Journal of Carcinogenesis

Review Article

Targeted therapy for renal cell carcinoma: The next lap

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Published: 20 February, 2014
Journal of Carcinogenesis 2014,13:3
This article is available from: http://www.carcinogenesis.com/content/13/1/3

Received: 14 October, 2013
Accepted: 15 December, 2013

Abstract

Advances in rationally targeted therapeutics over the last decade have transformed the clinical care of advanced kidney cancer. While oncologists consolidate the gains of the wave of new agents, comprising a panoply of anti-vascular endothelial growth factor multi-targeted tyrosine kinase inhibitors and inhibitors of the mammalian target of rapamycin (mTOR), there is an increasing sense that a plateau has been reached in the short term. It is sobering that all currently approved targeted therapies have not yielded durable remissions and remain palliative in intent. In the context of recent insights in kidney cancer biology, we review promising ongoing and future approaches for kidney cancer therapeutics aimed toward forging new paths in the systemic management of renal cell carcinoma. Broadly, candidate agents for such innovative strategies include immune check-point inhibitors, anti-cancer stem cell agents, next-generation anti-vascular endothelial growth factor receptor and anti-mTOR agents as well as more investigational agents in the preclinical and early clinical development settings.

Keywords: Immunotherapy, renal cell carcinoma, targeted therapy, tyrosine kinase inhibitors

INTRODUCTION

Advances in targeted therapy has wrought a transformation in the clinical care of metastatic renal cell carcinoma (RCC), with the US Food and Drug Administration (FDA) approval of a series of agents active against the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways over the last decade, including sorafenib,[1,2] sunitinib,[3] bevacizumab,[4] temsirolimus,[5] everolimus,[6,7] pazopanib[8,9] and axitinib.[10,11] With the benefit of several years of clinical experience, it is recognized that while these agents clearly represented useful advances over traditional interferon-based therapies, none of these new agents have demonstrated durable long-term complete remissions in metastatic RCC, as has been possible in about 7% of individuals using high-dose interleukin (IL)-2 infusions.[12] Further, newer agents have generally shown only marginal benefits over the established predecessors in the same drug classes, raising concerns about a dearth of innovation. The maturation of this approach is represented through increasing discussions over optimal sequences and combinations of such therapies. The identification of novel therapies is therefore of interest for transcending the current therapeutic plateau. We review here recent insights on both clinical and laboratory fronts, focusing on new directions in rationally designed targeted therapy, including targeted immunotherapy. Given the importance of developing new directions beyond the current state of the art of management, this review will favor discussions of efficacy over toxicity.

Access this article online

Quick Response Code:

Website: www.carcinogenesis.com

DOI: 10.4103/1477-3163.127638

BIOLOGY

Epithelial RCC is a heterogeneous disease comprising multiple entities. Several major histological subtypes are recognized, including clear cell renal cell carcinoma (ccRCC) (~75%), papillary RCC (~15%) and chromophobe RCC (5%), with mixed tumors also being commonly seen. Most recently in late 2013, the International Society of Urological Pathology proposed the Vancouver Classification of Renal Neoplasia[13] recognizing rarer variants such as tubulocystic RCC, acquired cystic disease–associated RCC, clear cell (tubulo) papillary RCC, the MiT family translocation RCCs (in particular t (6;11) RCC) and hereditary leiomyomatosis RCC syndrome–associated RCC. Each individual entity has distinct germline and somatic genetic and molecular expression programs,[14] serving as a potential basis for developing precision medicine guided approaches to diagnostic and therapeutic. We review here several key biological insights in the last 5 years which are likely to underpin upcoming investigational drug development for RCC.

Progress in genetics

The key insight for ccRCC biology was the identification of germline von Hippel-Lindau (*VHL*) mutations underpinning the VHL syndrome, a hereditary multi-tumor syndrome in the early 1990s,[15] and the corresponding identification of somatic *VHL* mutations in sporadic ccRCC. Long recognized since the 19th century, the myriad manifestations of VHL syndrome included ccRCC, craniospinal and ophthalmic hemangioblastoma, pheochromocytoma, pancreatic and renal cysts. *VHL* is regarded as a gatekeeper gene of ccRCC[16] in view of its relatively high somatic mutation prevalence (30-60%) in ccRCC and the existence of somatic mutations in non-malignant renal cysts adjacent to the tumor. Over 90% of ccRCC tumors show loss of one arm of chromosome 3p, resulting in allelic loss of *VHL*. pVHL mediates the ubiquitination-mediated pathway of hypoxia inducible factor (HIF) degradation, with mutant pVHL forms resulting in excess HIF and consequently, upregulated angiogenesis and glucose transport. While each of these downstream pathways is of therapeutic interest, angiogenesis inhibition in RCC has taken center stage since 2006 with the demonstration of clinical efficacy of tyrosine-kinase inhibitors and monoclonal antibodies in advanced RCC.

Several other germline alterations have been implicated in RCC (*MET* activating mutations in hereditary papillary RCC, *FH* mutations in hereditary leiomyomatosis-RCC syndrome, *FLCN* mutations in Birt-Hogg-Dube syndrome), but unlike *VHL*, these germline mutations are rarely identified in sporadic tumors. Hence, whereas it is commonly assumed that similar pathways are dysregulated in sporadic renal tumors, it is less clear that therapeutic strategies aimed at these genetic alterations and downstream pathways represent an optimal strategy.

In recent years, next-generation sequencing techniques have provided further insights into the genetics of RCC, highlighting several key biological themes through identification of somatic mutations of genes involved in sporadic RCC, particularly ccRCC. Notably, high frequencies of truncating somatic mutations in genes involved in chromatin modification have been demonstrated in several studies.[17-19] In particular, involved genes included histone modifying genes *PBRM1*, *SETD2*, *KDM5C*, *KDM6A* and *BAP1,*[20,21] and genes involved in the ubiquitin-mediated proteolysis pathway.[21] *PBRM1* encodes the BAF180 protein, a subunit of the SWI/SNF complex which targets chromatin. BAP1 encodes for BRCA1 associated protein-1, which is involved in histone deubiquitination. This body of work has been received with significant interest as animal models have by and large been unable to directly recapitulate the link between *VHL* mutation and carcinogenesis,[22] suggesting that additional genetic "hits" are required for renal carcinogenesis to occur. In the above studies, deoxyribonucleic acid (DNA) repair has also been identified as a possible theme in ccRCC, with mutations identified in *PMS1*, *WRN* and *NBN*, which are genes encoding DNA repair enzymes. It is expected that over the next few years, the molecular pathways dysregulated by these recently discovered somatic mutations will be unraveled.

Additional recent comprehensive molecular characterization studies of ccRCC have been conducted in the USA[23] and Japan,[24] integrating techniques such as whole-exome sequencing, whole-genome sequencing, ribonucleic acid (RNA) sequencing, array-based expression, micro-RNA profiling and methylation analyses. These have generally confirmed the findings of the earlier next-generation sequencing studies, but several themes were in addition highlighted, including recurrent mutations of PI3K-AKT-mTOR pathway; expression studies demonstrated metabolic derangement in aggressive ccRCC where genes involved in the pentose phosphate pathway and the glutamine pathway were overexpressed, with down regulation of genes expressed in the tricarboxylic acid cycle. The Japanese group additionally identified hotspot *TCEB1* mutations in a small proportion of samples (8/240) mutually exclusive with *VHL* mutations. These mutations prevented elongin C-pVHL binding, with consequent HIF accumulation. While translation into therapies will take time, these insights into novel biological themes will certainly serve as the foundation for a fruitful clinical research program aimed at identifying newer therapeutic approaches.

Tumor heterogeneity and single cell analysis

Recent landmark articles studying tumor heterogeneity have provided considerable insight into the complex architecture of ccRCC. The presence of intratumor heterogeneity has been elegantly and directly demonstrated using spatially separated samples obtained from primary and metastatic RCC tumors,[25] as well as through single cell analysis using the high throughput sequencing approaches.[26] Practically, this work provides important guidance on therapeutic failure through intratumor heterogeneity – in essence, given the variation of mutations spatially and between cells, the sobering concern that rationally targeted therapy based on targeting mutant pathways in the cancer cell will be fundamentally limited in curative potential is a real problem that has to be confronted. From a more basic point of view, these studies showing extensive intratumor heterogeneity as well as convergent phenotypic mutational evolution highlight that most next-generation sequencing approaches today utilizing bulk tissue may underestimate the diversity of mutations and expression profiles within a single tumor. It therefore provokes the question whether approaches that indirectly target cancer through tumor microenvironment or the immune system may have superior outcomes; certainly the observation that high-dose IL-2 is of curative potential in metastatic RCC[12] supports this idea.

Cancer stem cell markers

The CSC hypothesis suggests that tumors are sustained by a subpopulation of cells, known as CSCs or tumor-initiating cells, which are able to initiate and renew tumor recapitulating the tumor of origin.[27] In ccRCC, a putative marker CD105, also known as endoglin, has been reported to distinguish a rare subpopulation of cells that exhibit CSC properties.[28,29] These CD105-positive cells demonstrate clonal growth, express stem cell markers and are able to recapitulate tumors in immunosuppressed mice. Importantly, these cells release microvesicles that are proangiogenic and enhance lung metastases, suggesting a role in the formation of the pre-metastatic niche.[30] IL-15 has been identified as a possible agent to target these cells for differentiation.[31] Other markers have been investigated as putative markers for CSCs, including CD133,[32] and the side population using the Hoescht 33342 dye efflux study,[33] but these have not reliably demonstrated CSC properties. Overall, it is suggestive that CD105 may be of potential value as a novel target though there are potential concerns of off-target effects.

THERAPEUTIC STRATEGIES

Many new agents are being evaluated for the treatment of metastatic RCC, which may be broadly and somewhat arbitrarily classified into "canonical" and "emerging" approaches, depending on whether the agent has activity in previously established biological pathways of RCC management. Canonical approaches would include small molecule tyrosine kinase inhibition, with special focus on the VEGF and PDGF pathways, vascular endothelial growth factor receptor (VEGFR) blockade and mTOR inhibition. Emerging approaches would include agents at the preclinical and early clinical stages focused on novel pathways in RCC. Clinical trials that are currently open are summarized in Table 1.

Canonical approaches

A slew of tyrosine kinase inhibitors

There have been an abundance of anti-VEGFR small molecules approved for RCC therapeutics, including sunitinib,[3] sorafenib,[1] pazopanib[9] and axitinib.[11] Indeed, while there are some differences in terms of toxicities between the agents in clinical practice, there has been little evidence to suggest clear advantages in efficacy, with pazopanib being most recently demonstrated to be non-inferior to sunitinib in terms of survival in the first-line management of metastatic RCC.[34] It is not clear that comparisons of differences in survival between Phase 3 trials are meaningful for deriving information on efficacy. While comparison studies are useful to guide daily practice, it is also true that such trials of drugs in the same class are unlikely to yield major concrete gains based on the current state of the art. Currently, many such agents are being investigated in Phase II and III trials, including dovitinib, tivozanib, cedirafenib, regorafenib, vandetanib and more. In what may be a herald for the future for Phase III trials for agents in this class, tivozanib was recently rejected by the U.S. FDA for concerns over overall survival relative to sorafenib,[35] and dovitinib failed to demonstrate progression-free survival over sorafenib.[36] It may be noted that chemical modification through drug encapsulation may be an interesting strategy to modify the properties of drugs, including efficacy and toxicities, allowing for a more favorable biodistribution. While liposomal formulations of cytotoxics such as doxorubicin and paclitaxel are commonly used in the clinical practice, similar methods for the TKIs are still in development,[37] and outcomes in the human setting have not been established.

Anti-VEGF/VEGFR blockade

Bevacizumab was the first in the class of anti-VEGFR monoclonal antibodies to be approved for use in metastatic RCC in combination with interferon.[38] Several other related agents are under investigation, including ziv-aflibercept (a soluble decoy receptor that binds to VEGF) and ramicirumab (a fully human IgG1 mAb targeting VEGFR-2) are currently under evaluation in Phase II studies (NCT00357760 and NCT00515697).[39]

Table 1: Novel rationally targeted agents currently under investigation in RCC*

NCT number	Agent	Phases	Description
NCT01672775	AGS-16C3F	I	Anti-ENPP3 antibody-drug conjugate
NCT01497821	AMG 172	I	Anti-CD70 antibody-drug conjugate
NCT01283048	BKM-120	I	PI3K inhibitor
NCT01806064	TRC105	I	Anti-endoglin antibody
NCT01677390	SGN-75	I	Anti-CD70 antibody-drug conjugate
NCT01482156	BEZ235	I	PI3K/mTOR kinase inhibitor
NCT01005797	Panobinostat (LBH589)	I	Histone deacetylase inhibitor
NCT01480154	MK2206	I	AKT inhibitor
NCT01548482	Trebananib	I	Angiopoietin 1 and 2 neutralizing peptibody
NCT01391143	MGA271	I	Anti-B7-H3 antibody
NCT01460134	CDX-1127	I	Anti-CD27 monoclonal antibody
NCT01038778	Entinostat	I/II	HDAC inhibitor
NCT01582009	Panobinostat (LBH589)	I/II	HDAC inhibitor
NCT00184015	Bortezomib	I/II	Proteosome inhibitor
NCT01762033	sonepcizumab (LT1009)	II	Anti-sphingosine-1-phosphate antibody
NCT00357760	Ziv-Aflibercept	II	Soluble receptor that binds to VEGF-A, VEGF-B and PDGF
NCT01835158	Cabozantinib	II	c-Met and VEGFR-2 inhibitor
NCT01688973	Tivanitinib	II	c-Met inhibitor
NCT01664182	Trebananib	II	Angiopoietin 1 and 2 neutralizing peptibody
NCT01727089	TRC105	II	Anti-endoglin antibody
NCT01441765	CT-011	II	Anti-PD-1 antibody
NCT01793636	AZD2014	II	mTOR inhibitor
NCT00566995	Vandetanib	II	VEGFR-2 and EGFR inhibitor
NCT01524926	Crizotinib	II	ALK inhibitor
NCT01865747	Cabozantinib	III	c-Met and VEGFR-2 inhibitor
NCT01668784	Nivolumab (BMS-936558)	III	Anti-PD-1 antibody

*Search on 28/9/2013 of clinical trials.gov requiring open, recruiting interventional trials of known status for "RCC" (286 hits) with subsequent manual curation. This list does not include trials that have closed. RCC: Renal cell carcinoma; mTOR: Mammalian target of rapamycin; HDAC: Histone deacetylase; VEGF: Vascular endothelial growth factor; PD-1: Programmed death-1; VEGFR-2: Vascular endothelial growth factor receptor-2; EGFR: Epidermal growth factor receptor; ALK: Anaplastic lymphoma kinase

The many splendored PI3K-AKT-mTOR pathway

The molecular signaling pathway of PI3K/AKT/mTOR[40] has been regularly implicated in RCC, where most recently, recurrent pathway mutations have been identified in comprehensive next generation sequencing studies as described above.[23,24] Of interest, it should be noted that in the Japanese analysis,[24] although 26% of cases had mutations involving the PI3K-AKT-mTOR pathway, the most commonly mutated gene in this pathway mTOR had only a mutant prevalence of 5.7%. In addition, other than the known tumor suppressor genes (PTEN, tuberous sclerosis complex 1 [TSC1] and TSC2), the remaining mutations in other genes were not truncating in nature. The canonical pathway is activated by the binding of growth factors/ligands such as insulin-like growth factor or fibroblast growth factor (FGF) to their respective receptors leading to the recruitment of PI3K. This initiates a cascade of events starting with the conversion of phosphatidylinositol-4,5-phosphate (PIP2) to PIP3 which in turn activates AKT. Activated AKT indirectly activates mTOR through a phosphorylation of a number of targets downstream. Once activated, mTOR affects cell growth, proliferation, angiogenesis and metabolism.[41] mTOR exerts its effects through 2 different multiprotein signaling complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2).[41] mTORC1 is activated by the inhibition of TSC2, which subsequently activates ribosomal S6 kinase and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1). In cancer cells, 4E-BP1 phosphorylation results in translation initiation. Activation of the mTORC1 downstream targets results in modulation of the activity of cell cycle regulating proteins like HIF, FGF, VEGF, STAT3, cyclin D and c-Myc.[42-44] Activated mTORC2 phosphorylates the hydrophobic motif of the AGC kinase family thereby inducing AKT activation.[45] Strong expression of various mTOR pathway proteins (PI3K, p-AKT, p-MTOR, p-70S6K) is observed in RCC relative to non-neoplastic kidney.[46,47] Beyond temsirolimus and everolimus, there have been a slew of second generation mTOR inhibitors that have been developed and are currently being evaluated in clinical trials. Therapies developed against this pathway target it at several levels. These include selective inhibitors of mTOR itself, AKT, PI3K individually or combination of mTOR/PI3K inhibitors. A number of new mTOR inhibitors like AZD8055 have shown promising activity in pre-clinical studies[48] and have entered Phase I trials.[49] Amongst the PI3K inhibitors, BKM120 has shown good preclinical activity and is being evaluated in by itself and also in combination with drugs like bevacizumab in metastatic RCC patients who had failed anti-VEGFR therapy (NCT01239342). A dual inhibitor of PI3K and mTOR (NVP-BEZ235) has demonstrated better *in vitro* antiproliferative effects compared to rapamycin[50] and is currently in Phase I/II trials (NCT01453595). All this activity suggests that the PI3K-AKT-mTOR pathway remains of high interest from the perspective of drug discovery, particularly in the context of patients who have developed resistance to anti-VEGFR therapies,[51] consistent with the current fundamental insights afforded by next generation sequencing as described above.

Emerging therapeutics

Immune reinvigoration through programmed death-1 and programmed death ligand-1 inhibition

PD-1 and PD-L1 inhibitors are an exciting new class of agents targeting cancer cells via an immune modulated

mechanism ("immune checkpoint blockade").[52] The PD-1 pathway is an important tumor-evasion mechanism, with the two principal components of the PD-1 pathway comprising PD-1 (CD279), an inhibitory receptor expressed on the surface of activated T cells, B cells and myeloid cells and PD-L1, which is expressed on cancer cells. When PD-1 and PD-L1 are bound in a complex, T cell proliferation and survival is inhibited. Conversely, PD-1 blockade leads to auto-reactive T cell formation.[53] PD-L1 expression has been associated with poor prognosis in both primary and metastatic RCC.[54-56] Thus, targeting either PD-1 or PD-L1 may stimulate the immune system and enhance tumor-specific cytotoxicity of T-cells. Currently, anti-PD-1 inhibition with nivolumab (BMS-936558) is already being evaluated in a Phase III study in metastatic RCC (NCT01668784). The basis for this was derived from observations of durable responses for nivolumab in heavily pretreated metastatic RCC approximating 27%,[57] as well as early data showing reasonable safety profiles, even after long term continuous dosing.[58] Currently, PD-L1 antibody activity is also being actively investigated, with potentially exciting outcomes. In two recent reports, durable responses (including complete responses) were also observed in metastatic RCC with PD-L1 antibody (MPDL3280A).[59,60] Potential tumor biomarkers of efficacy have been identified for anti-PD-L1 antibody such as PD-L1 status and low IL-17 expression. These biomarkers may provide guidance as to further mechanistic evaluation.[59] The continuous rather than bimodal expression of these proteins represents a challenge for PD-L1 as a clinical-grade biomarker.[56] Overall, toxicities of these agents seem fairly limited and these very exciting results show the significant potential for targeted immunotherapy to transform RCC management in the short term. A major area for future development may be the adjunctive use of stimulatory agents for anti-tumor immunity, given the recent discovery of mechanisms of immune escape through PD-L1 mediated immune down regulation.[61] Indeed, multiple studies are currently ongoing exploring combinations of these agents with dendritic cell vaccines (NCT01441765), tyrosine kinase inhibitors or ipilumumab (NCT01472081).[62]

Anti-CSC approaches

The identification of CD105/endoglin as a potential CSC marker in ccRCC is an important advance,[28] and the biology of this has been discussed above. The evaluation of anti-CD105/endoglin antibodies in RCC is a logical extension of this work. A Phase II trial (NCT01727089) evaluating TRC105, a chimeric IgG1 monoclonal antibody that binds CD105 (endoglin), is currently recruiting patients with RCC. In a Phase I trial, dose-limiting toxicities was essentially hypoproliferative anemia,[63] which is a likely off-target effect arising from the expression of CD105 in hematopoietic stem cells.[64]

Anti-angiogenesis as a common endpoint

Beyond anti-VEGFR TKIs and antibody blockade, inhibition of other pathways is being considered toward a common endpoint of anti-angiogenesis. Vascular disrupting agents (VDA) recognize and disrupt tumor blood supply by targeting dysmorphic endothelial cells and pericytes on the tumor vasculature. Compared to the anti-VEGFR and mTOR inhibitors, VDAs exert a cytotoxic rather than cytostatic effect. Small molecule VDAs are either flavonoids or tubulin binding agents. An example of such a drug is BNC105, which is a tubulin polymerization inhibitor. A multicenter Phase I/II clinical trial testing the combination of BNC105 and everolimus in the second-line treatment of mRCC has been recently completed (NCT01034631).

Inhibition of the angiopoietin/TIE2 pathway through the use of agents such as trebananib (AMG 386) is also being considered both alone and in combination with other agents including sorafenib,[65] sunitinib and temsirolimus (NCT01548482). Currently, AMG 386 does not appear to improve progression-free survival when used in combination with sorafenib versus sorafenib alone.[65]

The Notch pathway which mediates angiogenesis has been identified as another potential target in anticancer drug development. A Notch signaling pathway inhibitor, R04929097, is currently in use in a Phase I trial in mRCC patients that have failed anti-VEGF therapy (NCT01141569).

Antibody drug conjugates

ADCs represent a novel method in the treatment of mRCC. Such conjugates have received significant attention since positive results in breast cancer were reported for TDM-1,[66] a conjugate of the monoclonal antibody trastuzumab and the cytotoxic maytansine. These ADCs are composed of a monoclonal antibody that can bind to specific target receptors (antigens) on the RCC cell and a conjugated cytotoxic payload. The main target of this antibody is CD70 that is expressed on these cells. An example of this drug antibody conjugate is MDX-1203 which is conjugated to rachelmycin (CC1065) (prodrug), which exerts an alkylating action on adenine in dividing cells resulting in cell death.[67] This conjugate is currently under evaluation in advanced RCC patients (NCT00944905) and results are pending. Other anti-CD70 agents currently being investigated include MDX-1411 (NCT00656734) and SGN-75 (NCT01015911).

Carbonic anhydrase IX targeting

Radio-labeled antibodies are also being evaluated in mRCC patients, particularly through targeting of CAIX, a cell surface antigen. This cell surface antigen is highly expressed in RCC but is absent in normal renal

epithelium.[68] G250 is a murine monoclonal antibody that targets CAIX and a chimeric version of this antibody, cG250 has shown antibody dependent cellular toxicity against RCC cells *in vitro*.[69] This antibody has also been tested in preclinical trials in combination with interferon gamma with promising synergistic tumoricidal activity noted.[70] A Phase II study has been conducted,[71] and a study of cG250 conjugated to yttrium-90 is currently ongoing (NCT00199875).

Histone deacetylase inhibitors

Of late a new class of drugs called histone deacetylase (HDAC) inhibitors have come to the forefront of cancer therapeutics. This was after the discovery that aberrant HDAC activity play an important role in carcinogenesis.[72] Its activity seems related to the recruitment of the BcL-2 family of genes. HDAC inhibitors that have been tested in metastatic RCC include LBH589 (panobinostat) and entinostat. In a recent phase II trial of patients that have had at least one prior TKI or mTOR inhibitor, panobinostat was well-tolerated but with no objective responses noted.[73]

Other candidate pathways

There are several candidate pathways of strong interest in RCC as identified in the pre-clinical setting. Signal transducer and activator of transcription 3, also known as STAT3, is a transcription factor which in humans is encoded by the STAT3 gene. It is involved in several signaling pathways that regulate cell survival and proliferation and it is aberrantly activated in RCC.[74] A STAT3 inhibitor (WP1066) has demonstrated antiproliferative activity in RCC cell lines and *in vivo* on murine xenografts.[75] Similarly, aurora kinases, oncogenic serine-threonine kinases that regulate the cell cycle, are key regulators of mitosis and have been found to be overexpressed in RCC.[76] Preclinical work has demonstrated that inhibition of these pathways through VX680 (a pan-aurora kinase inhibitor) similarly leads to significant cell death in RCC *in vitro* and in animal models, with additional anti-angiogenic effects.[76]

CONCLUSION

The systemic management of RCC has matured in recent years, with the development of a slew of rationally targeted therapies focusing on inhibition of the VEGF and mTOR pathways. The primary therapeutic approach to metastatic RCC remains palliative in nature, with the notable exception of a limited subset of patients experiencing durable complete remissions with high-dose IL-2. Beyond consolidating past gains through improved combinations and sequencing of existing agents, several promising leads for rationally targeted treatment have opened-up new directions for exploration and clinical investigation, with the hope of continuing to advance clinical care.

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How to cite this article: Kanesvaran R, Tan M. Targeted therapy for renal cell carcinoma: The next lap. J Carcinog 2014;13:3.

Source and Support: ???? **Conflict of Interest:** R. K. is an advisory board member for Glaxo-Smith-Kline. M. H. T. has filed patents for predictive biomarkers for kidney cancer.

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