

Molecularly Targeted Agents for Renal Cell Carcinoma: The Next Generation

C. Lance Cowey, MD, and Thomas E. Hutson, DO, PharmD, FACP

Dr. Cowey is an Attending Physician in the Genitourinary Oncology and Melanoma Program and Dr. Hutson is Director of Genitourinary Oncology for Texas Oncology, PA at the Baylor University Medical Center, Sammons Cancer Center in Dallas, Texas, and Co-Chair of GU research for US Oncology, The Woodlands, Texas.

Abstract: With the approval of several molecularly targeted agents over the past few years, the landscape of renal cell carcinoma (RCC) management has drastically changed. Response rates and survival have improved with these new agents compared to the previous standard of cytokine-based therapy. Many new agents are in various stages of development, and how these novel therapies will be incorporated into the paradigm of RCC treatment is yet to be determined. The development of optimal sequencing and combinations of these drugs is important to improving patient outcomes and overcoming resistance mechanisms.

Address correspondence to:

C. Lance Cowey, MD

3535 Worth Street

Dallas, TX 75246

E-mail: lance.cowey@usoncology.com

Phone: 214-370-1800

Fax: 214-370-1987

Introduction

In the last 5 years, no other cancer has undergone a more dramatic change in its management as has renal cell carcinoma (RCC). Previously, RCC had been a disease with dismal outcomes due to a limited number of effective treatment options. The standard of care for RCC previously consisted of the use of cytokines, which held benefit for only a small minority of patients.¹ Additionally, it has been widely demonstrated that RCC is resistant to conventional cytotoxic chemotherapy commonly used for other cancers.^{1,2} However, since 2006, 6 novel molecularly targeted agents have been approved by the US Food and Drug Administration (FDA) for the treatment of RCC.

The development of these new therapies occurred following more than a decade of advancement in the understanding of the molecular biology of RCC. Most crucial to the development of these novel therapeutics was the pivotal discovery of the tumor suppressor von Hippel Lindau protein (pVHL) and its relationship to the hypoxia inducible factors (HIF) 1 and 2. Through loss of pVHL, the transcription factors HIF 1 and 2 are allowed to accumulate and transcriptionally activate a variety of genes including vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF; Figure 1).³ VEGF and PDGF are critical mediators of tumor angiogenesis in RCC and other tumors. The mammalian target of rapamycin (mTOR) complex represents another important therapeutic target in RCC and functions, in part, to promote HIF synthesis during cellular stress.

Keywords

Renal cell carcinoma, targeted agents, VEGF inhibitors, mTOR inhibitors, pazopanib, axitinib, bevacizumab

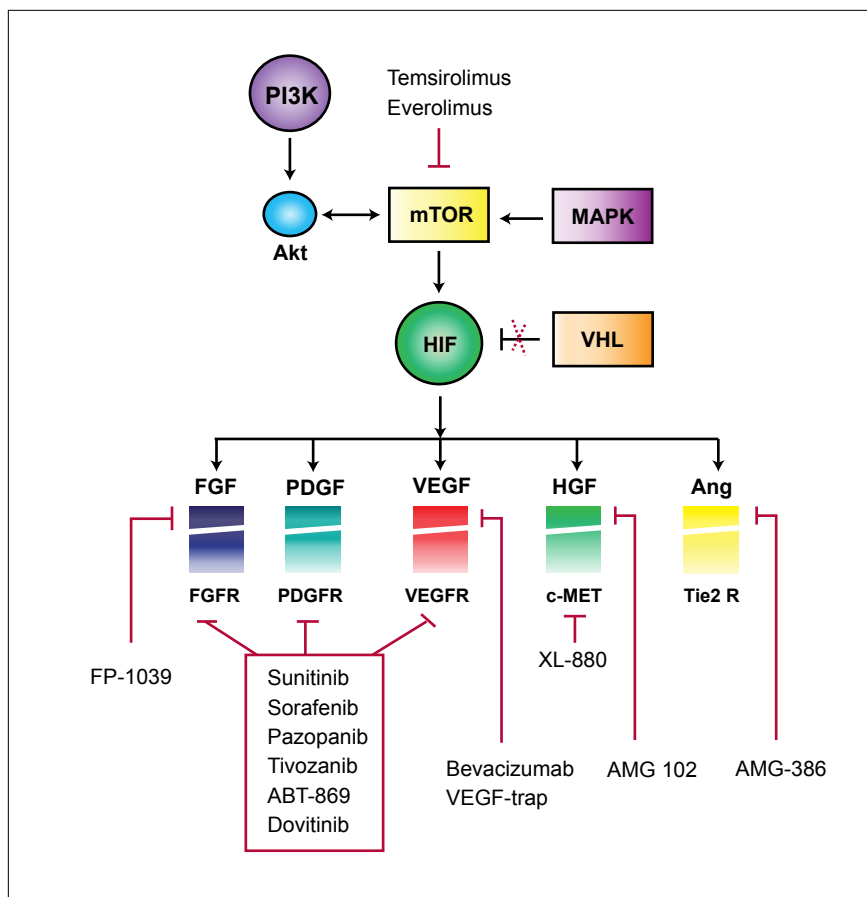


Figure 1. Molecular signaling pathways critical to renal cell carcinoma pathogenesis and select therapeutic inhibitors.

Ang=angiotensin; c-MET= mesenchymal-epithelial transition factor; FGF=fibroblastic growth factor; FGFR=FGF receptor; HGF=hepatocyte growth factor; HIF=hypoxia-inducible factors; MAPK=mitogen-activated protein kinase; mTOR=mammalian target of rapamycin; PDGF=platelet-derived growth factor; PDGFR=PDGF receptor; PI3K=phosphoinositide 3-kinases; VEGF=vascular endothelial growth factor; VEGFR=VEGF receptor; VHL=Von Hippel-Lindau.

The currently approved targeted agents for RCC can be divided into 2 main classes: those affecting the VEGF angiogenesis pathway and those affecting mTOR (specifically, mTORC1).⁴ Although the influx of novel therapies for RCC has been impressive, further agents continue to be developed, and how these agents will be incorporated with the existing ones will be a challenge for clinical researchers for years to come. This review provides a brief outline of the data supporting the currently approved drugs, as well as an overview of select “second-generation” targeted agents that are furthest in development and are poised to further broaden the therapeutic options for RCC (Table 1).

Current Generation of Targeted Agents for the Treatment of RCC

Sorafenib

Sorafenib (Nexavar, Bayer Healthcare) was the first non-cytokine drug to obtain FDA approval for the treatment of RCC. Sorafenib targets multiple kinases including VEGFR 1–3, PDGFR- α , - β , RAF, FLT-3, and c-kit. In a phase III, randomized, placebo-controlled trial of 903 patients with good or intermediate-risk metastatic

clear cell RCC who had progressed on cytokine therapy, sorafenib had a superior progression-free survival (PFS) of 5.5 months compared to 2.8 months for placebo ($P<.01$).⁵ Toxicities included diarrhea, rash, fatigue, and hand-foot syndrome. A recently published phase II study comparing sorafenib to interferon in untreated metastatic RCC patients showed similar PFS between the 2 agents (5.7 vs 5.6 months, respectively); however, improved responses and quality of life were seen in the sorafenib-treated group.⁶ Based upon the current level of evidence, sorafenib is generally employed in the second-line or subsequent line of therapy.

Sunitinib

Sunitinib (Sutent, Pfizer), a multitargeted, tyrosine kinase inhibitor that targets VEGFR1–3, PDGFR- α , - β , FLT-3, and c-kit, was FDA approved within weeks of sorafenib. Sunitinib has been tested in a large, phase III, randomized trial in the first-line metastatic clear cell RCC setting compared to the previous standard cytokine therapy, interferon.⁷ Sunitinib was found to have a significantly greater PFS compared to interferon (11 vs 5 months, respectively; $P<.001$). The overall response rate (ORR) was also significantly higher, with

Table 1. Targeted Agents With Phase II or Greater Level of Evidence

Drug	Inhibits	Level of Evidence	Trial Design	Activity
VEGF inhibitor				
Sunitinib*	VEGFR1–3, PDGFR- α , - β , FLT-3, and c-kit	Phase III	First-line	ORR, 31%; PFS, 11 months
Sorafenib*	VEGFR 1–3, PDGFR- α , - β , RAF, FLT-3, and c-kit	Phase III	Second-line; cytokine refractory	ORR, 10%; PFS, 5.5 months
Bevacizumab*	Monoclonal antibody to VEGF	Phase III	First-line; bevacizumab plus interferon	ORR, 25–31%; PFS, 8.5–10.2 months
Pazopanib*	VEGFR1–3, PDGFR- α , - β , and c-kit	Phase III	First-line or cytokine refractory	ORR, 30%; PFS, 9.2 months
Axitinib	VEGFR 1–3, PDGF, and c-kit	Phase II	Two trials: cytokine refractory or sorafenib refractory	ORR, 22.6–44%; PFS, 7.4–15.7 months
Tivozanib	VEGFR 1–3	Phase II	No prior VEGF	ORR, 28%; PFS, 11.8 months
ABT-869	VEGFR 1–3, PDGFR, Flt3, and CSF1R	Phase II	Second-line or greater, prior sunitinib	ORR, 18%; PFS, 4.9 months
mTOR inhibitor				
Temsirolimus*	mTORC1	Phase III	First-line, poor risk	ORR, 8.6%; PFS, 10.9 months
Everolimus*	mTORC1	Phase III	Second-line or greater, sunitinib and/or sorafenib refractory	ORR, 1%; PFS, 4.0 months

*Agents that are FDA approved.

c-kit=CD117; CSF1R=colony stimulating factor 1 receptor; Flt3=FMS-like tyrosine kinase 3; mTORC1=mammalian target of rapamycin complex 1; ORR=overall response rate; PDGFR=platelet-derived growth factor receptor; PFS=progression-free survival; RAF=serine/threonine kinase; VEGFR=vascular endothelial factor receptor.

31% of patients having responses compared to only 6% in the interferon arm ($P<.001$). The overall survival for this trial has recently been reported, and although the survival was prolonged in the sunitinib group, it did not reach significance (26 vs 22 months; $P=.051$).⁸ This lack of significance can be attributed to a high number of patients in the interferon arm eventually receiving treatment with sunitinib, and who therefore may possibly be benefiting from this drug as a second therapy. Based on the results of this phase III trial, sunitinib was approved for the treatment of advanced and metastatic RCC.

Bevacizumab

Bevacizumab (Avastin, Genentech) is a monoclonal antibody that selectively binds VEGF-A and all its isoforms. In the phase III AVOREN (Avastin for Renal Cell Cancer) study, 649 treatment-naïve patients with metastatic RCC were randomized to receive either bevacizumab with interferon or interferon alone.⁹ The median PFS was found to be significantly longer in the bevacizumab-containing arm compared to the interferon-alone arm

(10.2 months vs 5.4 months; $P=.0001$). An ORR of 31% was seen in the bevacizumab arm compared to 13% in the interferon-alone arm ($P=.0001$). In a similar randomized, phase III Cancer and Leukemia Group B (CALGB) study, 732 patients with untreated metastatic RCC received either bevacizumab with interferon or interferon alone.¹⁰ A PFS of 8.5 months was seen in the bevacizumab arm compared to 5.2 months in the interferon-alone arm ($P<.0001$). The combination of bevacizumab and interferon gained FDA approval in July 2009 for the treatment of metastatic RCC.

Temsirolimus

Temsirolimus (Torisel, Wyeth) was the first in its class of inhibitors of the mTOR complex to be approved for the treatment of metastatic RCC. Unlike other trials, which excluded most poor-risk patients and non-clear cell types of RCC, temsirolimus was studied in a phase III trial evaluating its use in these groups. In this study, 626 patients with untreated, metastatic RCC with poor prognostic features were randomized to receive temsiro-

limus, interferon, or a combination of temsirolimus and interferon.¹¹ Poor prognostic features included time from diagnosis to randomization of less than 1 year, poor performance status, hypercalcemia, anemia, elevated lactate dehydrogenase, and more than one organ of metastatic involvement.¹² Patients receiving temsirolimus had a significantly prolonged overall survival compared to the interferon-alone group (10.9 vs 7.3 months). Based on this study, temsirolimus was approved in May 2007 for the treatment of metastatic RCC. The role for temsirolimus in clinical use has been in the first-line treatment of RCC patients with poor prognostic features.

Everolimus

Everolimus (Afinitor, Novartis) is an orally bioavailable mTOR inhibitor that has been approved for the treatment of metastatic RCC patients who have progressed on sorafenib or sunitinib. In a pivotal, randomized, double-blinded, phase III trial, 410 patients with metastatic RCC who had failed sorafenib, sunitinib, or both drugs were randomized to receive either everolimus or placebo.¹³ At the 2009 American Society of Clinical Oncology (ASCO) meeting, an updated analysis of this trial showed that the median PFS of those patients receiving everolimus was 4.9 months compared to 1.9 months for those receiving placebo (hazard ratio [HR], 0.33; $P < .001$).¹⁴ The common side effects of everolimus are fatigue, stomatitis, and rash. Everolimus is a reasonable standard for second-line therapy for patients who have progressed on first-line sunitinib or sorafenib.

Selected Second-Generation Agents for the Management of RCC

Pazopanib

Pazopanib (Votrient, GlaxoSmithKline) is the most recent targeted agent to obtain FDA approval for the treatment of RCC. It is a multitargeted tyrosine kinase that inhibits VEGFR1–3, PDGFR- α , - β , and c-kit. A phase II study evaluating the efficacy and tolerability of pazopanib was recently published.¹⁵ In this study, 225 patients who were treatment naïve or had prior treatment with a cytokine or bevacizumab were enrolled to receive pazopanib 800 mg daily. The study was originally started as a randomized phase II trial; however, following the first interim analysis in which a response rate of 38% was seen in the first 60 patients, the trial design was changed to a single-arm, open-label study. The ORR was determined to be 35% for this cohort, with a median PFS of 52 weeks. Common side effects included diarrhea, fatigue, and hair depigmentation.

Sternberg and colleagues recently published the results of a randomized, phase III, placebo-controlled

trial of pazopanib.¹⁶ In this study, 435 patients with metastatic clear cell RCC who were treatment naïve or had received prior cytokine therapy were randomized 2:1 to pazopanib or placebo. The PFS was found to be 9.2 months for those receiving pazopanib compared to 4.2 months for the placebo arm (HR, 0.46; $P < .0001$). A response rate of 30% was seen in the pazopanib group, which is similar to that found in the phase II study. The common side effects of pazopanib were diarrhea, hypertension, hair depigmentation, nausea, and elevation of alanine transaminase (10% grade 3). Most side effects were grade 1 or 2 in severity, suggesting that pazopanib retains its efficacy as a potent tyrosine kinase inhibitor (TKI) while being very tolerable. Based on these findings, pazopanib is the most recent targeted agent to obtain FDA approval, doing so on October 19, 2009.

An ongoing phase III study comparing pazopanib to sunitinib will shed light on whether one of these VEGFR TKIs is more effective or better tolerated than the other as first-line treatment for metastatic clear cell RCC (NCT00720941). In this study, approximately 876 treatment-naïve patients will be randomized to either pazopanib or sunitinib. The primary objective is to determine PFS, and second-line objectives include documenting the overall survival, response rate, adverse events, and differences in quality of life.

Axitinib

Axitinib (Pfizer) is a potent inhibitor of VEGFR 1–3, PDGF, and c-kit that is in development for the treatment of metastatic RCC. It has been evaluated in 2 phase II trials in the cytokine-refractory setting and the VEGF inhibitor refractory setting. In the first study, 52 patients who were refractory to interferon or interleukin-2 were enrolled to receive axitinib 5 mg twice daily.¹⁷ The objective response rate for the group was 44%. The median time to progression was 15.7 months, and median survival was 29.9 months.

In a separate phase II study, 62 metastatic RCC patients who were refractory to sorafenib therapy received axitinib, which was started at 5 mg twice daily and titrated up as tolerated from a side-effect and hypertension standpoint.¹⁸ Axitinib was titrated to greater than 5 mg in 53% of patients. The ORR was found to be 22.6% with a median PFS of 7.4 months. The median overall survival was 13.6 months. Interestingly, almost 75% of these sorafenib-refractory patients were treated in the third-line or greater setting with prior treatments including sunitinib, bevacizumab, temsirolimus, cytokines, and cytotoxic chemotherapies.

Axitinib is now being studied in a large, multicenter, phase III trial comparing its efficacy against sorafenib in the first- and second-line setting (NCT00678392). A

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smaller phase II trial is evaluating the role of axitinib dose escalation in a randomized fashion in metastatic RCC patients (NCT00835978).

Tivozanib

Tivozanib (AV-951, Aveo Pharmaceuticals), a potent inhibitor of VEGFR 1–3, has been evaluated in a large, phase II, randomized, discontinuation trial. In this study, which was recently reported at ASCO 2009, 272 patients with metastatic RCC and no prior VEGF targeted therapy were treated with tivozanib for 16 weeks.¹⁹ After this time point, patients who had more than 25% tumor reduction continued tivozanib therapy, whereas those with less than 25% shrinkage were randomized to continue tivozanib or begin placebo therapy. The ORR was 28% for the tivozanib-treated group. The median PFS had not been reached at the time of presentation. Due to the efficacy seen in this study, a large, international, multicenter, phase III trial comparing tivozanib to sorafenib in the first-line setting is under way (NCT01030783).

ABT-869

ABT-869 (Abbott Laboratories) is a receptor TKI that selectively inhibits VEGFR 1–3, PDGFR, Flt3, and CSF1R. In phase I testing, ABT-869 showed clinical activity in a variety of tumor types with side effects that were tolerable and typical for VEGF inhibitors.²⁰ Unlike other agents, the optimal administration of this drug was based on dosing per kg of body weight (0.25 mg/kg, maximum dose 25 mg). A multicenter, single-arm, phase II study of ABT-869 was presented at ASCO 2009.²¹ Fifty-three patients with metastatic clear cell RCC who had failed prior sunitinib were treated with ABT-869. The ORR was found to be 6.8%. An additional 54% of the patients obtained stable disease as their best response. The median PFS was 4.9 months. Common adverse events were diarrhea, fatigue, hypertension, nausea/vomiting, and hand-foot syndrome.

AMG 386

The first in its class, AMG 386 (Amgen) is a unique agent that targets angiotensin-1 and -2. AMG 386 consists of a fusion protein made up of a peptide and the Fc portion of an antibody with angiotensin specificity. Blockade of VEGF signaling in tumors ultimately results in escape mechanisms, which allow resistance and re-vascularization with growth of the tumor (discussed in more detail below). Angiotensin is a transcriptional target of HIF. Angiotensin binds to its receptor, Tie2, on the surface of vascular endothelial cells resulting in intracellular signals for proliferation and motility. Thus, this pathway may serve as an important escape mechanism culminating in VEGF-targeted therapy resistance.

AMG 386 has been evaluated in the phase I setting in 32 patients with solid tumors.²² The drug was found to be tolerable, with only 12% of patients having a greater than grade 1 toxicity. The most common side effects were proteinuria, fatigue, and peripheral edema. Pharmacodynamic imaging with dynamic contrast enhanced magnetic resonance imaging confirmed decreased intratumoral flow, consistent with the drug's anti-angiogenic properties. Currently, AMG 386 is being evaluated in many different tumor types. In RCC, 2 phase II studies are ongoing: a combination study with sunitinib in the first- or second-line (cytokine refractory) setting (NCT00853372), and a combination study with sorafenib versus sorafenib alone (NCT00467025). These trials will provide insight into the importance of the role of the Ang/Tie2 pathway in developing resistance to primary VEGF inhibition.

Other Agents in Development for RCC

There are a large number of agents having a variety of mechanisms of action that are in the early stages of clinical development (Table 2). Fibroblastic growth factor (FGF) likely plays an important role in bypassing VEGF inhibition to re-establish angiogenesis. Several agents that target the FGF pathway, including both a TKI (dovitinib [Novartis]) and a unique peptibody consisting of the extracellular domain of the FGF receptor and the Fc portion of immunoglobulin G, (FP-1039 [Five Prime Therapeutics]) are in development. Dovitinib is being studied in a phase II trial as a single agent for the treatment of refractory RCC (NCT00715182), while FP-1039 is still in early phase I development (NCT00687505). BNC105P (Bionomics) represents a new class of agents with a unique ability to alter angiogenesis by mechanically disrupting tumor vasculature. A combination trial with this agent and everolimus has recently opened for accrual for refractory RCC (NCT01034631). Regardless of the novelty of the function of any agent, in order to be clinically applicable, it must show appropriate tolerability and efficacy compared to the currently available agents.

New Agents in the Management of Non-clear Cell RCC

Most of the previous phase III trials excluded non-clear cell RCC histologies, and, therefore, little data are available on the best management of these cancers. Several trials are currently evaluating the role of existing agents such as sunitinib and everolimus in the management of papillary RCC, which is the second most common RCC subtype (including NCT00541008 and NCT00688753, respectively). Activation of cMET through hepatocyte

Table 2. Select Novel Classes With Unique Mechanisms of Action and Representative Agents

Drug	Type	Stage of Development
c-MET inhibitors		
XL 880	Small molecule inhibitor	Phase II
AMG 102	Monoclonal antibody	Phase II
FGF inhibitors		
Dovitinib	Small molecule inhibitor	Phase II
FP-1039	Neutralizing peptibody	Phase I
Angiopoietin inhibitors		
AMG-386	Neutralizing peptibody	Phase II
Vascular disrupting agent		
BNC105P	Small molecule inhibitor	Phase II
VEGF peptibody		
VEGF-trap (afibercept)	VEGF binding peptibody	Phase II

VEGF=vascular endothelial growth factor.

growth factor signaling (HGF) results in subsequent promotion of cell survival and invasion.²³ Activating mutations in c-MET have been found to be a critical mediator of carcinogenesis in hereditary papillary RCC tumors. cMET mutations are uncommon in nonhereditary forms of papillary RCC; however, there are other molecular findings such as trisomy 7 and gain of 7q31. Two upcoming agents in this class include XL880 (Exelixis; also known as GSK089), a small molecule inhibitor of c-MET, and AMG 102 (Amgen), a humanized monoclonal antibody to HGF.^{24,25} A phase II trial with XL880 is currently enrolling patients with papillary RCC (NCT00726323), and an update on the progress of this trial was given at ASCO 2009. This trial is evaluating 2 different drug dosing cohorts (a 5 days on, 9 days off cohort and a continuous dosing cohort). The 5 days on, 9 days off cohort has completed enrollment, and of 35 evaluable patients, there were 4 partial responses and 27 patients with stable disease as the best response. The continuous dosing cohort had 9 evaluable patients: 2 had a partial response and 7 had stable disease as the best response. Side effects were noted to be mostly grade 1/2 in severity and included fatigue, hypertension, nausea/vomiting, diarrhea, and elevated liver transaminases.

Incorporation of Second-generation Molecularly Targeted Agents in the Treatment of RCC

Currently there are 6 agents approved for the management of metastatic RCC, giving the practitioner an array of treatment options for patients. As further therapies are evaluated in RCC, this number will likely grow; however, the path to approval should become more stringent, as proof of clinical benefit over currently available agents will be needed. Cytokine and placebo comparator arms are no longer appropriate in clinical trial design due to the availability of these proven effective therapies. Despite this hurdle, novel therapies are necessary to advance the field, as the current agents have potential for substantial toxicity, and there is need to further improve survival for RCC patients.

One way that new agents will find a place in the management of RCC will depend on their ability to improve survival and have more favorable tolerability profiles than existing agents. Pazopanib, the most recently approved VEGF TKI agent, is poised to do just that, as it does appear to have a lower toxicity profile. However, its tolerability and efficacy compared to sunitinib have yet to be confirmed in the phase III head-to-head study previously mentioned. More studies such as this will be needed to evaluate other new agents as they try to make a place for themselves in a crowded market. Other ways in which novel agents will have an opportunity to improve RCC management will be to aid in overcoming resistance mechanisms, which are currently being defined.

Importance of Resistance in the Development of Targeted Therapies

An increasing knowledge of RCC pathogenesis has led to a plethora of potential molecules to target with therapy, but also an understanding of the molecular complexity of the disease. As HIF stabilization leads to numerous gene targets being activated, and currently available agents are only able to inhibit a small number of these targets, many potential pathways of drug resistance likely exist within the HIF pathway alone. Identifying the most important pathways and targeting them with novel agents is therefore key to advancing the outcomes for this disease. A comprehensive review of resistance to targeted agents has been reported elsewhere.²⁶

Given the importance of VEGF utilization in RCC, much of the research to date has been evaluating the factors that may contribute to resistance against VEGF inhibitors rather than mTOR inhibitors. Both preclinical and clinical imaging data show that VEGF inhibition ultimately fails with formation of new blood vessels in the RCC tumors.^{27,28} Many mechanisms have been proposed to explain RCC's ability to curtail VEGF pathway

inhibition. Many of the proposed mechanisms suggest that alternative signaling pathways to re-establish angiogenesis are employed, such as increasing levels of FGF, angiopoietin, and interleukin-8.²⁹⁻³¹ Additionally, as VEGF inhibition results in a hypoxic and nutrient-depleted state, HIF-1 α is stabilized in both tumor and stromal cells allowing for further upregulation of protumorigenic factors. In other cancer types, resistance to tyrosine kinase inhibition therapy is mediated by mutations in the tyrosine kinase; for example, BCR-ABL is altered in chronic myelogenous leukemia and the epidermal growth factor receptor in non-small cell lung cancer. However, in RCC tumors, resistance to VEGF TKI therapy is not due to mutations in the drug target. This characteristic is highlighted by RCC xenograft models in which tumors that develop VEGF inhibitor resistance after exposure lose this resistance when being transported to treatment-naïve mice.³² This phenomenon suggests that tumor environmental factors (even distant to the local tumor microenvironment) may play a critical role.

Although the search for relevant molecular biomarkers to aid in predicting sensitivity to existing RCC therapies is actively ongoing, current clinical decision-making to determine first- and second-line therapy is often based on clinical factors such as histologic subtype, risk factor assessment, and prior therapy. A population of RCC patients who are truly refractory (ie, resistant to therapy from treatment onset as opposed to development of resistance over time) to either VEGF or mTOR inhibition likely does exist and, therefore, validation of novel predictive biomarkers will be necessary in order to improve success for these patients. Molecular phenotypes based on levels of intratumoral HIF-1 and -2 expression as well as other gene expression patterns have been identified, but they require prospective validation. In one study, in RCC tumors that expressed both HIF-1 and HIF-2, the Akt/mTOR and MAP kinase pathways were upregulated, as opposed to tumors that only expressed HIF-2, in which c-Myc activity was found to be enhanced.³³ The effect that these findings may have on the individualized selection of targeted agents is yet to be determined.

Fortunately, complete cross-resistance among current VEGF-targeted therapies is uncommon for most patients, which allows for sequential therapy of these agents. This lack of cross-resistance is exemplified by the results of such studies that evaluated sorafenib followed by sunitinib,³⁴ sunitinib followed by sorafenib,³⁵ bevacizumab followed by sunitinib,³⁶ and sorafenib followed by axitinib.¹⁸ The addition of new agents will give the clinical researcher more options to aid in overcoming resistance, whether it is to the VEGF or mTOR pathway. The optimal means of overcoming resistance either through sequencing of therapies or combining therapies that have nonoverlapping targets is an important clinical question that remains to be answered.

Novel Targeted Therapy Sequencing and Combination Therapy

Novel agents have the opportunity to increase RCC management options by incorporation into sequencing or combination regimens. There are several ongoing trials, which will build evidence on the proper sequence of targeted therapies in RCC. In terms of optimal choice of drug class in the first-line setting, the RECORD-3 (Renal Cell Cancer Treatment With Oral RAD001 Given Daily-3) phase III trial (NCT00903175) is being performed to evaluate everolimus followed by sunitinib versus sunitinib followed by everolimus in the first-line setting, with a primary endpoint of PFS. In the second-line setting, the AXIS (Axitinib as Second-line Therapy for Metastatic Renal Cell Cancer) trial (NCT006892) will compare the efficacy of sorafenib versus axitinib, with prior TKI and mTOR inhibitor therapy allowed. Similarly, temsirolimus and sorafenib are being compared as second-line agents for TKI refractory patients in the TORISEL 404 trial (NCT00474786). These studies will help establish either mTOR inhibitors or subsequent TKIs as the second-line treatment of choice for patients who have failed first-line therapy.

Combination trials are also being performed and may have potential advantages over sequential therapy. One obvious advantage is that of vertical and horizontal pathway inhibition. Vertical inhibition involves targeting 2 separate molecules in the same pathway (eg, Akt and mTOR) and thus may result in improved “potency” of single pathway inhibition. Horizontal inhibition involves using agents that do not inhibit overlapping pathways, such as mTOR inhibitors and VEGF inhibitors. This approach has the potential to squelch a tumor’s ability to utilize alternative pathways to develop resistance. Despite the potential for higher response rates with combined agents, survival outcomes such as PFS and overall survival will need to be lengthened in order to prove superior to sequential agent use.

One interesting trial evaluating the role of combination therapy is the BeST (Bevacizumab, Sorafenib and Temsirolimus in Advanced Renal Cell Carcinoma) study (NCT 00378303) in which bevacizumab alone, bevacizumab and temsirolimus, bevacizumab and sorafenib, and temsirolimus and sorafenib are being compared. In a similar multi-arm design, the TORAVA (Investigation of Torisel and Avastin; NCT00619268) study is comparing sunitinib alone, bevacizumab plus temsirolimus, and bevacizumab plus interferon in the first-line setting. Another first-line combination study, RECORD-2 (Renal Cell Cancer Treatment With Oral RAD001 Given Daily-2), is evaluating bevacizumab plus everolimus versus bevacizumab plus interferon.

The results of these sequencing and combination studies should further define the proper administration

of the existing classes of agents, VEGF targeted agents and mTOR inhibitors. Establishing important resistance mechanisms and targeting those mechanisms through either novel combinations of existing agents or new drug development will be critical to prolonging survival in metastatic RCC.

Conclusion

Although the field of kidney cancer has seen a dramatic increase in the approval of effective agents in the last several years, the development of new, targeted agents continues. Because the mechanism of resistance to therapy is likely complex, having a large arsenal of therapeutics is advantageous. New agents within the VEGF inhibitor class, which are furthest in development, include pazopanib, axitinib, ABT-869, and tivozanib. Upcoming agents with novel mechanisms of action include AMG-386, XL880, AMG-102, BNC-105, and dovitinib. Optimal sequencing and combinations of currently approved agents and therapeutics in development will play a key role in lengthening survival endpoints for metastatic RCC.

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