases of human clinical development.<sup>61,62</sup> One of the key roles played by ras proteins is signal transduction from membrane-bound growth factor receptors to downstream molecules, such as the Raf/Mek/Erk cascade and rac and rho pathways.<sup>61,63</sup> Ultimately, downstream activation of the Raf/Mek/Erk kinase cascade leads to modulation of gene expression via phosphorylation of transcription factors important in cell transformation, cell growth and proliferation, all of which are vital to carcinogenesis. The *ras* family of oncogenes (constitutively activated and mutant) has been commonly identified in a variety of neoplastic conditions.<sup>64-67</sup> Thus, as a molecular target, *ras* and its downstream signaling molecules have attractive features

for therapeutic exploitation.<sup>68,69</sup> BAY 43-9006 also appears to prevent angiogenesis through blockade of the receptor tyrosine kinases VEGFR2 and PDGFR- $\beta$ .<sup>70</sup> Furthermore, inhibition of *c-raf* may promote cell death in endothelial cells downstream of VEGFR2 activation.<sup>71</sup>

To date more than 500 patients have been treated with BAY 43-9006 in early phase clinical trials.<sup>72-76</sup> Early pharmacokinetic observations have established good oral bioavailability (in a fasted state or with a moderate fat meal), linear pharmacokinetics with a prolonged plasma half-life ranging over 16–53 hours, multiple dose accumulation increases with increasing dose frequency, and there is no further increase in BAY 43-9006  $C_{max}$  or area under the curve (AUC) values beyond 7 days.

The safety and toxicity profile of BAY 43-9006 observed in early phase I studies are encouraging. In general, toxicities have been mild to moderate and included reversible cutaneous (rash and hand-foot syndrome) toxicity, diarrhea, and fatigue. Dose-limiting toxicities have included diarrhea, skin toxicity, fatigue, and hypertension in doses exceeding 600–800 mg twice daily on different dosing schedules. Preliminary analyses show no apparent relationship between plasma BAY 43-9006  $C_{max}$ /AUC values and rash. The drug is well tolerated at the recommended phase II dose of 400 mg twice a day continuously.

Ratain and colleagues<sup>77</sup> have presented data on a large phase II randomized discontinuation trial of BAY 43-9006 in advanced solid tumors. Over 400 patients with advanced cancer were enrolled in this trial. In this unusual trial design all patients were treated for a 12-week period with 400 mg of BAY 43-9006 given twice a day. After the initial 12 weeks, if patients had more than 25% tumor growth they were removed from the study. If there was a 25% reduction in the tumor size, the patients continued on the study in an open-label fashion until disease progression. The patients whose tumors stayed within 25% of their original size were randomly assigned to receive BAY 43-9006 or placebo.

In this large phase II trial, 65 of the patients enrolled had kidney cancer and were evaluable for response. Of these 65 kidney cancer patients, 25 (38%) had at least a partial response and 18 (28%) had stable disease. These encouraging results have led to a large industry-sponsored phase III trial of BAY 43-9006 versus best supportive care. All histologies of kidney cancer are eligible. This trial is currently open and accruing patients.

### BMS-247550

Epothilones are a new class of microtubule-binding agents. Preclinical evaluation of epothilones in taxane-resistant models has demonstrated activity. Epothilones have demonstrated the ability to induce microtubular bundling and lead to mitotic arrest.<sup>78,79</sup> Unlike paclitaxel, epothilones appear to have preclinical activity against cell lines overexpressing P-glycoprotein.<sup>80,81</sup>

BMS-247550 (Ixabepilone, Bristol-Myers Squibb) has been evaluated in 3 times daily, 5 times daily, weekly, and every-21-days schedules. Due to a hypersensitivity reaction, both oral histamine-1 and histamine-2 blockers are given prior to dosing. The toxicities observed have included fatigue, myalgias, neuropathy, and myelosuppression.<sup>82-84</sup> The neurosensory deficits have been described in a symmetric, “glove and stocking” distribution, and 2 patients (8.0%) had grade 3 neuropathy necessitating treatment cessation.<sup>82</sup> Pharmacokinetic analysis of BMS-247550 demonstrate that the AUC appears to be linear with dose, and the mean half-life is 36 hours.<sup>85</sup>

A phase II trial of BMS-247550 in advanced kidney cancer has been presented.<sup>86</sup> Patients received BMS-247550 at 6 mg/m<sup>2</sup>/day for 5 consecutive days every 3 weeks. Thirty-nine patients were enrolled, and 214 cycles were administered at time of presentation. Four patients (10%) had a partial response. Pharmacodynamic evaluation of VHL gene status and protein levels with clinical responses to BMS-247550 are ongoing. The ASCO 2004 presentation demonstrated that response to BMS-247550 correlated with well differentiated histology and tumors with abundant overexpression of VHL-regulated proteins.

## Conclusion

The mainstay for advanced kidney cancer has been either IL-2 or interferon- $\alpha$ . Response rates for both of these agents are low, and there are few long-term survivors. There are several novel agents, currently in clinical trials, which may ultimately prove to be of benefit in this highly refractory disease. This review mentions some of the compounds currently being studied in advanced kidney cancer.

An exciting aspect of these new agents is their varying mechanisms of action (Table 1). Bevacizumab, erlotinib, SU011248, CC-5013, BAY 43-9006, and BMS-247550 all appear, in preclinical testing, to inhibit tumorigenesis via different pathways. Clinical trials are now starting to combine these drugs, such as bevacizumab and erlotinib, to determine if they may have greater efficacy than any single agent alone.

As promising as these agents may be, there are many unanswered questions. Although immunotherapy, with interferon- $\alpha$  and IL-2, still has a place in this advanced solid tumor, the future role of these agents are unclear. Will these novel drugs prove to be superior to IL-2 and interferon- $\alpha$ ? Can the addition of immunotherapy improve the response rates of these new compounds? A randomized phase III trial of interferon- $\alpha$  plus bevacizumab versus bevacizumab alone is currently ongoing. The role of immunotherapy with these compounds needs to be further defined.

The role of cytoreductive nephrectomy has shown a modest benefit prior to interferon in advanced kidney cancer. Is there a role for removing the primary tumor when using these new compounds?

Are these drugs actually achieving what they are designed to do? For example, are intratumoral VEGF levels decreas-

ing in kidney cancer patients after treatment with bevacizumab? What is happening to the tumor tissue phosphorylation status of the VEGF, PDGF, and c-Kit receptors, as well as downstream markers, in patients receiving SU011248? Perhaps most importantly, how do we develop methods to predict who will benefit the most from these targeted therapies?

These agents can only be fully evaluated with the commitment of the urologists, medical oncologists, and—most importantly—the patients to enroll in clinical trials. Trials that incorporate biological studies, to determine how these agents work, should be of highest priority. Although expensive and time-consuming, these biological correlatives may ultimately help us answer how these novel agents actually affect the tumor. In this exciting time of molecular targeted therapies, all patients with advanced kidney cancer should be evaluated for clinical trials.

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