

Novel Therapeutics for Metastatic Renal Cell Carcinoma*

Thomas E. Hutson, DO, PharmD¹ and Robert A. Figlin, MD²

The treatment of metastatic renal cell carcinoma (RCC) has changed dramatically during the past few years. Sunitinib malate, sorafenib tosylate, bevacizumab with interferon α , temsirolimus, and everolimus have improved clinical outcomes in randomized phase 3 trials by inhibiting the vascular endothelial growth factor and related pathways. Combinations and sequences of these agents are being evaluated. Other novel agents are in clinical development, some of which target novel pathways not yet exploited as therapy for RCC. Recently reported and ongoing clinical trials will help further define the role of these agents as therapy for metastatic RCC. **Cancer 2009;115(10 suppl):2361-7. © 2009 American Cancer Society.**

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Renal cell carcinoma (RCC), a highly vascular disease, is known to be resistant to chemotherapy, with no single agent showing significant antitumor activity.^{1,2} In the United States, more than 50,000 new cases and 13,000 deaths were predicted to occur from RCC in 2008.^{3,4} An improved understanding of the biology of RCC has resulted in the development of novel agents that target important pathways involved in angiogenesis and tumor growth. In particular, the vascular endothelial growth factor (VEGF) pathway and the mammalian target of rapamycin (mTOR) signal transduction pathway have been used to date. Sunitinib malate,^{5,6} sorafenib tosylate,⁷ temsirolimus,⁸ bevacizumab with interferon,^{9,10} and everolimus¹¹ have demonstrated significant improvements in disease control, progression-free survival (PFS), and overall survival (OS) (sunitinib and temsirolimus), resulting in regulatory approval of 3 new therapies for metastatic RCC in as many years. A variety of other factors important in angiogenesis and tumor growth have been identified (including tie-2/angiopoietin, c-met, integrin, and Akt), and novel inhibitors of these factors are being evaluated in patients with advanced RCC (Tables 1 and 2). In addition, immune modulating agents and traditional cytotoxic chemotherapy continue to be developed. The utility of these new agents as therapy either alone or in combination with VEGF-directed therapy has yet to be defined. Herein, we review novel therapeutics under development for advanced RCC.

Corresponding author: Robert A. Figlin, MD, Division of Medical Oncology, City of Hope Comprehensive Cancer Center, 1500 East Duarte Road, Duarte, CA 91010; Fax: (626) 301-8233; rfiglin@coh.org

¹Genitourinary Oncology Program, Baylor Sammons Cancer Center, Dallas, Texas; ²Division of Medical Oncology and Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, California

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Table 1. VEGFR Tyrosine Kinase Inhibitors in Metastatic Renal Cell Carcinoma: Preclinical Differentiation

Agent	VEGFR-2, nM/L	PDGFR	EGFR	FGFR	Other
Sorafenib	IC ₅₀ : 90	✓			Raf, c-kit
Sunitinib	IC ₅₀ : 10	✓		✓	Ret, c-kit, FLT-3
Axitinib	IC ₅₀ : 0.25	✓			
Cediranib	IC ₅₀ : <1.0	✓		✓	
Pazopanib	IC ₅₀ : 30	✓		✓	c-kit
Vandetanib	IC ₅₀ : 40		✓		Ret, c-kit
Bay73	✓	✓			Ret, c-kit
ABT-869	IC ₅₀ : 20	✓			c-kit, FLT-3
AVI-951	IC ₅₀ : 0.16	✓			c-kit
XL880	✓				MET

VEGFR indicates vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; IC₅₀, inhibitory concentration at 50%.

Selected VEGF Receptor Tyrosine Kinase Inhibitors in Clinical Development

Axitinib

Axitinib (AG-013736) is an oral multitarget tyrosine kinase receptor inhibitor against VEGF receptor (VEGFR) 1, VEGFR-2, and platelet-derived growth factor receptor (PDGFR) β (Table 1). In a phase 2 trial in 52 patients with advanced cytokine-refractory RCC treated with 4-week cycles of axitinib at 5 mg twice daily, 24 (46%) achieved a partial response (PR).¹² The median PFS has not been reached after a 12- to 18-month follow-up. Grade 3 to 4 hypertension was the most important toxic effect observed in 15% of patients. No cases of neutropenia or thrombocytopenia above grade 1 were found. A phase 2 trial of axitinib in patients with sorafenib-refractory RCC was recently reported.¹³ A total of 62 patients were enrolled in this multi-institutional trial. All patients had previously received sorafenib, and 9 of 62 patients had also received sunitinib. Overall, 57% of patients experienced some degree of tumor regression, with a median PFS of >6.1 months. A PR was seen in 14% of patients, and 36% of patients had stable disease (SD). Treatment-related grade 3 to 4 adverse events included hypertension (16%), fatigue (14%), and hand foot syndrome (14%). A phase 3 trial has recently opened comparing axitinib to sorafenib as second-line therapy in metastatic RCC patients with progression after front-line therapy (sunitinib, bevacizumab with interferon, or temsirolimus).

Pazopanib

Pazopanib (GW786034) is an orally administered multitargeted inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- α , PDGFR- β , and c-kit (Table 1). A multinational phase 2 randomized discontinuation trial of pazopa-

nib in 225 patients with metastatic clear cell RCC has completed accrual, and the final results were recently presented.¹⁴ All patients received 800 mg/d of oral pazopanib for the first 12 weeks, at which point patients who had SD were randomized 1:1 to continue pazopanib or receive placebo. Sixty-seven percent of patients in this study were treatment naive, and in 33% 1 prior therapy had failed (23% cytokines, 8% bevacizumab, 2% both). In the first 60 patients enrolled in this study, PR was seen in 40% and SD in 42% at week 12 by independent review.¹⁵ Based on the significant level of "early" activity, the independent data safety monitoring committee recommended discontinuing the randomized portion of the trial, and all patients received pazopanib. On final analysis, the clinical benefit rate (complete response [CR], PR, and SD) was 79%, with 3 confirmed CRs and 33% of patients achieving a PR on independent review. The median duration of response was 68 weeks, and the PFS was 11.9 months. Most common adverse events included transaminase level elevation, diarrhea, fatigue, nausea, and fatigue. A randomized, placebo-controlled, multicenter, international phase 3 study evaluating pazopanib in patients with locally advanced and/or metastatic RCC who are untreated or in whom prior cytokine treatment had failed has also recently completed accrual, and the results are anxiously awaited. In addition, a phase 3 noninferiority trial comparing pazopanib to sunitinib as initial therapy for metastatic clear cell RCC is under way.

Selected c-Met Inhibitors in Clinical Development

XL880

XL880 is an orally administered c-met inhibitor that also targets the VEGFR. The c-met pathway may be

Table 2. Angiogenesis and Other Pathway Inhibitors in Clinical Development for Advanced Renal Cell Carcinoma

Inhibitor	Company	Type
VEGFR-TKIs		
Recentin (AZD2171)	AstraZeneca	Small molecule
Vandetanib	AstraZeneca	Small molecule
Pazopanib	GSK	Small molecule
Axitinib (AG-013736)	Pfizer	Small molecule
DAST (BAY 73-4506)	Bayer	Small molecule
Motesani (AMG706)	Amgen	Small molecule
Telatinib	Bayer	Small molecule
Brivanib	BMS	Small molecule
Angiocept (CT322)	BMS	Small molecule
ABT-869	Abbott	Small molecule
OSI-930	OSI	Small molecule
CEP-11981	Cephalon	Small molecule
CHIR-258	Chiron	Small molecule
XL880	GSK	Small molecule
XL820	Exelixis	Small molecule
XL647	Exelixis	Small molecule
Integrin inhibitors		
Volociximab (M200)	PDL/BIB	Monoclonal antibody
Vitaxin (MEDI-522)	MedImmune	Monoclonal antibody
CNT-095	Centocor	Monoclonal antibody
Cilengitide (EMD 121974)	Merck	Small molecule
E7820	Eisai	Small molecule
ATN-161	Attenuon	Peptide
Others		
CP-868,596 (PDGF)	Pfizer	Small molecule
AMG-386 (angiopoietin)	Amgen	Protein
VEGF targeting		
Bevacizumab (Avastin)	Genentech	Monoclonal antibody
Aflibercept (VEGF-TRAP)	Regeneron	Protein
PTC299	PTC Therapeutics	Small molecule
INGN 241	Introgen	Adenovirus
VEGFR targeting		
IMC-1121B	ImClone	Antibody
CDP791	UCB group	Antibody fragment
c-MET inhibitors		
AMG 102	Amgen	Monoclonal antibody
XL880	Exelixis	Small molecule
XL184	Exelixis	Small molecule
ARQ-197	ArQule	Small molecule
PF2341066	Pfizer	Small molecule
MP-470	SuperGen	Small molecule

VEGFR indicates vascular endothelial growth factor receptor; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

altered in sporadic papillary RCC and in the hereditary papillary RCC syndrome. *MET* activation drives tumor cell division and survival. XL880 is able to inhibit the mutated activated *MET* receptor and therefore has potential application as therapy for *MET*-driven tumors,

including papillary type II RCC. Based on the responses observed in the phase 1 studies^{16,17} and the predicted activity of XL880 in papillary kidney cancer, a study of XL880-201 was initiated to test XL880 in patients with papillary kidney cancer.¹⁸ XL880 was dosed at 240 mg orally daily 5 days on and 9 days off. This study is expected to accrue 34 patients, including 17 with *MET*-activating mutation and 17 without *MET*-activating mutation. The protocol was amended to allow patients with tumor-only *MET*-activating mutation (sporadic) to be enrolled in the *MET*-activated cohort. In addition, those patients with activated *MET* mutations may have received prior therapies, including anti-VEGF-directed therapy. Results have been reported for the first 3 patients with postbaseline tumor measurements and include 1 patient with a PR and 2 patients with SD >3 months. Enrollment in this study continues.

Selected Akt Inhibitors in Clinical Development

Perifosine

Although its precise mechanism of action is not completely clear, recent data suggest that perifosine inhibits activation of Akt by interfering with the interaction between its Pleckstrin homology domain and phosphatidylinositol (3,4,5)-trisphosphate, thereby precluding its translocation to the plasma membrane and activation by *PDK1*. The phosphoinositide 3-kinase (PI3K)/Akt signaling pathway regulates numerous anabolic processes essential for cell cycle progression and survival. This pathway has been shown to be frequently activated in RCC, and inhibitors of PI3K signaling have shown significant anti-tumor activity in both in vitro and in vivo RCC tumor models. In a recent randomized phase 2 trial comparing different perifosine dosing schedules (daily vs weekly administration) in patients with a variety of solid tumors, perifosine was found to be active in patients with RCC.¹⁹ Of the 212 patients enrolled in the first year of the study, 13 had RCC, and 7 of these were evaluable for response. Three (43%) had documented PRs, and an additional 2 (29%) had long-term disease stabilization. The most commonly observed toxic effects were nausea, vomiting, diarrhea, and fatigue. Based on this promising clinical activity, a phase 2 trial of perifosine in patients with advanced RCC in whom sorafenib or sunitinib treatment

had failed has opened to accrual. All patients will be treated with perifosine administered as a once daily oral dose of 100 mg. The primary endpoint of the trial is PFS, and objective response rate will also be reported.

Angiopoietin/Tie-2 Inhibitors in Clinical Development

AMG 386

AMG 386 is a fusion protein containing a synthetic peptide exhibiting high affinity for angiopoietins fused to the constant region of human immunoglobulin (Ig) G1. In vitro and in vivo studies demonstrate potent binding of AMG 386 to Ang 2 (2 pM) and moderate binding to Ang 1 (1 nM), thereby inhibiting the interaction with Tie-2. Ang2 is up-regulated at sites of angiogenesis and can act in a paracrine fashion on endothelium, inducing neovascularization.^{20,21} Although the exact mechanism of over-expression is unknown, Ang2 messenger RNA is up-regulated in clear cell RCC compared with normal renal epithelium and may be related to hypoxia-inducible factor 1.²² In a phase 1 trial of AMG 386 in combination with bevacizumab, AMG 706, or sorafenib, serious adverse events occurred in 11 patients, including fatal hemorrhage in 2 patients (with bevacizumab), grade 4 intestinal perforation (with AMG 706), hemorrhagic bullae in 1 patient (with AMG 706), and fever in 1 patient (with AMG 706).²³ Other nonserious adverse events included fatigue, hyperglycemia, diarrhea, hypoalbuminemia, hypocalcemia, and lymphopenia. Preliminary efficacy results from these studies show both PR and SD in patients with a variety of solid tumors, including RCC.²⁴ To further evaluate AMG 386 in combination with VEGF-directed therapy, a placebo-controlled, randomized, phase 2 study of AMG 386 administered at a dose of either 3 mg/kg or 10 mg/kg intravenously weekly combined with sorafenib 400 mg orally twice daily in patients with clear cell RCC has open to enrollment. The primary endpoint of the study is PFS.

Monoclonal Antibodies

VEGF-Trap

VEGF-Trap (AVE0005) is a potent angiogenesis inhibitor comprising portions of human VEGFR1 (Flt-1) and VEGFR2 (KDR) extracellular domains fused to the Fc portion of human IgG. VEGF-Trap potently binds VEGF-A and neutralizes all VEGF-A isoforms plus pla-

cental growth factor. It has been administered both intravenously and subcutaneously in phase 1 trials, and early evidence of activity in RCC was observed.²⁵ The Eastern Cooperative Oncology Group is planning a randomized phase 2 trial to evaluate 2 doses of VEGF-Trap for metastatic or unresectable RCC previously treated with a receptor tyrosine kinase inhibitor.

Immunostimulatory Agents

CTLA-4

CTLA-4 is an inhibitory molecule that blocks binding of B7 to CTLA-4, thereby preventing costimulation and down-regulating T-cell activation. By preventing the action of CTLA-4, an anti-CTLA-4 antibody can augment and prolong T-cell immune responses. In a phase 2 study in patients with advanced RCC, 41 patients received MDX-010, a human IgG1 antibody to CTLA-4, every 3 weeks.²⁶ In the first cohort (N = 21), patients received 3 mg/kg intravenous once followed by 1 mg/kg intravenous every 3 weeks, and in the second cohort (N = 20), patients received 3 mg/kg intravenous infusion every 3 weeks until unacceptable toxic effects or progression. Adverse events were primarily autoimmune, with 3 patients in the first cohort and 9 patients in the second cohort experiencing significant autoimmune toxic effects. This included enteritis (n = 9), hypophysitis (n = 2), and meningitis (n = 1). One patient in cohort A had an objective response (relative risk, 5%), whereas 5 of 20 patients in cohort B responded (relative risk, 20%). All responses were partial, and durations are 18, 8, 8 or more, 8 or more, 6 or more, and 4 or more months. Three of the 6 responding patients had previously received interleukin-2 (IL-2), although the impact of this factor is still under analysis. All 6 responding patients were among the 12 patients showing autoimmune manifestations, with no responses in the other 29 patients ($P = .0002$).

Trovax

RCC appears to have high levels of the oncofetal antigen 5T4 (>90%), which suggests that these patients could benefit from a 5T4-targeted product such as TroVax (Oxford BioMedica, Oxford, UK). TroVax consists of an attenuated poxvirus that delivers 5T4 gene and elicits an immune response against 5T4.²⁷ Two phase 2 trials of TroVax combined with interferon or IL-2 were recently

reported.^{28,29} In the first trial, TroVax plus interferon α was administered to 11 patients with metastatic RCC.²⁸ 5T4-specific cellular and humoral responses were monitored and clinical responses assessed by measuring changes in tumor burden by computed tomography (Response Evaluation Criteria in Solid Tumors [RECIST] criteria). Subcutaneous interferon (9MU) was administered 3 times a week. All patients treated were receiving first-line systemic therapy, with 10 having clear cell and 1 papillary histology. Administration of TroVax alongside interferon α was safe and well tolerated, with no serious adverse events attributed to TroVax. All 11 patients mounted 5T4-specific antibody responses, and 4 (36.4%) mounted cellular responses. No objective tumor responses were seen, but the overall time to progression was longer than expected for interferon alone, ranging from 9 to 42 or more weeks (median time to progression, 41 weeks). In the second trial, 25 patients with metastatic papillary or clear cell RCC were treated with IL-2 administered in 8-week cycles as a subcutaneous injection at a dose of 250,000 U/kg in Week 1 (Days 1-5) and 125,000 U/kg in Weeks 2 to 6 (Days 1-5) followed by 2 weeks off for up to 48 weeks, combined with TroVax administered by intramuscular injection every 3 to 4 weeks for the first 4 injections and every 8 to 12 weeks thereafter.²⁹ 5T4-specific cellular and humoral responses were monitored and clinical responses assessed according to RECIST criteria. TroVax was well tolerated, with no serious adverse events attributed to vaccination. Of 25 intent-to-treat patients, 21 mounted 5T4-specific antibody responses. Three patients showed a CR (2 for 24 or more months and 1 for 12 or more months), 6 patients had disease stabilization (6 to 21 or more months), and the remainder had progressive disease. Median PFS and OS were 3.4 or more months (1.5 to 24.8 or more months) and 12.9 or more months (1.9 to 24.8 or more months), respectively. A statistically significant correlation was detected between the magnitude of 5T4-specific antibody responses and PFS and OS (both $P < .05$). A phase 3 trial evaluating the combination of TroVax with interferon, IL-2, sunitinib, or sorafenib as front-line systemic therapy for patients with metastatic clear cell RCC is ongoing.

Conclusion

Significant and long-awaited advances in the treatment of advanced RCC have occurred during the past few years.

Sunitinib malate, sorafenib tosylate, temsirolimus, bevacizumab with interferon, and everolimus have demonstrated significant improvements in clinical benefit with manageable side effects. A variety of other novel targeting agents are currently under development for the treatment of metastatic RCC, including mTOR inhibitors, VEGF ligand inhibitors, and tyrosine kinase inhibitors. Further elucidation of the complex signaling pathways believed to be crucial in the pathogenesis of RCC will enable both discovery of new agents and the unprecedented opportunity to clinically and biologically define the effects of these agents in individual patients. The novel agents described in this review may provide a meaningful benefit to patients, with the hope of either greater antitumor efficacy or improved tolerability over currently available treatment options.

The dilemmas that clinical scientists face when evaluating new agents in RCC are what findings constitute sufficient proof of concept to warrant further evaluation alone or in combination, and what population of patients offers the greatest chance to identify active agents that warrant further evaluation. Potential strategies for future studies that might be productive include the following:

1. Develop agents that demonstrate the possibility of complete remissions.
2. Develop agents that either alone or when combined offer the patient unmaintained remissions.
3. Revisiting the role of immune-based therapies when combined with targeted agents may open up the possibility of integrated immune/targeted therapy.
4. Second- and third-generation targeted agents similar in their mechanism of action to commercially available agents must quantitatively add to our prior success. We cannot move the field through incrementalism.
5. Novel agents and novel targets should be tested in the highest-quality patient to ensure a fair assessment of proof of concept. These agents should not be restricted to the population of patients that has failed all commercially available agents.

Kidney cancer research is at a unique time in its evolution. Strategies need to continue to address the unmet medical needs, which will require innovative approaches, novel targets and their inhibitors, therapy directed at individual's own biology, and the development of markers to have a early readout for the approach, the drug, or the patient.

OPEN DISCUSSION

The questions and discussion below follow from the oral presentation given at the Third Cambridge Conference on Innovations and Challenges in Renal Cancer and do not correspond directly to the written article, which is a more general review.

Discussion After Dr. Robert A. Figlin's Presentation.

Michael Atkins: Does anyone feel that blocking VEGFR1 is also critically important and that focusing on just VEGFR2 may potentially be a problem?

Brian Rini: The potent and selective inhibition of the VEGF receptor family makes a difference, at least from what I have seen clinically. Can you be even more potent and even more selective? I do not think so.

Jeffrey Sosman: The key is understanding the mechanism of resistance that develops with treatment, because that is what we are going to have to target.

Dr. Figlin: Is it the endothelial cell that is developing a resistance, or is it just the feedback loops that go back to the tumor?

William Kaelin: The current dogma, right or wrong, is that the tumor cell is changing as well as the host, but that the endothelial cells are genetically stable and are not the source of the resistance.

Dr. Atkins: If you can maximally or optimally block the VEGF pathway with axitinib and it has fewer off-target effects, why would you try to put 2 drugs together? We may not be able to do any better than this.

Dr. Sosman: You still have resistance in that pathway.

Dr. Figlin: How do we test new drugs? In a proof of concept pre-sunitinib window-of-opportunity trial? How do we power that trial? Or in a post-upfront VEGF receptor-treated population? Are we sure that the signal we get will be valid and valuable?

Dr. Rini: There is room to test new agents as initial therapy if there is a biochemical rationale that they work in that setting.

Dr. Kaelin: If the future is combinations, maybe what we want is the cleanest, most potent VEGF inhibitor on which to build.

Dr. Figlin: We are going to start to take the best of what we have and place it in the upfront setting. We are going to design high-quality combination trials that answer questions about combinations versus single agents. For example, are we past the cytotoxic chemotherapy era

of combination therapy, and do we have to think about a new paradigm? We have to define whether that new paradigm is combination targeted therapy or sequential targeted therapy, and not be bound by that history, because that history may not be right. We also have to consider the low tolerance for toxicity in the community.

Dr. Atkins: There is a role for examining different treatment schedules. One of the nice things about imaging models is that they can help sort out whether or not an alteration in the schedule can delay the development of resistance more readily than a physical exam or CT-based tumor measurements.

Dr. Figlin: One of the other opportunities is to ask whether imaging can tell us what is happening at year 1 after stopping therapy.

Dr. Rini: As we get more effective agents, issues of whether we can take breaks safely and when to restart therapy will be important. Today, if what we are doing is working, I am hesitant to stop.

Dr. Atkins: That is a different question than trying to determine what is the optimal schedule to start treatment with. It is possible that an intermittent schedule might delay the time to angiogenic escape, a feature of acquired resistance by maintaining the tumor's dependence on the VEGF pathway for angiogenesis.

Dr. Rini: So, when do we start these drugs? If we can delay 6 months upfront, in essence we have added 6 months of disease control onto their total tumor burden control without toxicity.

Conflict of Interest Disclosures

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