

# Metastatic renal cell carcinoma: update on epidemiology, genetics, and therapeutic modalities

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**Abstract:** The treatment of advanced renal cell carcinoma (RCC) remains a major therapeutic challenge for clinicians. Despite advances in the understanding of the immunobiology of RCC and the availability of several novel targeted agents, there has been little improvement in the survival of patients with metastatic RCC. This review will focus on the recent understanding of risk factors and treatment options and outcomes of metastatic RCC, in particular, targeted therapeutic agents that inhibit vascular endothelial growth factor and mammalian target of rapamycin pathways. Prospective studies are required to determine whether sequential targeted therapy will further improve progression-free survival in RCC. Ongoing research to develop novel agents with better tolerability and enhanced efficacy in the treatment of metastatic RCC is required.

**Keywords:** metastatic renal cell carcinoma, targeted treatment, immunotherapy, cytokines

## Introduction

Renal cell carcinoma (RCC) is usually a highly vascularized malignancy arising from the lining of the proximal convoluted tubules within the kidney, and is the most common form of kidney cancer in adults.<sup>1,2</sup> Most RCCs are asymptomatic and are detected incidentally on imaging. The classic triad of symptoms (macroscopic hematuria, abdominal mass, and flank pain) occur in less than 20% of patients.<sup>3</sup> Both genetic and environmental risk factors for RCC have been identified, but the etiology of a large proportion of RCCs remains unclear. Patients with metastatic RCC have a poorer prognosis, as these cancers are relatively resistant to chemoradiotherapy. Since the introduction of targeted therapy, overall progression-free survival has improved to over 15 months from less than 5 months with nontargeted therapy, but the optimal methods and frequency of delivery of these agents are largely unclear. This review will focus on the treatment outcomes of metastatic RCC, including surgery, radiotherapy, and targeted and nontargeted therapies. Nonparenchymal kidney cancers (eg, urothelial tumors) and kidney cancers in children (eg, Wilms's tumor) will not be discussed.

## Prevalence

RCC is the 14th most common cause of cancer in the general population, accounting for 2%–3% of all new cancer cases detected per year worldwide. The estimated worldwide incidence of RCC is 15 cases per 100,000 population, but there is a higher incidence in males (annual incidence of 20.7 per 100,000 population) compared with females (annual incidence of 10.5 per 100,000 population).<sup>4</sup> The incidence of RCC varies among countries, and is up to 15-fold higher in Europe, North America, and Australia compared to Asia and Africa, suggesting the possibility of dissimilar patterns

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of risk-factor exposure among various countries (Figure 1).<sup>5</sup> The incidence of RCC peaked in the mid-1990s, possibly reflecting the improvement in imaging modalities, but has since declined.<sup>5,6</sup> Better understanding of RCC risk factors allowing target intervention to avoid or modify potential risk factors may have contributed to the decreasing incidence over the last decade.<sup>5</sup>

In kidney-transplant recipients, de novo RCC of the native kidneys is the second most common cancer occurring post-transplant, after nonmelanoma skin cancer.<sup>7</sup> Although de novo RCC can develop in the renal allograft, the incidence is much lower (0.2%–0.5%) compared to de novo RCC of the native kidneys (1%–5%).<sup>8,9</sup> In kidney transplant recipients, the risks of developing RCC from native kidneys are ten- to 100-fold greater compared with end-stage kidney disease patients on dialysis.<sup>10,11</sup> Apart from the traditional risk factors associated with RCC identified in the general population, there is a strong association between increasing dialysis duration pretransplant and development of RCC in kidney-transplant recipients.<sup>8,12</sup> The median time to diagnosis of RCC in the transplant recipients and general population is comparable, at 132 months (range 1–244 months), but RCCs in kidney-transplant recipients generally have a more favorable prognosis (except for stage IV RCC) compared with similar cancers in the general population.<sup>7,13</sup> In the general population and kidney-transplant recipients, RCCs confined to the kidney

have a better prognosis and are potentially curable following partial or total nephrectomy. Metastatic RCCs are poorly responsive to treatment and have a poorer prognosis.<sup>14</sup>

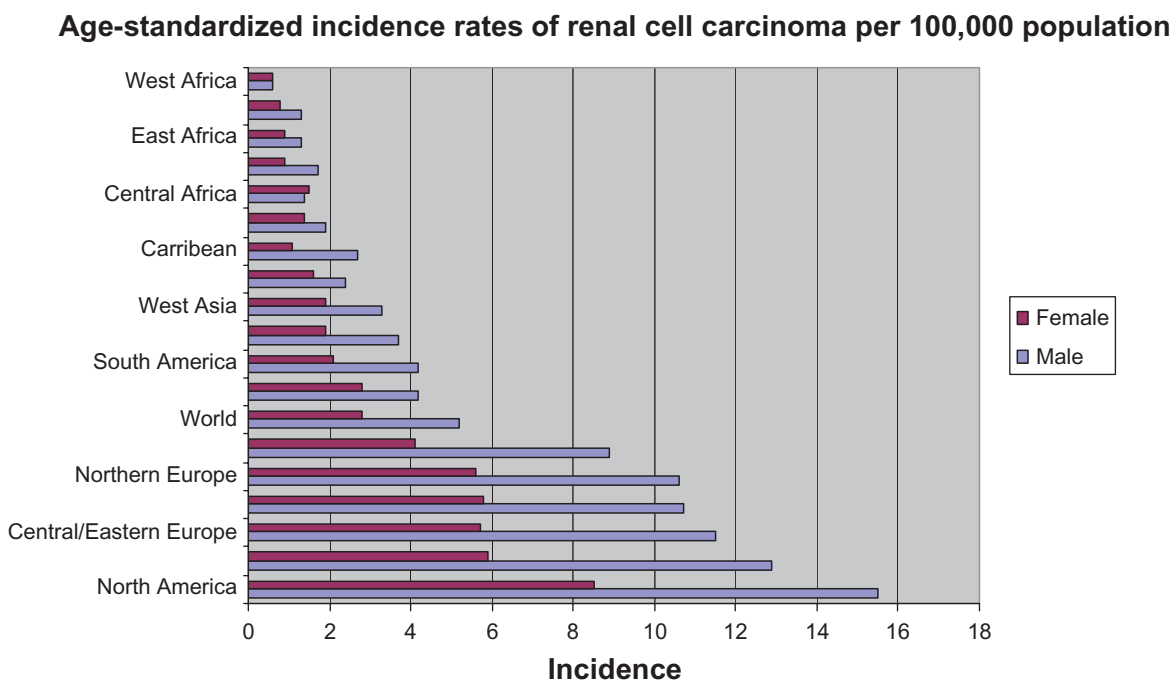
The mean age at diagnosis of RCC in the general population is 64 years, and the incidence of RCC continues to rise with increasing age (Figure 2).<sup>15</sup> Although the majority of RCCs are localized at the time of diagnosis, one in three cases are at an advanced stage on initial presentation. The 5-year survival rates of patients with and without metastatic disease at presentation are 10% and 85%, respectively.<sup>16</sup>

## Risk factors

Risk factors for RCC include genetic and environmental factors, and these are shown in Table 1. There is a strong association between increasing body mass index and the risk of RCC, such that for every 5 kg/m<sup>2</sup> increase in body mass index, there is a 24% and 34% increased risk of RCC in males and females, respectively.<sup>5</sup> Similarly, tobacco exposure is associated with a 50% and 20% greater risk of RCC in males and females, respectively.<sup>5</sup>

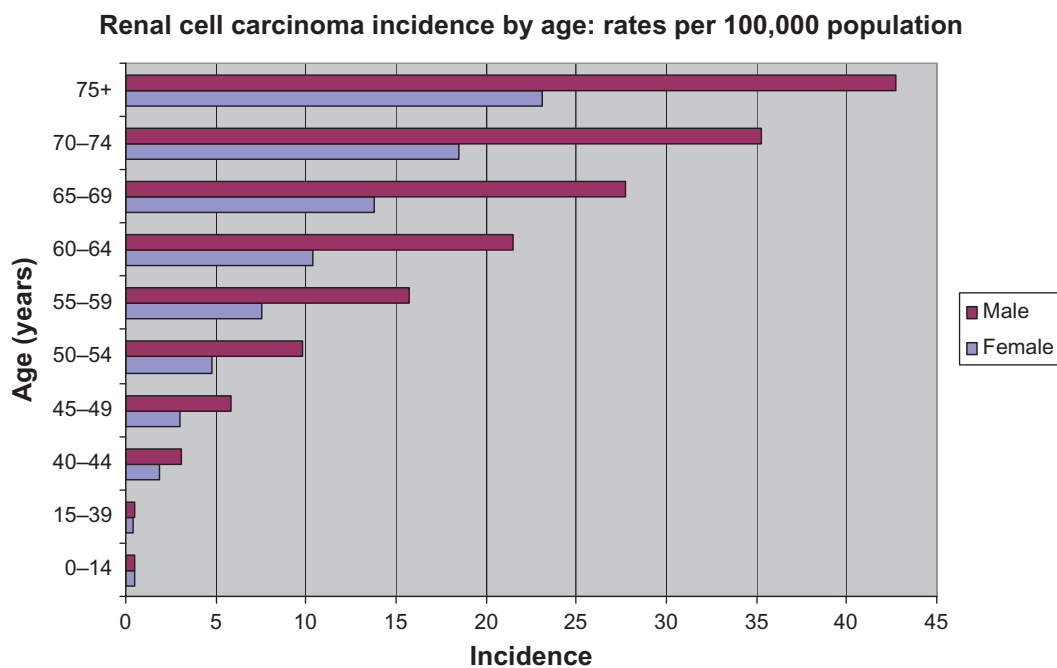
## Genetic factors

The identification of several gene mutations has provided new insights into the immunobiology of RCC, which is crucial in prognosis and the future development of novel treatment for this cancer. Although the most recognized



**Figure 1** Age-standardized incidence rates of renal cell carcinoma according to sex and country.

**Notes:** Data extracted from Cancer Research UK.<sup>17</sup> Original source of data from Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: <http://globocan.iarc.fr>. Accessed July 16, 2013.<sup>18</sup>



**Figure 2** Incidence rates of renal cell carcinoma stratified by age-group.

**Notes:** Data extracted from Cancer Research UK.<sup>17</sup> Original source of data from Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: <http://globocan.iarc.fr>. Accessed July 16, 2013.<sup>18</sup>

genetic abnormality in RCC is inactivation of the Von Hippel–Lindau (VHL) tumor-suppressor gene, a recent large-scale screen has identified mutations of the SWI/SNF chromatin-remodeling complex gene *PBRM1* to be a common finding in up to 40% patients with RCC.<sup>19</sup> Individuals with familial VHL syndrome are predisposed to develop multiple RCCs at

a younger age, often in association with other nonmalignant tumors, including pheochromocytomas and central nervous system (CNS) hemangiomas. The underlying genetic defect of this syndrome is inactivation of the *VHL* gene, a tumor-suppressor gene encoding for VHL protein.<sup>20</sup> It is generally believed that the development of RCC in individuals with VHL syndrome requires an inherited *VHL* gene mutation (ie, protein's normal function is reduced or lost), followed by a second acquired mutation of the companion allele. However, sporadic cases of RCCs attributed to acquired biallelic *VHL* gene inactivation are not uncommon.<sup>21</sup> VHL protein undergoes posttranscriptional modification to form the E3 ubiquitin–ligase complex, which hydroxylates and degrades hypoxia-inducible factor (HIF)-1 $\alpha$  and HIF-2 $\alpha$  under normoxic conditions.<sup>16,22–25</sup> In the presence of *VHL* gene inactivation and/or hypoxic conditions, active HIF proteins heterodimerize and promote transcription of proproliferative and proangiogenic proteins, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which result in abnormal cellular growth and the potential for tumor formation.<sup>26</sup> VEGF is a potent inducer of angiogenesis and vasculogenesis, and the binding of VEGF to VEGF receptor (VEGFR)-2 leads to upregulation of molecules crucial in the proliferation, migration, and survival of endothelial cells.<sup>27</sup> Cancers that are able to overexpress VEGF are capable of growing and metastasizing. Although one

**Table 1** Modifiable and nonmodifiable risk factors associated with the development of renal cell carcinoma

Nonmodifiable	Modifiable
Age	Obesity <sup>5</sup>
Sex	Smoking <sup>5</sup>
Height <sup>138</sup>	Hypertension <sup>139</sup>
Acquired cystic disease <sup>140</sup>	Drugs
– End-stage renal disease patients on maintenance dialysis	– Nonsteroidal anti-inflammatory drugs <sup>141</sup>
	– Aristolochic acid <sup>142</sup>
	– Occupational exposure to arsenic/cadmium/trichloroethylene
Prior radiotherapy	Multiparous females <sup>5</sup>
Family history (especially sibling) <sup>143</sup>	
Thyroid carcinoma	
Genetics	
– Von Hippel–Lindau syndrome	
– Hereditary papillary renal cell carcinoma	
– Hereditary leiomyomatous renal cell carcinoma	
– Birt–Hogg–Dubé syndrome	

of the main actions of VEGF-targeted therapy is inhibiting new blood-vessel growth, therefore starving the tumor cells of the necessary oxygen and nutrients to sustain continued growth, the full therapeutic potential of this agent is relatively complex and likely to involve multiple mechanisms.<sup>28</sup> The mammalian target of rapamycin (mTOR) pathway is also capable of regulating cellular growth in response to hypoxic conditions. mTOR is a serine/threonine kinase activated in a pathway involving VEGF along with other growth factors and protein kinases.<sup>29</sup> In RCC, mTOR expression is significantly increased, and tumors with high levels of mTOR expression have been shown to be more aggressive and associated with a poorer prognosis. Interestingly, the use of chemotherapeutic agents and ionizing radiation have been shown to enhance mTOR expression by activating upstream regulators of mTOR, which in part may contribute to the lack of efficacy of these therapies in the treatment of RCC.<sup>30</sup>

Although multiple genetic mutations have been identified for all RCC subtypes, *VHL* gene inactivation appears to be restricted to clear-cell RCC. Other reported genetic mutations identified for clear-cell RCCs include deletions of parts of chromosome 3p, mutation of gene *PBRM1*, gain of chromosome 5q and loss of 8p, 9p, and 14q; trisomy of chromosomes 7 and 17, loss of the Y chromosome, gain of chromosomes 12, 16, and 20, mutation of the tricarboxylic acid cycle enzyme fumarate-hydratase (a tumor-suppressive gene), and rare mutations of the Met proto-oncogene reported for papillary RCCs; and mutations of the tumor-suppressor folliculin gene and loss of chromosomes 1, 2, 6, 10, 13, 17, 21, and Y reported for chromophobe RCCs.<sup>19,31–33</sup>

## Types of renal cell carcinoma

Although there are multiple histological subtypes of RCC, clear-cell RCCs are the most common and account for up to 80% of RCC in the general population. The characteristic histological appearance of clear-cell RCCs is the clear cytoplasm and well-defined cell membrane, with the transparent cytoplasm attributed to accumulation of cholesterol esters, glycogen, and phospholipids.<sup>20</sup> In contrast to the general population, papillary cell RCC is the predominant cancer type in kidney-transplant recipients (15% versus [vs] 44%) and is more likely to be bilateral and multifocal at initial presentation.<sup>10</sup> Chromophobe RCCs are relatively uncommon, and account for up to 5% of RCC in the general population. This tumor type rarely metastasizes and has the best prognosis, with 5-year survival approaching 90%, compared to 10% survival for patients with metastatic clear-cell or papillary RCC.<sup>34</sup>

## Prognostic factors for renal cell carcinoma

The Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score is a useful tool for predicting survival amongst those with advanced-stage disease treated with immunotherapy or chemotherapy.<sup>35</sup> The MSKCC score was derived from a cohort of 400 patients who had received interferon (IFN)-based therapy for metastatic RCC, and comprises Karnofsky performance status, lactate dehydrogenase (LDH) level, hemoglobin level, serum calcium level, and prior nephrectomy. The median survival of patients with an MSKCC score of 0 is 20 months (favorable prognosis), reducing to 10 (intermediate prognosis) and 4 months (poor prognosis) in those with scores of 1–2 and 3–5, respectively. Another large multicenter study of 645 patients treated with VEGF-targeted therapy demonstrated that prognostic categories derived from performance status, calcium level, hemoglobin level, neutrophil count, platelet count, and time from diagnosis reliably predicted survival and may be superior compared to the MSKCC score by more accurately reclassifying patients into the correct prognostic categories by almost 10% (survival in intermediate- and poor-prognosis groups of 27 and 9 months respectively).<sup>36</sup> Other adverse prognostic factors identified in other studies include failed treatment with radiotherapy, multiple metastatic sites, sarcomatoid differentiation, elevated alkaline phosphatase, neutrophilia, and thrombocytosis.<sup>37–39</sup>

Several inflammatory and tumor-specific biomarkers have recently been identified as important prognostic markers of survival in patients with metastatic RCC. There is an inverse association between serum interleukin (IL)-6 level and progression-free and overall survivals. Serum IL-6 level above 35 pg/mL is associated with a fourfold increased risk of cancer-related mortality.<sup>40</sup> The modified Glasgow Prognostic Score derived from a cohort of 169 patients, and showed a strong association between a score calculated from C-reactive protein and serum albumin and cancer-specific survival (hazard ratio [HR] 5.13, 95% confidence interval [CI] 2.89–9.11;  $P < 0.01$ ).<sup>41</sup> Although several tumor biomarkers, such as carbonic anhydrase IX, HIF-1- $\alpha$ , p53, VEGFR-1, B7-HI, and survivin, appear promising in further improving the prognosis of cancer mortality, the clinical utility of these markers has not been widely adopted because of their availability and cost (Table 2).<sup>25,38,42</sup>

## Treatment options for renal cell carcinoma

The finding that RCCs are relatively insensitive to standard chemotherapeutic regimens has led to the development of

**Table 2** Prognostic indicators of renal cell carcinoma

Patient factors	Tumor factors	Laboratory parameters
Performance status	Tumor subtype	Albumin
Smoking	Metastasis ( $\geq 2$ sites)	C-reactive protein
	Time from diagnosis to treatment	Hemoglobin
	Retroperitoneal nodal metastasis	Lactate dehydrogenase
	Failed treatment with radiotherapy	Neutrophil count
	Sarcomatoid differentiation	Platelet count
		Lymphocyte count
		Alkaline phosphatase
		Calcium level
		Interleukin-6

immunotherapeutic agents aimed at potentiating antitumor immune surveillance. Both dendritic cells (DCs) and T cells have been identified in tumor tissue, which indirectly suggests the importance of these immune cells in the immunobiology of RCC.<sup>43</sup> Spontaneous tumor remission in the absence of treatment occurs in less than 2% of cases, but cytoreductive nephrectomy (CN) has been associated with regression of metastatic RCC, possibly by reducing tumor-derived T-cell-inhibitory factors and reducing tumor-derived growth factors.<sup>16,44</sup>

## Cytoreductive nephrectomy

Although the role of CN remains controversial in metastatic RCC, it is generally accepted that surgery is often necessary as an adjunctive treatment to immunotherapy (eg, IFN- $\alpha$ ).<sup>45</sup> Furthermore, CN may provide symptomatic relief, often associated with a modest improvement in survival (median 3–6 months), especially in those with large tumor bulk or paraneoplastic syndromes.<sup>46,47</sup> Tumor size, performance status presurgery, and recurrence/growth of tumor postsurgery are well-recognized prognostic factors known to affect survival following CN.<sup>14</sup> In patients with limited metastatic disease, metastasectomy may be considered in younger patients, those with solitary non-CNS lesions, and those with disease detected over 12 months following CN, with the expectation of achieving a 5-year survival of 30%.<sup>20,47</sup>

In a large retrospective series of 566 patients with metastatic RCC, the investigators identified hypoalbuminemia, elevated LDH levels, tumor stage T3 or above, symptomatic metastatic disease, presence of liver metastasis, and retroperitoneal or supradiaphragmatic lymph-node involvement were factors associated with poorer survival.<sup>48</sup> Furthermore, patients with four or more of these risk factors did not benefit from CN. In kidney-transplant recipients, symptomatic disease and tumor size of  $>40$  mm were associated with poorer survival following CN.<sup>10</sup>

In patients with large tumors, the use of neoadjuvant targeted therapies to reduce tumor bulk has allowed successful CN to proceed.<sup>49</sup> A study comparing 44 patients with metastatic RCC who had received neoadjuvant targeted therapies (bevacizumab or sorafenib) prior to CN to a matched cohort of 58 patients who had undergone CN at the outset showed a possible survival benefit with neoadjuvant treatment (18% vs 31% mortality in neoadjuvant/CN and CN groups, respectively).<sup>50</sup> Another small study of patients with metastatic RCC showed a lack of survival benefit in those who had received targeted therapy (sorafenib/sunitinib) following CN compared to targeted therapy alone (median progression-free survival of 12 vs 9 months, respectively).<sup>46</sup> A retrospective study of 188 patients with metastatic RCC demonstrated that patients who had received targeted therapy without CN had a higher median overall survival of 13 months, compared with a median of 8 months in historical patients who had received IFN- $\alpha$  without CN.<sup>51</sup> Nevertheless, the role of adjuvant targeted therapy prior to CN remains debatable and, future studies addressing the role of CN with sequential targeted therapy are required.

In kidney-transplant recipients with allograft RCC, nephron-sparing surgery can be considered if the tumor is superficial and its size is  $<4$  cm, but renal allograft nephrectomy is often undertaken if the allograft has failed or if the tumor is multifocal.<sup>10,52</sup> Regular ultrasonography of the renal allograft following nephron-sparing surgery is essential to detect tumor recurrences.<sup>53</sup>

## Stereotactic radiotherapy

The benefit of radiotherapy in the treatment of RCC remains unclear and is not recommended.<sup>42</sup> A recent meta-analysis (n = 735 in a total of seven trials: five retrospective and two prospective studies) demonstrated that postnephrectomy radiotherapy significantly reduced the risk of local and/or regional recurrences by 53% (pooled odds ratio 0.47, 99% CI 0.33–0.68), but this benefit did not translate to an improvement in disease-free survival or overall survival.<sup>54</sup> Although the incidence of adverse events was similar in those receiving or not receiving radiotherapy, there were six deaths from gastrointestinal and hepatic toxicities, which were thought to be directly attributable to radiotherapy. The suggestion that computer tomography-based planning prior to radiotherapy might be associated with improved response rate and reduced incidence of adverse events will need to be carefully examined in future studies. Nevertheless, it is unlikely that radiotherapy will be of benefit in many patients,

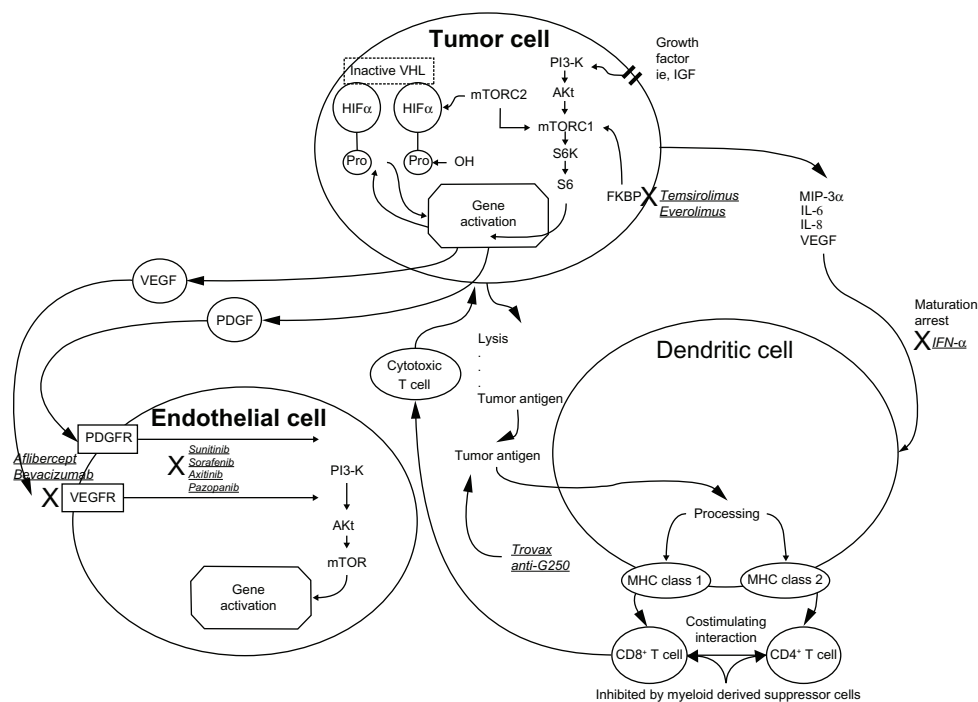
because up to 85% of patients who experience treatment failure will develop metastatic disease.<sup>55</sup>

Stereotactic body radiotherapy (SBRT) is a novel technique that utilizes short courses of intensive, highly focused radiation delivered to metastatic lesions. This technique appears promising, and is associated with excellent local control and stabilization of tumor growth (defined as lack of tumor activity on positron emission tomography scan or expansion of tumor size of <20%).<sup>56,57</sup> Multiple case series have demonstrated that SBRT was successful in both reducing local symptoms from tumor bulk and stabilization of the growth of metastatic lesions at both cranial and extracranial sites. Small tumor volume, greater numbers of fractions and dose per fraction, and higher biological effective dose of SBRT have been shown to be associated with improved symptom control from stabilization of metastatic tumor growth in up to 90% of cases.<sup>58–60</sup>

## Immune-based therapies

There has been considerable focus on the effectiveness of immunotherapy in patients with metastatic RCC.

Immune-based therapies can be broadly categorized into non-tumor-targeted and tumor-targeted therapies. Nontargeted therapies include subcutaneous IFN- $\alpha$  or intravenous or subcutaneous IL-2, both of which can induce a nonspecific graft versus tumor and inflammatory responses. Tumor-targeted therapies include VEGF and mTOR inhibitors (Figure 3), DC peptide-based vaccines (tumor antigens are presented by patient's antigen-presenting cells) and adoptive cell transfer, the latter utilizing ex vivo expanded tumor antigen-pulsed autologous lymphocytes that are reinfused back into patients.<sup>43,61</sup> Whilst targeted therapies may be associated with superior progression-free survival compared with IFN- $\alpha$ /IL-2, these nontargeted cytokine therapies have also been shown to induce sustained, drug-free remission. It has also been shown that VEGF-targeted therapy may be more effective at reducing tumor bulk compared with mTOR inhibitors.<sup>62</sup> In the absence of definitive randomized studies in the treatment of non-clear-cell RCC, it is generally recommended that this cancer type should be treated with sunitinib, sorafenib, or temsirolimus, but it remains unclear which agent is superior.<sup>63,64</sup>



**Figure 3** Site of actions of targeted therapy used in the treatment of metastatic renal cell carcinoma.

**Notes:** The tumor cell possesses inactive Von Hippel–Lindau (VHL), permitting the production of heterodimerized hypoxia-inducible factor (HIF) under normoxic conditions. Mammalian target of rapamycin (mTOR) activation further facilitates HIF production. HIF and S6 contribute to gene activation, leading to production of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), both of which act upon the endothelial cell to promote angiogenesis. Bevacizumab targets only VEGF, whereas sunitinib and sorafenib target VEGF receptors as well as PDGF and c-kit. Temsirolimus and everolimus inhibit the mTOR signaling pathway. Dendritic cells (DCs) are crucial in antitumor immunity, and mature DCs interact with both innate immune cells and antigen-specific T cells to elicit an immune response against tumor antigens. Tumor-derived factors such as VEGF, interleukin (IL)-6, and IL-8 may inhibit DC maturation, therefore escaping immune surveillance. Nontargeted therapies such as interferon (IFN)- $\alpha$  (by promoting maturation of DCs) and DC-based vaccination (by presenting tumor antigens to induce an antigen-specific cytotoxic T-cell response) are other effective treatment options for metastatic renal cell carcinoma.

**Abbreviations:** MHC, major histocompatibility complex; PI3-K, phosphatidylinositol 3-kinase; MIP, macrophage inflammatory protein; X, site of action; VEGF, vascular endothelial growth factor; FKBP, FK-binding protein; IGF, insulin-like growth factor, PDGFR, platelet-derived growth factor receptor.

## Nontargeted therapies

### Interferon- $\alpha$ and interleukin-2

IFN- $\alpha$  and IL-2 were the first two immunotherapeutic agents approved for use in metastatic RCC. IFN- $\alpha$  is administered subcutaneously, and IL-2 as an intravenous bolus or infusion. Although the precise antitumor properties of IFN- $\alpha$  have not been clearly defined, this cytokine has been shown to be capable of inhibiting angiogenesis and cell cycling, as well as enhancing the activity of several immune cells. IFN- $\alpha$  is the predominant type I IFN produced by plasmacytoid DCs.<sup>65</sup> Type I IFNs are capable of coordinating the innate and adaptive immune responses by directly affecting innate cells (eg, natural killer [NK] cells) as well as antigen-specific T cells and memory B cells.<sup>66</sup> The ability of plasmacytoid DCs to enhance cytotoxicity of NK and cluster of differentiation (CD8)<sup>+</sup> T cells as well as protecting DCs from NK cell-mediated lysis of immature DCs is mediated by their ability to produce type I IFN.<sup>67,68</sup> Type I IFN may also promote the cross-presentation and cross-priming of antigens by CD8<sup>+</sup> T cells,<sup>69</sup> as well as inducing T-cell activation (increased expression of CD69) and survival,<sup>70</sup> all of which may have an important role in antitumor immunity. IL-2 is produced by T cells in response to the interaction between antigen-presenting cells and T cells (including T-cell recognition of antigens presented by antigen-presenting cells), which leads to the activation and proliferation of antigen-specific T cells. Furthermore, IL-2 exerts an immunomodulatory effect by promoting the apoptosis of activated T cells and the maturation of regulatory T cells, the latter known to be capable of suppressing immune reactivity of other immune cells.<sup>71</sup>

Although the therapeutic potential of IFN- $\alpha$  in the treatment of metastatic RCC was identified in the 1980s, randomized controlled prospective trials involving this agent were not conducted until the 1990s. The first such study compared 41 patients receiving IFN- $\alpha$  (subcutaneous dose of 8 million units thrice weekly) and vinblastine (intravenous dose of 0.1 mg/kg thrice weekly) with 35 patients receiving hormonal therapy medroxyprogesterone (intramuscular dose of 500 mg weekly). Survival was similar between the two groups, but a greater proportion of the patients in the IFN- $\alpha$  vinblastine group had achieved partial or complete remission compared with patients in the medroxyprogesterone group.<sup>72</sup> A subsequent study randomized 160 patients to receive either vinblastine alone (dose of 0.1 mg/kg thrice weekly) or vinblastine in combination with IFN- $\alpha$  (dose of 3 million units thrice weekly, increasing to 18 million units after the first week) for 12 months or until disease progression.<sup>73</sup> Median survival (68 vs 38 weeks,  $P = 0.005$ ) and progression-free

survival (13 vs 9 weeks,  $P < 0.001$ ) in the vinblastine/IFN- $\alpha$  group were significantly better compared with the vinblastine group. A randomized study involving 335 patients with metastatic RCC demonstrated that patients randomized to IFN- $\alpha$  (two doses of 5 million units followed by 10 million units in the first week, then 10 million units thrice weekly for a further 11 weeks) had a 28% reduction in the risk of mortality (HR 0.72, 95% CI 0.55–0.94) compared with patients randomized to medroxyprogesterone acetate (300 mg daily for 12 weeks). Similarly, patients randomized to the IFN- $\alpha$  group had a survival advantage with median increase in survival of 2.5 months (95% CI 0.5–5.0 months).<sup>74</sup>

There have been multiple studies comparing the efficacy of IFN- $\alpha$  to IL-2, either alone or in combination. In a large multicenter trial involving 425 patients with metastatic RCC, patients randomized to IFN- $\alpha$  ( $18 \times 10^6$  IU subcutaneously three times a week for 10 weeks, followed by maintenance therapy for a further 12 weeks) achieved similar overall survival compared to patients randomized to IL-2 (four cycles of daily subcutaneous dose of  $18 \times 10^6$  IU per square meter of body surface area) and a combination of both agents (IL-2 with the addition of IFN- $\alpha$   $6 \times 10^6$  IU thrice weekly).<sup>75</sup> Patients receiving combination IFN- $\alpha$ /IL-2 were significantly more likely to achieve a clinical response (defined as 50% reduction in the size of all lesions on serial computed tomography imaging) compared with either therapy alone in intention-to-treat and on-treatment analyses ( $P < 0.01$ ). Patients receiving IL-2 therapy, alone or in combination, experienced higher rates of adverse events, including vasopressor-resistant hypotension and fevers. In another study involving 492 treatment-naive patients with metastatic RCC (any histological type, more than one metastatic site with Karnofsky score of  $\geq 80\%$ , normal liver function and hematological parameters, and baseline creatinine of  $< 160 \mu\text{mol/L}$ ), patients were randomized to receive medroxyprogesterone (oral dose of 200 mg daily), IFN- $\alpha$  (9 million IU thrice weekly), IL-2 (9 million IU daily or alternate daily), or in combination (IL-2 with IFN- $\alpha$  at 6 million IU per dose) for 12 weeks, extending up to 24 weeks in the absence of tumor progression. There was no significant difference in progression-free survival or overall survival between all four groups, suggesting no survival benefit with the use of cytokine therapies either alone or in combination.<sup>76</sup> Consistent with prior studies, IL-2 therapy, especially in combination with IFN- $\alpha$ , was associated with a much higher risk of adverse events compared with medroxyprogesterone (59% versus 10%,  $P < 0.001$ ) including performance impairment (30% versus 2%), weight loss and fever (27% versus 0%),

gastrointestinal disturbances (14% versus 1%), anemia (3% versus 0%), leukopenia (3% versus 2%), and neutropenia (4% versus 0%). Other randomized studies in previous untreated patients with metastatic RCC also demonstrated no survival benefit with the use of IL-2 or IFN- $\alpha$ , alone or in combination with other chemotherapeutic agents.<sup>77,78</sup> A recent systematic review of 6880 patients with advanced renal cell carcinoma who had received an immunotherapeutic agent in at least one study arm and reported remission or survival by allocation suggested that the use of IFN- $\alpha$  was associated with an improvement in median survival by 2.8 months.<sup>44</sup> The reported remission rates in patients participating in trials were 1.8% in the group receiving control/placebo therapies, 7.6% with single-cytokine therapy, 12.9% with combined-cytokine therapy, and 22.9% with high-dose IL-2 therapy. Future studies evaluating the role of IFN- $\alpha$  and IL-2 with targeted therapy as well as determining the optimal dose and duration of nonspecific cytokine therapy are required.

#### Anti-programmed death ligand 1 therapy

Programmed death-receptor ligand 1 (PD-L1), also called B7-H1, is a member of the B7 family, which on interaction with PD-1 negatively regulate T-cell receptor signaling.<sup>79</sup> It has been shown that aggressive forms of RCC express PD-L1 and the interaction between tumor cells PD-L1 and immune cells PD-1 contributes to immune dysregulation in these patients and promotes cancer progression.<sup>80</sup> In pre-clinical models, blockade of interactions between PD-1 and PD-L1 mediates antitumor activity, suggesting a potentially novel form of antitumor immunotherapy.<sup>81</sup> BMS-936559 is a humanized anti-PD-L1 monoclonal antibody, which inhibits PD-L1 binding to both PD1 and the T-cell ligand CD80. In a multicenter phase I study involving 207 patients with advanced solid organ cancers (including 17 patients with metastatic RCC), patients received 6-week cycles of intravenous anti-PD-L1 (doses of 0.3–10 mg/kg) up to a maximum of 16 cycles. An objective response was observed in most cancer types, including 12% of patients with RCC. Although adverse events were common, the majority of symptoms were mild, including infusion reactions, fatigue, diarrhea, rash, and pruritus.<sup>82</sup> BMS-936558, a humanized monoclonal antibody that blocks PD-1, appears to be equally efficacious in patients with advanced solid organ cancers and has been shown to produce an objective response in up to 27% of patients with RCC.<sup>83</sup> Most adverse events were mild, including fatigue, diarrhea, rash, anorexia, nausea, and pruritus, but 11% of patients experienced more severe adverse events, including pneumonitis and elevated transaminases. Phase II

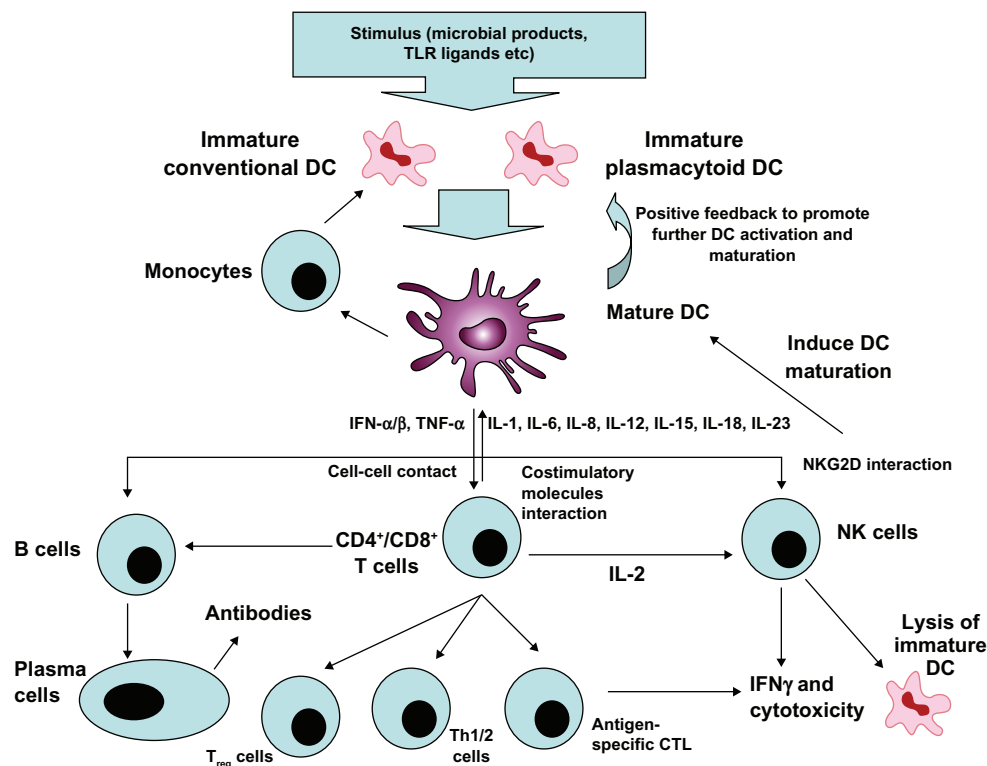
and III studies are currently under way to define further the role of these agents in the treatment of metastatic RCC.

#### Targeted therapies

##### Vaccines

Earlier vaccines used in the treatment of metastatic RCC were largely disappointing, but the newer peptide-based vaccines appear more promising. Antigen selection for vaccine design appears to be the key in the improved efficacy achieved with peptide-based vaccines, but nevertheless peptide-based vaccines do not provide a sustained antitumor response and should be considered as adjunctive therapy to other immunotherapeutic or chemotherapeutic agents.<sup>84,85</sup> In a randomized controlled trial involving the use of TroVax, a recombinant modified vaccinia virus Ankara vector encoding the oncofetal target antigen 5T4 peptide-based vaccine (TroVax Renal Immunotherapy Survival Trial), patients with metastatic RCC were randomized to receive MVA-5T4 peptide-based vaccine or placebo in combination with sunitinib, IL-2, or IFN- $\alpha$ .<sup>86,87</sup> Although a survival advantage was not demonstrated with the addition of this vaccine, a post hoc analysis restricted to a cohort of patients with lower-grade MSKCC did show a significant survival advantage if treated with TroVax vaccine and IL-2, compared with placebo (mortality HR 0.54, 95% CI 0.3–0.98;  $P = 0.046$ ). It remains unclear whether the poor response to vaccination is a reflection of inadequate vaccine dose or that tumors were lacking 5T4 expression, the latter being important for antitumor response. Another peptide-based vaccination complex to tumor necrosis factor- $\alpha$  or heat-shock proteins has been developed, and although this vaccine appears efficacious in murine RCC models, it has been disappointing in phase I human trials.<sup>85,88,89</sup>

DCs are a group of rare, heterogeneous, professional antigen-presenting cells that can initiate primary immune responses, and hence have the ability to regulate both innate and adaptive immune responses (Figure 4).<sup>90,91</sup> Precursor DCs, arising from bone marrow progenitors, enter tissues as immature DCs with superior phagocytic capabilities. DCs then encounter foreign antigens, such as bacteria and tumor antigens, resulting in the secretion of cytokines (eg, IFN) and activation of NK cells, macrophages, and eosinophils. Following antigen capture and processing, DCs undergo maturation and migrate to secondary lymphoid tissues, where they present processed antigen/peptide coupled to major histocompatibility complexes to T cells, allowing for selection and expansion of antigen-specific CD4<sup>+</sup> T-helper cells. These CD4<sup>+</sup> T-helper cells subsequently amplify the immune responses by regulating antigen-specific (eg, CD8<sup>+</sup>



**Figure 4** Overview of the relationship between dendritic cells and effector cells.

**Notes:** Immature conventional or plasmacytoid DCs mature in response to appropriate stimuli (eg, microbial products, TLR ligands). Mature DCs secrete immunoregulatory cytokines (including IFN- $\alpha$  and IL-12), and through cell–cell interactions modulate effector cell response including NK cells and B and T cells, as well as providing positive feedback to DCs to initiate ongoing activation and maturation. Activated effector cells could in turn modulate DC activation, maturation, and survival, as well as enhancing other effector cell functions through the production of cytokines (IFN- $\gamma$ ) and/or via cell–cell contact.

**Abbreviations:** DC, dendritic cell; IFN, interferon; IL, interleukin; NK, natural killer; CTL, cytotoxic T lymphocyte; T<sub>reg</sub> cells, regulatory T cells; Th, T helper; TLR, Toll-like receptor; TNF, tumor necrosis factor.

cytotoxic T cells, B cells), and antigen nonspecific (eg, macrophages, NK cells, and eosinophils) effector cells. As DCs have a prominent role in the initiation of innate and adaptive immune response against invading pathogens, they are likely to have an equally important role in antitumor immunity. The development of a tumor invariably involves the failure of the immune system to recognize tumor antigens, leading to an abnormal proliferation of tumor cells. Tumors may evade immune recognition directly or indirectly (via the production of suppressive cytokines and other mediators) by affecting normal DC and T-cell functions.

Following initial success in eliciting immunogenicity against antigens delivered by DCs in patients with cancer and HIV infection, therapeutic DC-based vaccines such as the US Food and Drug Administration (FDA)-approved DC-based vaccine against metastatic castration-resistant prostate cancer, have been developed and used in clinical studies to generate protective immunity against certain types of tumors.<sup>92–94</sup> These clinical studies in humans were initiated following observations in mice that *ex vivo* generated DCs could induce both humoral and tumor-specific immunity, and may be superior

to other forms of vaccines.<sup>92</sup> Established protocols involving mature DCs generated from CD34<sup>+</sup> bone marrow-precursor cells and monocytes have been successful in the induction of antitumor immunity. DCs used in vaccination-based protocols involving tumor antigen must be phenotypically mature to ensure that DCs are capable of migrating to secondary lymphoid organs to initiate tumor antigen-specific T-cell immunity when delivered into the host.<sup>95</sup> Various maturation stimuli have been trialed, including cytokines (eg, IL-1, IL-6, tumor necrosis factor- $\alpha$ , prostaglandin E<sub>2</sub>), Toll-like receptor ligands, CD40 L, major histocompatibility complex-binding antigens (including peptides, protein, tumor lysates, apoptotic cells), and DNA and RNA transfection of DCs. DC-based vaccination strategy in human subjects has been shown to induce antigen-specific T-cell response and may even generate tumor antigen-specific cytotoxic T lymphocytes in tumor tissues.<sup>96,97</sup>

DC-tumor peptide-based vaccination could potentially promote a vigorous tumor antigen-specific T-cell response in patients with RCC.<sup>98</sup> A systematic review of 29 randomized controlled trials of DC tumor antigen-based vaccination comprising a total of 906 patients with either metastatic

RCC or patients with recurrent or metastatic prostate cancer showed that the clinical benefit rate (a combined objective response rate with stable disease rate) was 48% in patients with metastatic RCC receiving DC-based vaccination. Meta-analysis of individual patient data demonstrated that cellular immune response and DC dose had a significant influence on clinical benefit rate in patients with metastatic RCC. Of patients with metastatic RCC, 92% had received prior surgery or radiotherapy, 17% had received prior chemotherapy, 36% had received prior immunotherapy, and 36% had received concomitant IL-2 or combined IFN- $\alpha$ /IL-2 with DC-based vaccine. There were a few mild adverse effects, particularly local reactions at injection sites and nonspecific constitutional symptoms, including fever and flu-like symptoms. Potential mechanisms of immune surveillance escape include the promotion of local lymphoid chemokine expression, such as tumor-derived macrophage inflammatory protein 3- $\alpha$ , which appears to promote recruitment of immature DCs into tumors, thereby inhibiting T-cell activation.<sup>99</sup> Other soluble factors, including IL-8, IL-6, and VEGF, may also inhibit DC maturation, and it is plausible that attempts to mature these immature DCs could lead to the enhancement of antitumor response.<sup>100</sup>

### Novel targeted therapies

Targeted therapies directed against the VEGF and mTOR pathways have become the treatment of choice for metastatic RCC, with activity against both primary and metastatic lesions (Table 3).<sup>36,42,101</sup> Bevacizumab is a humanized monoclonal antibody directed against VEGF, whereas sunitinib, sorafenib, and pazopanib are tyrosine kinase inhibitors that

target the downstream effects of VEGF activation. These tyrosine kinase inhibitors have differing binding affinities to molecular targets, and other than inhibition of VEGFR2 and VEGFR3, they may also inhibit PDGFR- $\beta$  and/or c-Kit. Temsirolimus and everolimus are specific mTOR kinase inhibitors.<sup>102</sup> Studies have identified several markers that predict response to treatment and/or survival, which include VEGF levels and gene single-nucleotide polymorphisms, particularly the Cytochrome P450 3A5\*1 allele. A tissue microarray-based immunohistochemical analysis of upstream and downstream elements of the mTOR pathway revealed pS6 as the strongest predictor of survival in both localized and metastatic RCC.<sup>103,104</sup> In murine models, loss of phosphatase and tensin homologue, which reverses the action of phosphatidylinositol 3-kinase PI3-K in activation of mTOR4, appeared to sensitize tumors to mTOR inhibition.<sup>105</sup>

Tumors have developed several ways to escape immune surveillance, and therefore become resistant to immunotherapeutic agents. RCCs have been shown to promote the development of myeloid-derived suppressor cells, possibly by production of granulocyte-macrophage colony stimulating factor, resulting in T-cell hyporesponsiveness against tumor cells.<sup>106,107</sup> It has also been shown that certain VHL mutations can lead to differences in VEGF activation, thereby resulting in the variable responses of RCC to VEGF inhibition.<sup>21</sup> Agents directed against mTOR signaling are active against the TOR1 complex subunit, which is important in the control of cell growth and proliferation, as well as stabilizing HIF-1- $\alpha$ .<sup>108</sup> In contrast, the TOR2 complex subunit is important in cell morphology and adhesion, as well as promoting

**Table 3** Summary of study outcomes using targeted therapy in the treatment of metastatic renal cell carcinomas

Treatment	Study population	Comparator	Median progression-free survival (months)	Objective response
Bevacizumab + IFN- $\alpha$ <sup>114,116</sup>	Treatment-naive and prior nephrectomies	IFN- $\alpha$	10 vs 5	31% vs 13%
		Sunitinib	17 vs 8	39% vs 24%
		Bevacizumab + temsirolimus	17 vs 8	39% vs 27%
Sunitinib <sup>116,119</sup>	Treatment-naive $\pm$ previous nephrectomies	IFN- $\alpha$	11 vs 5	31% vs 6%
		Bevacizumab + temsirolimus	8 vs 8	24% vs 27%
Sorafenib <sup>126,127</sup>	Treatment-naive $\pm$ previous nephrectomies	IFN- $\alpha$	6 vs 6	5% vs 9%
		Sorafenib + IFN- $\alpha$	7 vs 8	30% vs 25%
		Sorafenib + IL-2	9 vs 11	15% vs 27%
Pazopanib <sup>129</sup>	Treatment-naive or had previously failed cytokine-based therapy	Placebo	9 vs 4	–
Axitinib <sup>130</sup>	Failed prior treatment with sunitinib, bevacizumab/IFN-alpha, temsirolimus, or cytokine therapy	Sorafenib	7 vs 5	–
Temsirolimus <sup>62</sup>	Treatment-naive $\pm$ previous nephrectomies	IFN- $\alpha$	6 vs 3	Overall survival 11 vs 7 months
Everolimus <sup>132</sup>	Failed previous cytokine or targeted therapy	Placebo	4 vs 2	–

**Abbreviations:** IFN, interferon; IL, interleukin; vs, versus.

the expression of HIF-2- $\alpha$  expression (expression of HIF-1- $\alpha$  can be promoted by either the TOR1 or TOR2 complex).<sup>109</sup> Unlike the TOR1 complex, the TOR2 complex is resistant to inhibition of mTOR signaling, thus providing another avenue for mTOR inhibitor resistance in patients with metastatic RCC.<sup>110,111</sup> Increased insulin-like growth factor signaling as a result of loss of mTOR/S6k inhibition may contribute to mTOR resistance, but this remains debatable.<sup>109</sup> Mutation of the tricarboxylic acid-cycle enzyme fumarate-hydratase (a tumor-suppressive gene) leads to upregulation and accumulation of HIF-1- $\alpha$ , is more prevalent in papillary rather than clear-cell RCC, and may explain why papillary RCC may be more responsive to mTOR inhibition.<sup>109,112</sup>

### Bevacizumab

Bevacizumab is a recombinant humanized monoclonal immunoglobulin G<sub>1</sub> antibody produced in a mammalian cell-culture system. Bevacizumab competitively binds to and inhibits the activity of human VEGF both in vitro and in vivo.<sup>113</sup> In a large multicenter randomized controlled study of 649 patients with metastatic RCC (phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma), patients were randomized to receive intravenous bevacizumab (at a dose of 10 mg/kg every 2 weeks) together with subcutaneous IFN- $\alpha$  (dose of 9 million units thrice a week) or IFN- $\alpha$  with placebo.<sup>114</sup> All patients had prior nephrectomies and were treatment-naive. Patients were block-randomized according to the country of origin and prognostic grade determined by the MSKCC score. The study was terminated prematurely following interim analysis demonstrating that patients randomized to bevacizumab and IFN- $\alpha$  treatment achieved better progression-free survival compared to the IFN- $\alpha$ -alone group (median 10.2 versus 5.4 months,  $P < 0.001$ ). There were no significant differences between groups for the primary end point in overall survival, likely explained by the decision to unblind the study following interim analysis, with subsequent crossover of the placebo group to the bevacizumab and IFN- $\alpha$  treatment group (median overall survival in the bevacizumab/IFN- $\alpha$  treatment vs IFN- $\alpha$ /placebo group of 23.3 months vs 21.3 months, respectively;  $P = 0.34$ ). Fatigue, asthenia, proteinuria, and hypertension were the most frequently reported adverse events, particularly in the bevacizumab and IFN- $\alpha$  treatment group. Other less common adverse events ( $\leq 1\%$ ) attributed to the use of bevacizumab included bleeding, myocardial ischemia and infarction, left ventricular failure, gastrointestinal perforation, and thromboembolic events.<sup>115</sup>

The similarly designed CALGB 90206 and TORAVA trials showed that the combination of bevacizumab/IFN- $\alpha$  treatment was associated with higher median progression-free survival compared with other treatments (CALGB 90206 – bevacizumab/IFN- $\alpha$  8.5 vs IFN- $\alpha$  5.2 months; TORAVA – bevacizumab/IFN- $\alpha$  16.8 vs sunitinib 8.2 vs bevacizumab/temsirolimus 8.2 months).<sup>116,117</sup> These studies do suggest that the combination of bevacizumab and IFN- $\alpha$  may achieve superior response in patients with favorable prognosis or indolent disease. In contrast, the clinical benefit of combined therapy with bevacizumab and IL-2 remains unclear. In a phase II study, patients with untreated metastatic RCC who had received bevacizumab and low-dose IL-2 demonstrated an objective response rate of 15% with 38% of patients, with reduction in tumor burden of  $<30\%$ .<sup>118</sup>

### Sunitinib

Sunitinib is an orally active multi-tyrosine kinase inhibitor, which inhibits the actions of VEGF and angiogenesis, the latter via inhibition of VEGFR1 and VEGFR2 and PDGFR- $\beta$ . In a large international, multicenter, randomized controlled study of 750 patients with metastatic clear-cell RCC, patients were randomized to receive oral sunitinib (dose of 50 mg daily for 4 weeks) or IFN- $\alpha$  (sequentially escalating regimen to a maximum of 9 million units thrice weekly).<sup>119</sup> All patients were treatment-naive and were block-randomized according to several prognostic factors, including LDH level, Eastern Cooperative Oncology Group (ECOG) status, and previous nephrectomy. Even though patients in the IFN- $\alpha$  treatment group were allowed to cross over to the sunitinib group following interim analysis, patients randomized to the sunitinib group had significantly longer progression-free survival compared to the IFN- $\alpha$  group at the end of the study (11 months vs 5 months, respectively,  $P < 0.001$ ). There was no significant difference in overall survival between groups, likely reflecting crossover of patients between treatment groups. Common adverse events following sunitinib use were gastrointestinal symptoms (diarrhea, stomatitis), hepatotoxicity, constitutional symptoms (fatigue, reduced appetite), cardiovascular abnormalities (hypertension, prolonged QT interval and left ventricular dysfunction of no clinical significance), laboratory abnormalities (cytopenias, elevated lipase and uric acid) and hand-foot syndrome.<sup>115,120</sup> Fatigue was more common in patients randomized to IFN- $\alpha$ . Other randomized phase II and III trials involving sunitinib showed that the objective response rates were similar in those receiving intermittent (4 weeks of 50 mg/day followed by 2 weeks off treatment) and continuous dosing (32% vs 28%);

but there were lower objective response rates compared with bevacizumab and IFN- $\alpha$  treatment (24% vs 39%).<sup>116,121</sup> In other studies involving the use of sunitinib, greater frequency and severity of adverse events were observed in patients of Korean ethnicity, possibly related to a difference in the metabolism of this agent compared to other ethnic groups.<sup>122</sup> Furthermore, the efficacy of sunitinib in non-clear-cell RCCs has largely been disappointing.<sup>123</sup>

### Sorafenib

Sorafenib is an orally active multi-tyrosine kinase inhibitor, with inhibitory actions against several protein kinases, including VEGF, PDGFR, Raf-1, Flt-3, and c-Kit. Sorafenib is approved for use in advanced RCC and advanced hepatocellular carcinoma. A large multicenter trial (TARGET; treatment approaches in renal cancer global evaluation trial) randomized 903 patients with metastatic RCC to receive sorafenib (dose of 400 mg twice daily) or matching placebo.<sup>124</sup> Patients were block-randomized according to country of enrollment and prognostic score (low or intermediate risk on MSKCC score), and all patients had received prior systemic therapy. This study terminated prematurely when a planned interim analysis demonstrated that patients randomized to sorafenib had significantly lower risk of cancer progression compared to placebo (HR 0.44, 95% CI 0.35–0.55,  $P < 0.01$ ).

There was no significant difference in overall survival between groups, likely reflecting crossover of patients between treatment groups (ie, 48% of the placebo-assigned group crossed over to the sorafenib group following interim analysis). In a post hoc analysis censoring patients who had crossed over from placebo to sorafenib, median overall survival was significantly longer in the sorafenib group compared to placebo (17.8 months vs 14.3 months,  $P = 0.03$ ). In addition, sorafenib appears to be well tolerated, has similar efficacy in younger and elderly patients, and has been shown to be associated with improved health-status questionnaire scores across all age-groups.<sup>125</sup> Although there was a higher incidence of adverse events, especially in those aged  $< 70$  years, including myocardial ischemia ( $< 5\%$  vs  $0\%$ ), diarrhea (43% vs 13%), fatigue (36% vs 27%), hypertension (18% vs 2%), hand-foot syndrome (31% vs 6%), and rash (39% vs 15%) in patients who received sorafenib compared to placebo, this drug may be better tolerated compared to sunitinib. However, the cardiovascular-related adverse events associated with these agents are unlikely to be of clinical significance, and therefore sorafenib can be considered in patients with cardiovascular disease. A number of phase II trials comparing sorafenib with IFN- $\alpha$  or IL-2 alone or in

combination with sorafenib have failed to demonstrate any differences in median progression-free survival between treatment groups.<sup>126,127</sup> It has been shown that patients treated with either sorafenib or IFN- $\alpha$  with low serum levels of IFN- $\alpha$  receptor 2 mRNA had poorer prognosis,<sup>128</sup> and future studies evaluating the response of cancer treatment according to IFN- $\alpha$  receptor status are warranted.

### Pazopanib

Pazopanib is a potent, orally active multi-tyrosine kinase inhibitor of VEGFRs 1–3, PDGFR, and c-Kit, all of which are important in tumor growth and angiogenesis. It is approved for use in advanced RCC and soft-tissue sarcomas, but also has anti-tumor activities against ovarian cancers. A large randomized double-blind placebo-controlled trial was conducted involving 435 patients with locally advanced and/or metastatic RCC.<sup>129</sup> Recruited patients were either treatment-naive or had had previously failed cytokine-based therapy. Patients were block-randomized in a 2:1 ratio according to ECOG status (0 versus 1), history of previous nephrectomy, and prior systemic therapy to receive oral pazopanib (800 mg daily) or matching placebo. Similar to other studies, patients who had progressed on placebo were allowed to cross over to the pazopanib group. Patients randomized to pazopanib had significantly longer progression-free survival compared to placebo (median 9.2 months vs 4.2 months, respectively;  $P < 0.01$ ), independent of previous treatment with cytokine therapy. Treatment-related adverse events were more common in the pazopanib group, particularly hypertension and hepatotoxicity with elevated transaminases and diarrhea. Pazopanib-related mortality from cerebrovascular accident, gastrointestinal perforation, and rectal hemorrhage occurred in  $< 1\%$  of patients. Discontinuation rates attributed to adverse events were noted to be higher in those patients who had received previous cytokine therapy. Results of a recently completed large phase III noninferiority trial of 1110 patients with metastatic RCC randomized to pazopanib or sunitinib showed that both agents were equally efficacious, but pazopanib was better tolerated, with a significantly lower incidence of hand-foot syndrome, mucositis, and stomatitis (unpublished data).

### Axitinib

Axitinib is a potent, orally active inhibitor of VEGFRs 1–3 with minimal inhibitory effects of PDGFR and other receptor kinases such as c-Kit. A large multicenter randomized controlled study was conducted involving 723 patients with progressive metastatic RCC and failed prior treatment with

sunitinib, bevacizumab/IFN- $\alpha$ , temsirolimus, or cytokine therapy.<sup>130</sup> Patients were block-randomized according to ECOG status and previous systemic therapy to receive axitinib (5 mg twice daily, and if tolerated, increasing to a maximum of 10 mg twice daily) or sorafenib (400 mg twice daily). Patients randomized to axitinib had longer progression-free survival compared to patients receiving sorafenib (median progression-free survival 6.7 months vs 4.7 months, respectively), particularly those who had received axitinib following cytokine treatment (median progression-free survival 12.1 months vs 6.5 months). The use of axitinib was associated with a significantly lower risk of disease progression and/or mortality compared to sorafenib (HR 0.67, 95% CI 0.54–0.67;  $P < 0.01$ ). Treatment-related adverse events were more common in the axitinib group, particularly diarrhea, hypertension, fatigue, anorexia, nausea, and dysphonia.

### Temsirolimus

Temsirolimus is a derivative of sirolimus, a commonly used immunosuppressive agent in kidney and liver transplantation. Temsirolimus was approved for use in advanced RCC in 1997. This agent is a specific inhibitor of mTOR kinase, which inhibits the synthesis of proteins that are crucial in regulating tumor-cell proliferation, growth, and survival. By reducing VEGF, temsirolimus also inhibits tumor angiogenesis. A phase III randomized controlled study of 626 patients with metastatic RCC at high risk of progression (ie, patients with elevated LDH level, low hemoglobin, elevated corrected calcium, time from diagnosis to randomization of less than 1 year, Karnofsky performance score of 60–70, and multiple metastatic sites) were randomized to one of three treatment groups: weekly dose of intravenous temsirolimus (25 mg/week), thrice-weekly dose of subcutaneous IFN- $\alpha$  (3–18 million units per dose as tolerated), or weekly dose of oral temsirolimus (15 mg/week) in combination with thrice-weekly dose of subcutaneous IFN- $\alpha$  (3 million units per dose in the first week, increasing to 6 million units as tolerated).<sup>62</sup> Patients were block-randomized according to country of origin and previous nephrectomy. Almost 70% of patients randomized to temsirolimus were considered as having a poor prognosis by MSKCC score. Patients randomized to temsirolimus had significantly lower risk of all-cause mortality compared to the IFN- $\alpha$  group (HR 0.73, 95% CI 0.58–0.92;  $P < 0.01$ ). There was a nonsignificant trend towards longer median overall survival in the temsirolimus group compared with the combination temsirolimus/IFN- $\alpha$  and IFN- $\alpha$  groups (10.9 months vs 8.4 months vs 7.3 months, respectively).

Adverse events were relatively common in all groups, but particularly in patients receiving temsirolimus/IFN- $\alpha$  (87%), followed by those receiving IFN- $\alpha$  (78%), and temsirolimus (67%;  $P = 0.02$ ). Reports of asthenia were more common in the IFN- $\alpha$  group compared to the temsirolimus group (26% vs 11%, respectively). Rash, peripheral edema, and stomatitis were more common in temsirolimus-containing regimens, affecting between 20% and 47% of patients. Features of metabolic syndrome, including hypertension, dyslipidemia, and hyperglycemia, were more frequent in the temsirolimus groups. At the conclusion of this study, the authors suggested that temsirolimus was moderately effective in patients with metastatic RCC with poor prognostic indicators, but there was no additional benefit if IFN- $\alpha$  was combined with temsirolimus.

### Everolimus

Everolimus is a derivative of sirolimus, with a similar mode of action. Like sirolimus, everolimus has been approved in kidney transplantation to prevent the risk of rejection. Since 2009, it has also been approved for use in advanced RCC, although the dose used in RCC is much greater than the immunosuppressive dose in kidney transplantation.<sup>131</sup> A multicenter randomized controlled study of 410 patients with metastatic clear-cell RCC who had failed previous cytokine or targeted therapies were randomized in a 2:1 ratio to everolimus (10 mg daily) or matching placebo.<sup>132</sup> Patients were block-randomized according to MSKCC score and previous exposure to VEGF inhibitors. Patients randomized to everolimus had significantly longer median survival compared to placebo (4 months vs 1.9 months, respectively;  $P < 0.01$ ). Similar to other studies, there was no difference in overall survival between the two groups, likely reflecting the decision to allow patients with progressive disease to cross over from placebo to the everolimus group. Adverse events were relatively common in the everolimus group, particularly gastrointestinal complications (stomatitis and diarrhea), cytopenias, hyperglycemia, dyslipidemia, rash, and fatigue. Drug-related pneumonitis occurred in 8% of patients, with most responding to discontinuation of treatment. Drug discontinuation as a result of adverse events was more common in the everolimus group compared to placebo (10% versus 4%), but the tolerability of the drug was generally manageable with conservative management and/or reduction in dose, with most adverse events being grade I or II severity. At the conclusion of this study, the authors suggested that everolimus should be considered the agent of choice in patients who have failed VEGF therapy.

### Other novel, combination, and sequential therapies

There have been a few studies that have evaluated simultaneous use of multiple novel agents in the treatment of metastatic RCC. In a phase I study of three patients with metastatic RCC, a simultaneous use of intravenous temsirolimus 15 mg weekly in combination with 4 weeks of oral sunitinib 25 mg daily was associated with an unacceptably high risk of toxicity and treatment discontinuation.<sup>133,134</sup> A trial investigating the maximum tolerable doses of temsirolimus and sunitinib (Clinical Trials identifier NCT01122615) and two other trials to evaluate the efficacy of the combination sunitinib and bevacizumab (Clinical Trials identifier NCT01243359) or sorafenib and bortezomib (Clinical Trials identifier NCT01100242) in metastatic RCC are currently under way. Other novel agents of interest include an adenosine triphosphate-competitive mTOR inhibitor, A2D8055, which in combination with alphaCD40 antibody appears promising in a murine model of RCC.<sup>135</sup> A recently completed phase II study in treatment-naïve patients with metastatic RCC has demonstrated that treatment with cediranib, a potent angiogenesis inhibitor, was associated with an 85% clinical response rate (38% partial response) and a median overall survival of 29 months.<sup>136</sup>

Although the sequential inhibition of several pathways essential for tumor growth appears logical, the benefit of this approach in the treatment of metastatic RCC remains unclear, but should be considered in those with rapid disease progression and/or development of new tumor sites, or those with unacceptable drug-related toxicities.<sup>27</sup> Several small studies have shown that sequential treatment of patients with the tyrosine kinase inhibitor axitinib following first-line sorafenib or sunitinib was associated with median progression-free survival of 7.4 and 4.8 months, respectively.<sup>130,137</sup> A prospective randomized trial evaluating the efficacy of sorafenib followed by sunitinib versus sunitinib followed by sorafenib is currently under way and will provide further insight into the value of sequential treatment (<http://clinicaltrials.gov/ct2/show/NCT00732914>).

### Conclusion

Despite the increased availability of several therapeutic options for metastatic RCC, the prognosis of this disease remains relatively poor. The optimal treatment of metastatic RCC has yet to be elucidated, although targeted therapy is now considered the treatment of choice. Nevertheless, it is often likely that a combination of surgery, radiotherapy, and nontargeted and/or targeted agents is required for

disease control. Clinicians must be cognizant of the need to balance the risk and benefit of treatment and to tailor treatment according to the individual.

### Disclosure

The authors report no conflicts of interest in this work.

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