The Evolving Landscape of Metastatic Renal Cell Carcinoma

By Daniel Y. C. Heng, MD, MPH, and Toni K. Choueiri, MD, MSc

Overview: The treatment paradigm in metastatic renal cell carcinoma (mRCC) has evolved over the last 5 years. There are now seven approved targeted therapies against the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways. The use of targeted therapy, sequences, combinations, and investigational compounds will be discussed. Prognostic and predictive tools are detailed, although much work must be done to find predictive biomarkers in an effort to individualize therapy for patients.

THE ELUCIDATION of the von Hippel Lindau (VHL) tumor suppression gene associated with the hereditary and sporadic forms of clear cell renal cell carcinomas (RCCs) has sparked a revolution of targeted therapy for this disease. The loss of VHL leads to downstream accumulation of hypoxia inducible factor (HIF) and subsequent activation of tumor promoting pathways including VEGF.[1] In fact, malignancies of the kidney show the greatest range and maximum expression of VEGF,[2] suggesting a rational target in this disease. mTOR is a serine threonine kinase that is another important central target in RCC, as it enhances translation of proteins involved in cellular growth, survival, and angiogenesis.

Inhibitors of VEGF and mTOR have dominated the scene in the treatment of mRCC. These drugs have become commonplace in the treatment algorithm (Table 1) based on the registration phase III clinical trials.

Choices of Targeted Therapy

The list of choices for first-line targeted therapy is ever increasing. Oral VEGF tyrosine kinase inhibitors such as sunitinib[3] and pazopanib[4] and intravenous antibodies against VEGF such as bevacizumab[5,6] in combination with interferon-alpha have demonstrated a convincing progression-free survival (PFS) benefit in the first-line setting in patients with favorable or intermediate prognosis. Patients with poor prognosis benefit from temsirolimus (mTOR inhibitor),[7] as it is the only therapy to improve overall survival (OS) in the setting of a phase III trial in patients with poor prognosis.

After failure of initial therapy, there are also choices to be made. On progression after immunotherapy, sorafenib has demonstrated a PFS benefit compared with placebo.[8] After failure of initial VEGF therapy, both everolimus (mTOR inhibitor) and axitinib (VEGF inhibitor) have also demonstrated a PFS benefit. Everolimus was examined in patients who progressed taking initial sunitinib, sorafenib, or both drugs and were randomly selected to take everolimus compared with placebo. The PFS for the everolimus versus placebo group was 4.9 versus 1.9 months (p < 0.0001), respectively.[9] Axitinib was recently approved by the FDA based on the registration phase III trial of axitinib compared with sorafenib in patients previously treated with a broad range of frontline therapies, including mostly prior sunitinib and cytokines. The response rates and PFS for the axitinib versus sorafenib group was 19% versus 9% and 6.7 versus 4.7 months (p < 0.0001).[10]

Although there is no level I evidence for the drug of choice for patients in whom initial mTOR inhibitors failed, the use of a sequential targeted therapy not previously used remains a standard practice for these patients. This is also true for the choice of third-line targeted therapy, as there is no level I evidence to guide us in this setting.

We are now faced with several targeted therapies to choose from in each treatment setting. As we do not have any robust, externally validated predictors of response to targeted therapy, the choice of targeted therapy is usually based on physician preference, intravenous versus oral therapy, reimbursement issues, and toxicity profile. For example, patients with significant lung disease receiving oxygen or poorly controlled diabetes mellitus may not be optimal candidates for an mTOR inhibitor, as there is a risk of noninfectious pneumonitis and hyperglycemia with this class of agents. Similarly, patients with refractory hypertension treated with several antihypertensive agents or severe cardiovascular (CV) morbidities may not initially choose a VEGF inhibitor, as these are known to increase the risk of hypertension and CV events. These examples may be encountered in daily practice. However, no routine markers to predict response or toxicity to allow for a more informed decision about which targeted therapy to choose are available.

Sequences of VEGF and mTOR inhibitors are being investigated in several randomized trials including the RECORD 3 (NCT00903175), 404 study (NCT00474786), and START (NCT01217931) clinical trials (Table 2). These may help shed light onto the best sequence of drugs to use although they do not add to the personalized medicine approach.

Different combinations of targeted therapy have also been studied, including the TORAVA trial of temsirolimus and bevacizumab in the frontline setting, which demonstrated only increased toxicity and no convincing evidence of added benefit.[11] Other combinations such as sunitinib and bevacizumab have proven to be toxic and have adverse effects such as thrombotic thrombocytopenic purpura, which is rarely seen when the agents are used alone.[11] A phase III CALGB trial investigating second-line use of everolimus compared with everolimus plus bevacizumab is underway with OS as the primary endpoint (NCT01198158). Unless substantial differences in durable complete responses or OS are documented, combination therapy remains investigational.

Prognostic Factors in Advanced RCC

Prognostic factors have been developed to assist in patient counseling, risk-directed treatment, and clinical trial design. These clinical factors that predict prognosis are a combination of patient factors, indicators of tumor burden, pro-inflammatory markers, and treatment-related factors including prior cytoreductive nephrectomy.[12]

Many multivariable models such as the Memorial Sloan-Kettering Cancer Center (MSKCC) model[13] have been created in an effort to stratify groups of patients with different biology. More recently, the International mRCC Database Consortium developed criteria from a large population-based database of patients treated with VEGF targeted therapy. The independent predictors of poor OS include anemia, hypercalcemia, thrombocytosis, neutrophilia, a Karnofsky Performance Status of less than 80%, and a diagnosis-to-treatment interval of less than 1 year. Patients are then segregated into three risk categories: favorable risk (no risk factors, median OS not reached), intermediate risk (one to two risk factors, median OS of 27 months), and poor risk (three or more risk factors, median OS of 8.8 months).[14] This multivariable model has been externally validated in an even more modern set of patients treated with VEGF targeted therapy with median OSs at 44 months, 21 months, and 8 months for the favorable, intermediate, and poor risk groups, respectively ($p < 0.0001$). This same model has also been validated in a set of patients who were previously treated with VEGF inhibitors and received a second line of systemic therapy.[15] Data from these models suggest continued improvements in OS across different risk groups, which is a testament to the effectiveness of modern-day targeted therapy.

Prediction of Response to Targeted Therapy: Steps Toward Personalized Medicine

Currently there are no clinical factors or biomarkers that can conclusively predict which targeted therapies patients will respond to. There are some serum levels of proteins in

---

KEY POINTS

- There are now seven targeted therapies that are approved by the U.S. Food and Drug Administration for the treatment of metastatic renal cell carcinoma and are included in the treatment algorithm. The choice of drug is dependent on the context of the corresponding clinical trial, physician experience, drug availability, and patient preference.
- Currently there are no standard, routinely used baseline biomarkers to predict response and toxicities. Recent studies have found that the development of hypertension as well as other therapy-related toxicities and single nucleotide polymorphisms may indicate improved patient outcomes, but using these potential biomarkers still requires prospective validation.
- There are new agents on the horizon, including more targeted therapies and next-generation immunotherapy.

Table 1. A Proposed Treatment Algorithm for Patients with mRCC

Setting	Patients	Therapies with Level 1 Evidence	Other Options
First-Line Therapy	Good or intermediate risk	Sunitinib Pazopanib Bevacizumab + IFN	High dose IL-2 in highly select patients Sorafenib Clinical trial Observation in select patients
	Poor risk	Temsirolimus	Other VEGF inhibitors Clinical trial
Second-Line Therapy	Prior cytokines	Sorafenib Axitinib Pazopanib	Sunitinib Clinical trial
	Prior VEGF	Axitinib Everolimus	Targeted therapy not previously used Clinical trial
	Prior mTOR	No data available	Targeted therapy not previously used Clinical trial
Third-Line Therapy	Any	No data available	Targeted therapy not previously used Clinical trial

Abbreviations: IFN, interferon; IL, interleukin; mRCC, metastatic renal cell carcinoma; mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor.

---

the angiogenesis pathway that may be prognostic of OS, but predictive markers of response remain elusive.[12] Single nucleotide polymorphisms (SNPs) are single-base pair changes within a gene that may or may not affect gene function, and many have been explored for their prognostic or predictive value.

For patients treated with pazopanib, SNPs in two interleukin-8 and HIF1A loci were associated with a significant difference in PFS whereas SNPs in HIF1A, NR1/2, and three VEGFA loci were associated with overall response rates.[16] For patients treated with sunitinib, 136 patients with clear cell mRCC were examined to determine a favorable genetic profile, which was found to include an A allele in the CYP3A5 6986A/G loci, an absent CAT copy in the NR1/3 haplotype, and a TCG copy in the ABCB1 haplotype. Patients with this favorable profile had an improved PFS and OS compared to those without.[17] A VEGF SNP in a different loci was found to be associated with sunitinib-induced hypertension and another VEGF SNP and VEGF Receptor-2 SNP were found to be together associated with OS.[18] Another study found two VEGF Receptor-3 SNPs to be associated with PFS when treated with sunitinib.[19] These results are interesting but are currently restricted to the caucasian population, as there are substantial racial differences in SNPs. These SNPs require further prospective evaluation while ensuring correction for multiple testing to see whether incorporating them in the decision-making process of choosing targeted therapy for an individual patient improves outcome.

Recently, studies of toxicities due to targeted therapy have demonstrated better treatment outcomes when toxicity is encountered. For example, the development of hypertension during the first cycle of sunitinib treatment was associated with a better overall response rate, PFS, and OS.[20] Similar findings, including fatigue and hand-foot syndrome being

Table 2. Selected Ongoing mRCC Clinical Trials Investigating Sequencing, Combinations, and New Drugs

	Trials	Population	Randomization	Primary Endpoint
Sequencing	RECORD 3 Randomized Phase II NCT00903175	Treatment naive mRCC	Sunitinib → everolimus vs. everolimus → sunitinib	PFS of first-line treatment (finished accrual)
	START Trial Phase III NCT01217931	Treatment naive mRCC with nephrectomy	Pazopanib → bevacizumab vs. pazopanib → everolimus vs. everolimus → bevacizumab vs. everolimus → pazopanib vs. bevacizumab → pazopanib vs. bevacizumab → everolimus	Time to treatment failure of a sequence
	404 Study Phase III NCT00474786	mRCC refractory to sunitinib	Temsirolimus vs. sorafenib	PFS of second-line treatment (finished accrual)
Combinations	BEST Trial Phase III NCT 00378703	Treatment naive clear cell predominant mRCC	Bevacizumab vs. temsirolimus vs. bevacizumab + sorafenib vs. temsirolimus + sorafenib	PFS of first-line treatment
	CALGB 90,802 Phase III NCT01198158	mRCC with one prior VEGF inhibitor	Everolimus + bevaciuzmab vs. everolimus	OS
New Drugs	ADAPT Trial AGS-003 (Autologous Dendritic Cell Immunotherapy) Phase III	Treatment naive mRCC	AGS-003 with sunitinib/standard therapy vs. sunitinib/standard therapy	OS
	BMS936558 (PD-1 inhibitor) Phase II (phase III trial upcoming) NCT01354431	mRCC with at least one prior therapy	BMS936558 0.3 mg/kg q 3 weekly vs. BMS936558 2 mg/kg q 3 weekly vs. BMS936558 10 mg/kg q 3 weekly	PFS
	Dovitinib (TKI258) (FGF and VEGF inhibitor) Phase III NCT01030783	mRCC with clear cell component with one prior VEGF inhibitor and one prior mTOR inhibitor	Dovitinib vs. sorafenib	PFS of third-line treatment
	Tivozanib (AV951) (potent and specific VEGF inhibitor) Phase III NCT01030783	mRCC with clear cell component and previous nephrectomy	Tivozanib vs. sorafenib	PFS (data to be presented)

Abbreviations: FGF, fibroblast growth factor; mRCC, metastatic renal cell carcinoma; mTOR, mammalian target of rapamycin; OS, overall survival; PD-1, programmed death − 1; PFS, progression-free survival; VEGF, vascular endothelial growth factor.

associated with better outcomes, have been shown. These are important associations; however, clinicians should not discontinue targeted therapy if toxicities do not develop because the discriminatory value and accuracy in determining hypertension or other toxicities is unknown. Additionally, these biomarkers are only helpful once the administration of the drug has already started and thus do not help the clinician choose which drug to use initially.

Exploring New Agents and Mechanisms of Action

Newer agents are on the horizon to expand the treatment armamentarium in advanced RCC. They are not yet FDA approved at this time. A more potent and specific VEGF tyrosine kinase inhibitor Tivozanib (AV-951) is expected to report PFS endpoints against sorafenib in the treatment naive setting (Table 2). Dovitinib (TKI258) is a fibroblast growth factor (FGF) inhibitor as well as a VEGF inhibitor and is currently being studied as part of the GOLD trial against sorafenib in third-line therapy after failure of one VEGF and one mTOR inhibitor. The FGF pathway is hypothesized to be an angiogenic escape mechanism that is upregulated when the tumor develops resistance against our current VEGF and mTOR inhibitors. Dovitinib will test the hypothesis that targeting the FGF angiogenic escape mechanism will lead to further responses and prolongation of survival.

Next-generation immunotherapy is being investigated in mRCC. Programmed death-1 (PD-1) is a member of the immunoglobulin gene family and is expressed after T-cell activation to inhibit T-cell receptor signaling as a way to regulate the T-cell response. Higher preoperative soluble PD-1 ligand levels in patients with RCC were associated with larger tumors ($p < 0.001$), tumors of advanced stage ($p = 0.017$), grade ($p = 0.044$), and tumors with necrosis ($p = 0.003$). A doubling of these levels was associated with a 41% increased risk of death ($p = 0.010$).[21] Thus, not only is the upregulation of the PD-1 mechanism a potential prognostic factor, but it has become a potential target for next-generation immune-based targeted therapy.

BMS 936558 is a PD-1 inhibitor and was studied in a larger phase I multicenter trial where 126 patients (18 with RCC) were treated with several dose levels.[22] Across all doses, the most common adverse events grades 3 to 4 were fatigue (6.3%) and diarrhea (0.8%). One patient died with sepsis while being treated for drug-related grade 4 pneumonitis. There were 18 patients with mRCC, 16 of whom were treated with the 10 mg/kg dose. The objective investigator–assessed overall response rate was 31.2% (5 out of 16). The median duration of treatment was 7.6 months and the median duration of response was 4.0 months. Thus, a phase II dose-varying trial for mRCC is underway (Table 2), with a phase III trial anticipated shortly. This drug is promising but remains investigational at this time.

To further immunotherapy and personalized medicine, AGS-003 is being investigated. It is an autologous dendritic

cell immunotherapy in which a small tumor specimen isolated from the patient during nephrectomy or metastatectomy is taken along with a leukopheresis sample of monocytes that differentiate into dendritic cells. They are coelectroporated with the RCC and CD40L RNA and then eventually injected back into the patient. Recently, AGS-003 was studied along with sunitinib in a phase II trial of 21 patients with no grade 3 or 4 adverse events. The overall response rate was 38% and the median PFS was 11.2 months.[23] Because almost half of the patients had poor prognostic profiles,[14] this PFS is encouraging and warrants further study. Thus, a phase III randomized trial of AGS-003 with sunitinib/standard therapy compared with sunitinib/standard therapy is open and enrolling patients.

Conclusion

The treatment of mRCC has certainly evolved over the last 5 years, with more and more treatments available. There is an urgent need for biomarkers to help clinicians select which drug is most suitable for each specific patient. New drugs with different mechanisms of action are currently being investigated, making this an exciting time in the realm of mRCC research.

Authors' Disclosures of Potential Conflicts of Interest

Author	Employment or Leadership Positions	Consultant or Advisory Role	Stock Ownership	Honoraria	Research Funding	Expert Testimony	Other Remuneration
Daniel Y. C. Heng		Bayer; Novartis; Pfizer					
Toni K. Choueiri		Bayer; GlaxoSmithKline; Novartis; Pfizer			Pfizer		

REFERENCES

1. Rini BI, Small EJ. Biology and clinical development of vascular endothelial growth factor-targeted therapy in renal cell carcinoma. *J Clin Oncol.* 2005;23:1028-1043.

2. Jubb AM, Pham TQ, Hanby AM, et al. Expression of vascular endothelial growth factor, hypoxia inducible factor 1alpha, and carbonic anhydrase IX in human tumours. *J Clin Pathol.* 2004;57:504-512.

3. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med.* 2007;356:115-124.

4. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol.* 2010;28:1061-1068.

5. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. *J Clin Oncol.* 2010;28:2137-2143.

6. Escudier BJ, Bellmunt J, Negrier S, et al. Final results of the phase III, randomized, double-blind AVOREN trial of first-line bevacizumab (BEV) + interferon-α2a (IFN) in metastatic renal cell carcinoma (mRCC). *J Clin Oncol.* 2009;27:239s (suppl; abstr 5020).

7. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med.* 2007;356:2271-2281.

8. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med.* 2007;356:125-134.

9. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet.* 2008;372:449-456.

10. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet.* 2011;378:1931-1939.

11. Negrier S, Gravis G, Perol D, et al. Temsirolimus and bevacizumab, or sunitinib, or interferon alfa and bevacizumab for patients with advanced renal cell carcinoma (TORAVA): a randomised phase 2 trial. *Lancet Oncol.* 2011;12:673-680.

12. Tang PA, Vickers MM, Heng DY. Clinical and molecular prognostic factors in renal cell carcinoma: what we know so far. *Hematol Oncol Clin North Am.* 2011;25:871-891.

13. Motzer RJ, Bacik J, Murphy BA, et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol.* 2002;20:289-296.

14. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol.* 2009;27:5794-5799.

15. Heng DY, Xie W, Bjarnason GA, et al. A unified prognostic model for first- and second-line targeted therapy in metastatic renal cell carcinoma (mRCC): results from a large international study. *J Clin Oncol.* 2010;28:347s (suppl; abstr 4523).

16. Xu CF, Bing NX, Ball HA, et al. Pazopanib efficacy in renal cell carcinoma: evidence for predictive genetic markers in angiogenesis-related and exposure-related genes. *J Clin Oncol.* 2011;29:2557-2564.

17. van der Veldt AA, Eechoute K, Gelderblom H, et al. Genetic polymorphisms associated with a prolonged progression-free survival in patients with metastatic renal cell cancer treated with sunitinib. *Clin Cancer Res.* 2011;17:620-629.

18. Kim JJ, Vaziri SA, Rini BI, et al. Association of VEGF and VEGFR2 single nucleotide polymorphisms with hypertension and clinical outcome in metastatic clear cell renal cell carcinoma patients treated with sunitinib. *Cancer.* Epub 2011 Aug 31.

19. Garcia-Donas J, Esteban E, Leandro-Garcia LJ, et al. Single nucleotide polymorphism associations with response and toxic effects in patients with advanced renal-cell carcinoma treated with first-line sunitinib: a multicentre, observational, prospective study. *Lancet Oncol.* 2011;12:1143-1150.

20. Rini BI, Cohen DP, Lu DR, et al. Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst.* 2011;103:763-773.

21. Frigola X, Inman BA, Lohse CM, et al. Identification of a soluble form of B7-H1 that retains immunosuppressive activity and is associated with aggressive renal cell carcinoma. *Clin Cancer Res.* 2011;17:1915-1923.

22. McDermott DF, Drake CG, Sznol M, et al. A phase I study to evaluate safety and antitumor activity of biweekly BMS-936558 (anti-PD-1, MDX-1106/ONO-4538) in patients with RCC and other advanced refractory malignancies. *J Clin Oncol.* 2011;29 (suppl; abstr 331).

23. Figlin RA, Amin A, Dudek A, et al. Phase II study combining personalized dendritic cell (DC)-based therapy, AGS-003, with sunitinib in metastatic renal cell carcinoma (mRCC). *J Clin Oncol.* 2012;30 (suppl; abstr 348).