Updates on novel therapies for metastatic renal cell carcinoma

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Abstract: Metastatic renal cell carcinoma (RCC) poses one of the great therapeutic challenges in oncology. RCC is predominantly refractory to treatment with traditional cytotoxic chemotherapies, and until recently management options were limited to immunotherapy or palliative care. However, in the past few years we have experienced a sea change in the treatment of advanced RCC with the introduction of targeted therapies that derive their efficacy at least in part through alterations in tumor angiogenesis. The tyrosine kinase inhibitors sunitinib, pazopanib, and sorafenib, the monoclonal antibody bevacizumab (in combination with interferon- α), and the rapamycin analogs, temsirolimus and everolimus, are now approved agents in the United States for the treatment of metastatic RCC. Efforts to expand upon these successes include developing novel antiangiogenic agents, optimizing concomitant and sequential regimens, identifying predictors of response to specific treatments, and further dissecting the underlying molecular pathogenesis of RCC to reveal novel therapeutic targets.

Keywords: carcinoma, renal cell, therapeutics

Introduction

More than 54,000 new cases of cancer of the kidney and renal pelvis, and over 13,000 deaths related to kidney cancer, were estimated to occur in the United States in 2009 [Jemal *et al.* 2009]. While nephrectomy is the preferred treatment option for local disease, approximately 30% of patients with renal cell carcinoma (RCC) present with metastatic disease, and about one-third of patients with localized disease relapse following nephrectomy [Golshayan *et al.* 2008]. Cytotoxic chemotherapy is not effective in the treatment of metastatic RCC, with response rates of less than 5% and no impact on overall survival (OS) when compared with placebo or supportive care [Coppin *et al.* 2008; Cohen and McGovern, 2005]. For years, immune modulating therapy was the principal treatment option for patients with metastatic RCC. High-dose aldesleukin (interleukin-2 [IL-2]) was approved by the United States Food and Drug Administration (FDA) for the treatment of advanced RCC based on the results of phase II studies in which 7% of patients achieved durable complete responses (CRs) lasting greater than 10 years [Mcdermott and Atkins, 2006; Fyfe *et al.* 1995]. Patients treated with high-dose IL-2 are

at risk for capillary leak syndrome and hypotension that can require intensive care-level intervention. Interferon- α (IFN- α) immunotherapy is also used in the treatment of metastatic disease. IFN- α was shown to improve survival compared with medroxyprogesterone acetate or vinblastine, but IFN-based regimens are also associated with low response rates [Rini *et al.* 2009a]. Furthermore, only a limited subset of patients appears to sustain benefit from immunotherapy. For example, IL-2 and IFN treatment, individually or in combination, was not associated with improved progression-free survival (PFS) or OS when compared with medroxyprogesterone acetate for patients with intermediate prognosis metastatic RCC [Negrier *et al.* 2007].

High-dose IL-2 may continue to offer the best chance for achieving a durable CR for a highly select group of patients with favorable-prognosis metastatic disease. However, the significant associated toxicities and low overall response rate (ORR) necessitated investigation into novel therapies. Recent advances in our understanding of the molecular mechanisms underlying the development of RCC, particularly the unique relationship between RCC and angiogenesis,

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enabled the development of targeted therapies that comprise the current standard of care. Starting in December 2005 and up until this date, the tyrosine kinase inhibitors (TKIs) sunitinib, pazopanib, and sorafenib, as well as the rapamycin analogs, temsirolimus and everolimus, have been approved for use in the United States in the treatment of metastatic RCC. In addition, the combination of the antivascular endothelial growth factor (VEGF) antibody bevacizumab with IFN- α has been approved for use in Europe. In this article, we briefly discuss the biological rationale that promoted the generation of these agents and in this context discuss novel targeted therapies that may provide improved efficacy or diminished toxicity. We also discuss efforts to validate and expand upon existing prognostic factors for RCC in the age of targeted therapies. We limit our discussion to the treatment of clear cell RCC. For a review of advances in the treatment of non-clear cell renal cancer, we refer the reader to the recent article by Heng and Choueiri [Heng and Choueiri, 2009].

The biological basis for current targeted therapies in RCC

Conventional or clear cell RCC is the most common histologic subtype of kidney cancer, accounting for about 80% of cases [Golshayan *et al.* 2008]. The von Hippel–Lindau (VHL) tumor suppressor gene is silenced in most cases of sporadic RCC [Kaelin, 2004]. VHL encodes a protein, pVHL, which is a component of an E3 ubiquitin ligase for hypoxia-inducible factor α (HIF α) proteins that targets HIF α for degradation by the proteasome under conditions of normal oxygen tension. Under hypoxic conditions, or if VHL is silenced by mutation or methylation, HIF α proteins heterodimerize with HIF β to act as transcription factors for multiple hypoxia-inducible genes involved in proliferation, angiogenesis, and metabolism, including VEGF, platelet derived growth factor (PDGF), epidermal growth factor receptor (EGFR), transforming growth factor- α (TGF- α), and many others [Kaelin, 2004]. As shown in Figure 1, several targeted therapeutics for metastatic RCC disrupt signaling *via* HIF targets or upstream regulators of HIF expression to inhibit tumor growth and angiogenesis.

Current targeted therapies in RCC

Sorafenib tosylate and sunitinib malate inhibit multiple tyrosine kinases expressed on RCC tumor cells or on endothelial cells that relay

proliferative or angiogenic signals. Sorafenib blocks receptors for VEGF and PDGF (VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- β), as well as the tyrosine kinases Flt3 and c-Kit [Hutson and Figlin, 2007; Strumberg *et al.* 2005]. It also inhibits the serine/threonine kinase c-Raf and B-Raf. Sorafenib received FDA approval in 2005 for use in advanced RCC based on the results of a phase III trial that demonstrated improved median PFS for patients with cytokine-refractory metastatic RCC treated with sorafenib compared to patients in the placebo arm (5.5 versus 2.8 months, $p=0.000001$) [Escudier *et al.* 2005, 2007a, 2009a]. However, sorafenib failed to demonstrate an improvement in PFS compared with IFN in a randomized phase II study of treatment-naïve patients with metastatic RCC [Rini *et al.* 2009a; Szczylik *et al.* 2007].

Sunitinib is a polykinase inhibitor with efficacy against VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- α , PDGFR- β , Flt3, and c-Kit [Hutson and Figlin, 2007]. Phase II trials showed significant response rates in patients with metastatic RCC previously treated with cytokine therapy (IFN or IL-2), leading to FDA approval in January 2006 [Motzer *et al.* 2006a, b]. A subsequent phase III study demonstrated a significant improvement in PFS (11 versus 5 months, $p<0.001$) and an improvement in OS (26.4 versus 21.8 months, $p=0.051$) associated with sunitinib treatment when compared with IFN- α and established sunitinib as a ‘reference standard’ first-line treatment option for patients with metastatic RCC [Figlin *et al.* 2008; Motzer *et al.* 2007].

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase and central component of signaling pathways that govern cell proliferation, survival, metabolism, angiogenesis, and apoptosis (Figure 1). Temsirolimus and everolimus are allosteric inhibitors of the mTOR/Raptor complex known as mTORC1 [Le Tourneau *et al.* 2008]. Temsirolimus received FDA approval in 2007 and is considered first-line treatment for patients with high-risk, metastatic RCC, based on results from a phase III randomized trial comparing treatment with temsirolimus, IFN- α , or a combination of temsirolimus and IFN- α [Hudes *et al.* 2007]. OS was significantly improved for patients treated with temsirolimus (10.9 months) compared with those treated with IFN- α (7.3 months, hazard ratio [HR] 0.73, $p<0.008$) [Hudes *et al.* 2007]. The combination of temsirolimus and IFN- α did not lead to a significant

Figure 1. Therapeutic targets in renal cell carcinoma. AKT, serine/threonine protein kinase; GF, growth factor; GFR, growth factor receptor; HIF, hypoxia-inducible factor; IRS, insulin receptor substrate; mTOR, mammalian target of rapamycin; PDK, pyruvate dehydrogenase kinase; PI3K, phosphatidylinositol 3-kinase; PIP, phosphatidylinositol phosphate; PTEN, phosphatase and tensin homolog; RCC, renal cell carcinoma; RTK, receptor tyrosine kinase; VEGF, vascular endothelial growth factor; VHL, von Hippel–Landau. Modified with kind permission of Springer Science and Business Media from Figure 1 [Courtney and Choueiri, 2009].

change in overall survival (8.4 months) compared with IFN- α alone, perhaps due to the increased number of serious adverse events (AEs), or the decreased dose of temsirolimus administered in the combination arm [Hudes *et al.* 2007]. Everolimus received FDA approval in 2009 for the treatment of patients with metastatic RCC following previous antiangiogenic therapy with sorafenib or sunitinib therapy. In a randomized phase III study (RECORD-1) involving patients whose cancer had progressed through treatment with sunitinib, sorafenib, or both, treatment with everolimus was associated with an improvement in median PFS (4.0 months, 95% confidence interval [CI] 3.7–5.5) compared to treatment with placebo (1.9 months, 95% CI 1.8–1.9) [Motzer *et al.* 2008]. Following unblinding at the second interim analysis, patients receiving placebo were crossed over to the everolimus treatment arm [Kay *et al.* 2009]. Updated results for RECORD-1 presented at the American Society of Clinical Oncology (ASCO) 2009

Genitourinary Cancers (GU) Symposium revealed a 4.9-month median PFS (CI 4.0–5.5) for patients treated with everolimus compared with 1.9 months (CI 1.8–1.9) for patients who received placebo [Kay *et al.* 2009]. OS data were not mature.

Two phase III trials have demonstrated the efficacy of adding the recombinant anti-VEGF monoclonal antibody bevacizumab to IFN- α . CALGB 90206 randomized previously untreated patients to receive bevacizumab and subcutaneous IFN or IFN alone. Treatment with the combination arm was associated with an increased PFS (8.5 versus 5.2 months, $p < 0.0001$) and ORR (25.5% versus 13.1%, $p < 0.0001$) [Rini *et al.* 2008]. The median OS for patients treated with bevacizumab plus IFN- α was 18.3 months (95% CI; 16.5–22.5), compared with 17.4 months (95% CI; 14.4–20.0) for patients who received IFN- α alone, but this result did not meet criteria for statistical significance

[Rini *et al.* 2009b]. Similarly, an international trial (AVOREN) comparing treatment with the combination of IFN- α -2a and bevacizumab to IFN- α -2a plus placebo demonstrated an improved PFS with the addition of bevacizumab (10.2 versus 5.4 months, $p < 0.0001$) [Escudier *et al.* 2007b]. There was a trend toward improved median OS for patients treated with bevacizumab plus IFN (23.3 months) compared with patients who received placebo with IFN (21.3 months) (HR 0.86 [95% CI: 0.72–1.04], $p = 0.1291$) [Escudier *et al.* 2009b].

Novel anti-angiogenic agents

While the successes of targeted therapies with antiangiogenic properties have established new standards of care in the treatment of advanced RCC, there remains a profound need for new agents or combinations of treatments that will improve clinical activity and diminish treatment-associated toxicities. For example, although sunitinib is now a preferred first-line treatment for patients with good or intermediate risk metastatic RCC, the updated ORR as presented in 2008 was 47%, while 67% of patients experienced grade 3 or 4 treatment-associated toxicity according to FDA prescribing information (<http://www.access-data.fda.gov>) [Figlin *et al.* 2008]. Furthermore, to date only sunitinib and temsirolimus have demonstrated improvements in OS in clinical trials, albeit in quite different patient populations. Consequently, several novel targeted agents are currently being evaluated in clinical trials. Table 1 summarizes reported responses and toxicities associated with selected novel therapies for the treatment of metastatic RCC. Table 2 provides a possible treatment algorithm for metastatic RCC incorporating currently approved therapies and those undergoing evaluation in clinical trials.

Novel tyrosine kinase inhibitors

Pazopanib is a TKI that blocks VEGFR-1, VEGFR-2, VEGFR-3, PDGFR α , PDGFR β , and c-Kit [Rini *et al.* 2008]. Pazopanib demonstrated an improved PFS compared with placebo in a randomized discontinuation trial involving 225 patients with no or one prior systemic therapy [Hutson *et al.* 2007, 2008a]. Pazopanib treatment resulted in a low incidence of hand–foot syndrome, rash, and mucositis, toxicities that are frequently associated with other TKIs [Hutson *et al.* 2007, 2008a]. Results of a double-blind, phase III study comparing pazopanib with placebo in untreated ($N = 233$) and cytokine-treated ($N = 202$) patients revealed an

improvement in PFS with pazopanib (9.2 versus 4.2 months, $p < 0.0000001$) [Sternberg *et al.* 2009]. PFS was improved with pazopanib in both previously untreated (11.1 versus 2.8 months, $p < 0.0000001$) and in cytokine-pretreated patients (7.4 versus 4.2 months, $p < 0.001$) [Sternberg *et al.* 2009]. In October 2009, the FDA approved pazopanib for the treatment of advanced RCC. Pazopanib is now being compared with sunitinib as first-line therapy in an international phase III trial with an estimated enrollment of 876 patients with locally advanced or metastatic RCC who have received no prior systemic treatment (www.clinicaltrials.gov) [Sonpavde and Hutson, 2008]. The estimated study completion date is November 2010.

Axitinib is a TKI that inhibits VEGFR-1, -2, and -3 [Rixe *et al.* 2007]. A phase II study involving 52 patients with cytokine-refractory metastatic RCC demonstrated an ORR of 44.2% with axitinib treatment, including two CRs and 21 PRs, and a median time to progression (TTP) of 15.7 months [Rixe *et al.* 2007]. Median OS was 29.9 months [Rixe *et al.* 2007]. However, it should be noted that 22 patients did not have any unfavorable risk factors, and 28 patients experienced grade 3 or 4 AEs, the most frequent being hypertension, diarrhea, and fatigue [Rixe *et al.* 2007]. In a phase II study involving patients who were refractory to sorafenib ($N = 15$), sorafenib and cytokine therapy ($N = 29$), or sorafenib and sunitinib therapy ($N = 14$), response rates to axitinib were 27%, 28%, and 7%, respectively, demonstrating activity of axitinib in VEGFR-TKI-refractory patients [Dutcher *et al.* 2008; Sonpavde and Hutson, 2008]. A phase III study ($N = 540$) is currently enrolling with PFS as the primary endpoint that compares axitinib with sorafenib in the treatment of patients who have failed one prior systemic therapy (www.clinicaltrials.gov).

Tivozanib (AV-951) is another pan-VEGFR TKI that is being evaluated in a randomized discontinuation phase II study of patients with metastatic RCC who had received no prior VEGF-targeted therapy [Bhargava *et al.* 2009]. Following 16 weeks of treatment with AV-951, patients are evaluated for tumor response. Those in whom a $\geq 25\%$ decrease in tumor size is achieved continue with AV-951, while those with $< 25\%$ change in tumor burden are randomized to receive treatment with either AV-951 or placebo [Bhargava *et al.* 2009]. Interim data from this trial, presented

Table 1. Selected studies involving investigational agents for the treatment of metastatic renal cell carcinoma.

Agent	Study	Patient population	Number of patients	Results	References
Pazopanib	Phase III: pazopanib versus placebo	Metastatic dz	435	9.2 versus 4.2 mos PFS	[Sternberg <i>et al.</i> 2009]
Axitinib	Phase II	Untreated	233	11.1 versus 2.8 mos PFS	[Rixe <i>et al.</i> 2007]
		Cytokine treated	202	7.4 versus 4.2 mos PFS	
		Cytokine-refractory	52	44.2% ORR; median TTP 15.7 mos	
	Phase II	Metastatic dz	58		[Dutcher <i>et al.</i> 2008]
		Prior sorafenib	15	27% ORR	
		Prior sorafenib + cytokine	29	28% ORR	
AV-951	Phase II	Prior sorafenib + sunitinib	14	7% ORR	[Bhargava <i>et al.</i> 2009]
		No prior TKI	245	28% ORR	
		≤1 prior Rx	28	11% ORR	
Lenalidomide	Phase II	Metastatic dz	40	10% ORR	[Choueiri <i>et al.</i> 2006]
		Metastatic dz	14	0% ORR	
		Metastatic dz	46	5% ORR	
Perifosine	Phase II	Prior TKI	31	3% ORR	[Amato <i>et al.</i> 2008]
		Prior TKI	15	7% ORR	
		+ rapamycin analog			
AS1411	Phase II	Prior TKI	24	8% ORR	[Cho <i>et al.</i> 2009]
	Phase I	Advanced dz	12	17% ORR	[Miller <i>et al.</i> 2006]

dz, disease; mos, months; ORR, overall response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; TTP, time to progression.

Table 2. Treatment algorithm for metastatic renal cell carcinoma.

Therapeutic setting	Patient features	Therapy options
First-line therapy	Good and intermediate risk	Sunitinib, pazopanib, bevacizumab + IFN, high-dose IL-2 Clinical trial: sunitinib then sorafenib versus sorafenib then sunitinib
	Poor risk Any risk category	Temsirolimus Clinical trial: pazopanib versus sunitinib; bevacizumab + temsirolimus versus bevacizumab + IFN- α (versus sunitinib)
Second-line therapy	Prior cytokine therapy	Sorafenib, sunitinib
	Prior anti-angiogenic TKI	Everolimus Clinical trial: temsirolimus versus sorafenib (following sunitinib failure)
	Prior cytokine or anti-angiogenic therapy Prior rapamycin analog	Clinical trial: axitinib versus sorafenib Unknown

IFN, interferon; IL, interleukin; TKI, tyrosine kinase inhibitor.

at ASCO GU 2009 meeting revealed that either CR or PR was achieved in 28% of 245 evaluable patients at 16 weeks, while 63% had stable disease [Bhargava *et al.* 2009]. Hypertension was the most common all-grade, treatment-related AE, affecting 42% of patients. Minimal all-grade fatigue, diarrhea, and mucositis were observed (all <10%) [Bhargava *et al.* 2009].

A host of additional TKIs that target critical components of angiogenesis are currently

under investigation. These include cediranib, which blocks VEGFR-1 and -2, c-Kit, PDGFR β , and Flt4; vandetanib, which inhibits EGFR and VEGFR-2; ABT-869, an inhibitor of the VEGFRs, PDGFRs, Flt3, and c-Kit; BAY 73-4506, which targets the VEGFR, fibroblast growth factor receptor (FGFR), PDGFR, c-Kit, and RET tyrosine kinases, as well as the Raf and MAPK serine/threonine kinases; and GSK-089, a Met and VEGFR-2 inhibitor [Sonpavde and Hutson, 2008].

Non-TKI anti-angiogenic therapies

In addition to TKIs, agents that target angiogenesis by alternative mechanisms are also being studied in phase I and phase II clinical trials. Aflibercept, also known as VEGF Trap, binds VEGF directly. Unlike bevacizumab, which is an antibody to VEGF, aflibercept is derived from extracellular portions of VEGFR-1 and -2 [Holash *et al.* 2002]. A phase II randomized trial of aflibercept in patients with unresectable or metastatic RCC is underway (www.clinicaltrials.gov).

Lenalidomide, a derivative of thalidomide, possesses both anti-angiogenic and immunomodulatory properties. Lenalidomide results in diminished endothelial cell migration in response to angiogenic factors bFGF, VEGF, and TNF- α [Choueiri *et al.* 2006]. Three small phase II studies have examined the efficacy of lenalidomide in the treatment of metastatic RCC. In an open-label study involving 28 patients who had received at most one prior systemic therapy with the primary endpoint of ORR, PR was achieved in 3 patients (11%) lasting greater than 15 months, and 11 of 28 patients had stable disease for greater than 3 months [Choueiri *et al.* 2006]. Grade 3 or 4 AEs included fatigue (11%), skin toxicity (11%), and neutropenia (36%) [Choueiri *et al.* 2006]. In a second trial, 40 participants with metastatic disease received lenalidomide treatment with the primary endpoint of tumor response rate [Amato *et al.* 2008]. Of 39 evaluable patients, 23 (59%) had previously received immunotherapy or chemotherapy. One patient was observed to have a CR, 3 had PRs, and 21 had stable disease. The median duration of response was 6 months (2–22 month range), and median OS was 17 months [Amato *et al.* 2008]. The third reported lenalidomide trial in patients with RCC enrolled 14 patients; none experienced a CR or PR, while 8 (57%) had stable disease with a median TTP of 3 months [Patel *et al.* 2008].

Combination therapy and sequential therapy

An area of active investigation is to determine the optimum combination or sequencing of therapies for metastatic RCC. Combining established anti-angiogenic or immunomodulatory therapies presents an attractive approach to maximizing tumor response, but may result in excess toxicity. For example, despite yielding a promising response rate of 52% in a phase I study, the combination of sunitinib and bevacizumab was poorly

tolerated and required dose reductions or discontinuation in a significant number of patients [Feldman *et al.* 2008]. The FDA issued a safety alert regarding the combination of sunitinib and bevacizumab due to the high percentage of patients who experienced Grade 3/4 hypertension, hematologic complications, and vascular AEs (www.fda.gov/medwatch/safety/2008/MAHA_DHCP.pdf). A phase I study evaluating the combination of sorafenib and bevacizumab also yielded relatively high response rates, as 21 of 46 patients (46%) experienced a PR by RECIST criteria following two cycles of treatment [Sosman *et al.* 2008]. However, bevacizumab appeared to significantly increase sorafenib-associated toxicities, particularly hand–foot syndrome, and combining both agents reduced the maximal tolerated doses of each drug to a fraction of the full dose of each given as single-agent therapy [Sosman *et al.* 2008]. In addition, a phase I trial combining sunitinib with temsirolimus was terminated following the accrual of only three patients due to significant toxicity observed at low starting doses of both drugs [Fischer *et al.* 2008].

Despite these somewhat discouraging findings from combination studies, two ongoing studies have been designed to assess whether temsirolimus may be effectively combined with bevacizumab. TORAVA is a phase II multicenter, randomized, open-label study in which patients receive temsirolimus plus bevacizumab, IFN- α plus bevacizumab, or sunitinib as first-line systemic treatment (www.clinicaltrials.gov). INTORACT is a phase III randomized, open-label trial comparing bevacizumab plus temsirolimus with bevacizumab plus IFN- α in the first line, with an estimated enrollment of 800 patients (www.clinicaltrials.gov). In addition, the RECORD-2 study compares the safety and efficacy of everolimus and bevacizumab with IFN- α and bevacizumab, with an estimated enrollment of 360 patients (www.clinicaltrials.gov).

Several clinical trials are underway to evaluate optimal sequencing of targeted therapies. Everolimus is the only agent currently approved by the FDA for the treatment of kidney cancer following progression on TKI therapy. A phase I/II study of the combination of temsirolimus plus bevacizumab in TKI-refractory disease is underway [Merchan *et al.* 2009]. The accrual goal for the phase II portion of this trial is 40 patients, with the primary goal being to ascertain the

percentage of patients free of disease progression at 6 months, and secondary endpoints of toxicity and response rate [Merchan *et al.* 2009]. At interim analysis, PR was achieved in 4 of 25 (16%) of evaluable patients, while 18 of 25 patients (72%) had stable disease [Merchan *et al.* 2009]. An international, randomized trial with an estimated enrollment of 480 patients will compare the efficacy and tolerability of temsirolimus versus sorafenib following sunitinib failure, while a phase III study is ongoing that compares axitinib with sorafenib following disease progression on sunitinib treatment in a planned 540 patients, with PFS as the primary endpoint (www.clinicaltrials.gov). An alternative phase III study does not assume the superiority of sunitinib in the first line and randomizes previously untreated patients with low or intermediate Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic scores to receive sunitinib followed by sorafenib or sorafenib followed by sunitinib, with total PFS as the primary endpoint (www.clinicaltrials.gov). In addition, a study with an estimated enrollment of 390 patients (RECORD-3) is planned to assess the efficacy and safety of treatment with sunitinib followed by everolimus versus treatment with everolimus followed by sunitinib, with PFS as the primary endpoint (www.clinicaltrials.gov).

Predicting outcomes and toxicities in the era of anti-angiogenic targeted therapies

The MSKCC risk system stratifies patients with metastatic RCC into poor-, intermediate-, and favorable-risk categories based on the number of adverse clinical and laboratory parameters present. Poor prognostic factors are a Karnofsky performance status (KPS) <80, time from diagnosis to treatment (with IFN- α) <12 months, serum lactate dehydrogenase (LDH) >1.5 times the upper limit of normal (ULN), corrected serum calcium >10.0 mg/dl, and hemoglobin less than the lower limit of normal (LLN) [Motzer *et al.* 1999]. Patients in the favorable risk group have no poor prognostic factors, those in the intermediate risk category have one or two poor prognostic factors, and patients with poor risk RCC have more than two poor prognostic factors. This model was externally validated and extended to include prior radiotherapy and hepatic, pulmonary, or retroperitoneal lymph node metastases among the poor prognostic factors that independently predicted decreased survival [Mekhail *et al.* 2005]. However, the MSKCC prognostic factors model

was generated at a time when immunotherapy comprised the standard of treatment for metastatic RCC [Mekhail *et al.* 2005; Motzer *et al.* 1999, 2002].

To identify prognostic factors for OS in patients with metastatic RCC treated with VEGF-targeted therapies, Heng and colleagues evaluated baseline clinical and laboratory characteristics and outcomes for 645 patients who had received treatment with sunitinib (396), sorafenib (200), or bevacizumab (49) [Heng *et al.* 2009]. The study identified four of the five MSKCC poor prognostic factors (hemoglobin < LLN, corrected calcium > ULN, Karnofsky PS < 80, and time from diagnosis to treatment initiation <1 year) to be independent predictors of diminished survival, thereby validating elements of the MSKCC model in this patient population [Heng *et al.* 2009]. The authors also identified absolute neutrophil count > ULN and platelet count > ULN as independent adverse prognostic factors.

In addition to these clinical, cytologic, and metabolic prognostic factors, the molecular makeup of an individual's tumor cells may predict response to therapy. For example, VHL loss-of-function mutations appear to correlate with chance of responding to VEGF-targeted therapy [Choueiri *et al.* 2008]. VHL-deficient tumors also show mTOR-dependent increased uptake of fluorodeoxyglucose (FDG); therefore, positron emission tomography may have early predictive utility in evaluating the response to temsirolimus or everolimus treatment [Thomas *et al.* 2006]. A recent report also sheds new light on the potential importance of differential expression of HIF-1 α and HIF-2 α in RCC. Nathanson and colleagues analyzed VHL status and HIF- α expression in 160 primary tumors from patients with RCC [Gordan *et al.* 2008]. The authors identified three subtypes of RCC distinguished by VHL and HIF- α expression: those expressing wild-type VHL protein (VHL WT), tumors deficient in VHL that express both HIF-1 α and HIF-2 α (H1H2), and VHL-deficient tumors that express only HIF-2 α (H2) [Gordan *et al.* 2008]. Whereas VHL WT and H1H2 tumors showed activation of the Akt/mTOR and Erk/MAPK signaling pathways, proliferation of H2 tumors appeared to be driven by c-Myc activation [Gordan *et al.* 2008]. Interestingly, HIF-1 α antagonizes c-Myc activity in certain settings [Gordan *et al.* 2008; Kaelin, 2008; Kaelin and Ratcliffe, 2008]. One can speculate

that VHL WT and H1H2 tumors may respond better to growth factor receptor inhibitors such as sunitinib and sorafenib than H2 tumors [Gordan *et al.* 2008; Kaelin, 2008].

Current data for selecting the appropriate first-line treatment for a given patient is limited. There is rationale for choosing alternative treatments based on a patient's MSKCC risk category and available PFS and OS data. For example, sunitinib, or the combination of bevacizumab plus IFN, are viable first-line options for many patients with low or intermediate risk metastatic RCC. When choosing between these options, or among available second-line therapies following disease progression, we must also take into account the specific toxicity profiles of these targeted therapies as they relate to the individual patient. Hypertension, hand-foot syndrome, fatigue, leukopenia, diarrhea, and increased lipase are among the most common Grade 3 or 4 toxicities associated with sunitinib and sorafenib, while the most common severe side effects of temsirolimus include fatigue, mucositis, hypertriglyceridemia, hyperglycemia, and hypophosphatemia [Hutson *et al.* 2008b]. The combination of bevacizumab and IFN, meanwhile, is most frequently associated with diarrhea, hypertension, fatigue, and proteinuria, and increases the risk for both arterial and venous thromboembolic events [Schmidinger and Zielinski, 2009]. Patient comorbidities are therefore important considerations in treatment selection, and molecular predictors of treatment-related toxicities are being investigated. For example, select non-synonymous single nucleotide polymorphisms (nsSNPs) may distinguish patients at risk for experiencing severe sunitinib-associated toxicities from those without severe side effects [Faber *et al.* 2008].

Evolving treatment approaches

Inhibition of phosphatidylinositol 3-kinase signaling

The rapamycin analogs temsirolimus and everolimus have demonstrated efficacy in the treatment of metastatic RCC. However, our growing understanding of the phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR signaling cascade provides insight into potential means of improving on the outcomes achieved by rapamycin analog treatment [Courtney and Choueiri, 2009]. For example, rapamycin analogs inhibit

the mTORC1 complex, a key regulator of protein synthesis and cell-cycle entry [Le Tourneau *et al.* 2008]. However, rapamycin may not be an effective inhibitor of mTORC2, which contributes to Akt activation [Meric-Bernstam and Gonzalez-Angulo, 2009]. Furthermore, rapamycin treatment can result in Akt activation in some circumstances, for example through loss of mTORC1-mediated negative feedback upstream of PI3K (Figure 1) [Meric-Bernstam and Gonzalez-Angulo, 2009]. ATP competitive inhibitors that can effectively block both mTORC1 and mTORC2 may have improved clinical utility. Direct inhibitors of PI3K, or dual PI3K/mTOR inhibitors, are being evaluated in early-phase clinical trials [Yuan and Cantley, 2008]. In addition, perifosine, a heterocyclic alkylphospholipid that is intended to alter Akt signaling by disrupting interaction with membrane phospholipids, has demonstrated limited clinical response for patients with RCC. In a phase II study involving 46 patients who had received one prior VEGFR inhibitor (Group A, $N=31$) or prior VEGFR inhibitor and mTOR inhibitor therapy (Group B, $N=15$), 1 of 30 evaluable patients in Group A and 1 of 14 in Group B experienced a PR, while 12/30 and 7/14 had stable disease lasting more than 12 weeks one patient experienced a PR and 10 had stable disease at the time of analysis [Vogelzang *et al.* 2009]. In a second phase II trial of 24 patients with metastatic RCC refractory to either sunitinib or sorafenib, PR was realized in 2 patients, and 10 patients had stable disease >12 weeks, resulting in a 50% PFS at 12 weeks [Cho *et al.* 2009].

Aptamers as targeted therapeutic agents

Aptamers are short peptides or oligonucleotides, either RNA or single-stranded DNA, that form stable structures that resist degradation and are capable of binding target proteins with high affinity [Ireson and Kelland, 2006]. AS1411 is a 26-nucleotide DNA aptamer that binds nucleolin. Nucleolin is proposed to play a role in mRNA stabilization and ribosomal assembly, and AS1411 appears to destabilize mRNA [Soundararajan *et al.* 2008; Ireson and Kelland, 2006]. An extended phase I dose-escalation study of AS1411 included 12 patients with RCC [Miller *et al.* 2006]. One patient experienced a CR, one had a partial response, 9 had stable disease, and none experienced serious toxicities [Miller *et al.* 2006]. A single-arm phase II study of AS1411 in patients with RCC who have

failed prior treatment recently completed accrual (www.clinicaltrials.gov).

Conclusions

Advances in our understanding of the molecular events necessary for RCC growth and survival have paved the way for the development of targeted therapies that are now the standard of care for patients with metastatic disease. The recent introduction of an array of compounds with anti-angiogenic and anti-proliferative properties has dramatically expanded the treatment options for patients with metastatic RCC. However, despite these advances, there is much room for improvement. The majority of patients fail to experience significant and durable tumor response to currently approved TKIs, rapamycin analogs, and VEGF-targeted antibody therapy, and improvements in OS observed with these compounds in phase III trials are still not ideal. In addition, toxicities associated with these treatments are common and can be substantial. Ongoing clinical trials with novel agents look to improve upon the successes realized with the introduction of these drugs with increased response rates and diminished severity of side effects.

Conflict of interest statement

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