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# Treatment Algorithms in Metastatic Renal Cell Carcinoma, Including the Potential Role of the Novel Oral Mammalian Target of Rapamycin Inhibitor Everolimus

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**Article info**

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**Abstract**

***Context:*** Few treatment options were available for metastatic renal cell carcinoma (mRCC) until the development of novel targeted agents directed against angiogenesis and tumour growth.
***Objective:*** This review discusses current targeted therapies for mRCC and outlines the position of everolimus, a novel, orally administered inhibitor of the mammalian target of rapamycin (mTOR), in current treatment algorithms.
***Evidence acquisition:*** Medical literature was retrieved from PubMed during January 2009. Additional relevant articles were included from the bibliographies of retrieved literature.
***Evidence synthesis:*** Targeted treatment for mRCC can be categorised for the following patient groups: previously untreated patients, those refractory to immunotherapy or chemotherapy, and those refractory to vascular endothelial growth factor (VEGF)–targeted therapy. Sunitinib and bevacizumab (combined with interferon alfa) are generally considered first-line treatment options in patients with favourable or intermediate prognosis. Temsirolimus is considered a first-line treatment option for poor-risk patients. Either sorafenib or sunitinib may be valid second-line treatments for patients who have failed prior cytokine-based therapies. For patients refractory to treatment with VEGF-targeted therapy, one recommendation is to switch to an agent with a different mechanism of action or molecular target, for example, an mTOR inhibitor. Everolimus (RAD001) has shown promising efficacy in the first phase 3 clinical trial in patients with mRCC with favourable, intermediate, and poor risk whose disease had progressed on VEGF-targeted therapy.
***Conclusions:*** Increasing clinical evidence is clarifying appropriate first- and second-line treatment with targeted agents for patients with mRCC. Based on good results of published phase 3 clinical data, the potential use of everolimus in the second-line setting has been recognised in recent (2008 and 2009) guidelines, including those of the European Society of Medical Oncology, the European Association of Urology, the European Organisation for Research and Treatment of Cancer Genitourinary Group, the Spanish Oncology Genitourinary Group, the French Urology Association, the UK consensus guidelines, the National Comprehensive Cancer Network (United States), and Cancer Care Ontario (Canada).


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## 1. Introduction

Renal cell carcinoma (RCC) originates in the renal cortex and accounts for approximately 90% of renal tumours [1]. In 2002, there were approximately 200 000 new kidney cancer cases worldwide [2]. RCC mainly affects patients >40 yr of age, occurring predominantly in the seventh and eighth decades of life [3]. Clear-cell carcinoma represents the majority (75–85%) of RCC cases and, therefore, is often explored in clinical trials [3,4]. Furthermore, 25–30% of patients have metastatic RCC (mRCC) at diagnosis, which is associated with poor prognosis (eg, 5-yr relative survival is estimated at approximately 10%) and is notoriously resistant to conventional radiation therapy or chemotherapy [3,5].

Until recently, few treatment options were available for mRCC, and patients who became refractory to standard-of-care treatments faced a particularly dismal outlook. The need for more effective treatments and increased understanding of pathogenic processes—for example, the involvement of the von Hippel-Lindau and hypoxia-inducible factor pathway in clear-cell RCC [6]—led to the development of novel targeted therapies directed against angiogenesis and tumour growth [7]. Several of these therapies, including sunitinib, sorafenib, temsirolimus, and bevacizumab, are available for clinical use and are revolutionising the treatment of mRCC [8]. In addition, everolimus (RAD001) gained US Food and Drug Administration approval in March 2009 for the treatment of patients with advanced RCC after failure of treatment with sunitinib or sorafenib. European Union approval for use of everolimus in patients with advanced RCC whose disease progressed on or after treatment with vascular endothelial growth factor (VEGF)–targeted therapy was granted in August 2009.

This article discusses current targeted treatment approaches in the first- and second-line mRCC settings as well as modifications to existing treatment algorithms based on recently available data from trials investigating everolimus.

## 2. Evidence acquisition

Medical literature was retrieved from PubMed during January 2009. Additional relevant articles were included from the bibliographies of retrieved literature.

## 3. Evidence synthesis

### 3.1. Current treatment approaches utilising novel targeted agents

At present, treatment for mRCC with molecularly targeted agents can be broadly divided into the following categories: previously untreated patients, those refractory to immunotherapy or chemotherapy, and those who have failed treatment with VEGF-targeted therapy [9]. An important consideration that influences treatment decisions is the Memorial Sloan-Kettering Cancer Centre (MSKCC) prognostic risk stratification system, which is widely used to define patient profiles and provide an indication of overall survival (OS) [10–12]. In this system, five prognostic factors are used to categorise patients with mRCC into three risk groups: favourable (no risk factors), intermediate (one or two risk factors), and poor (three or more risk factors) [10]. Median OS times were shown to be separated by ≥6 mo between each of the three risk groups [10].

### 3.2. Treatment-naïve patients

Clinical trials assessing the efficacy and safety of the oral mammalian target of rapamycin (mTOR) inhibitor everolimus in the first-line setting are currently underway. RECORD-2 is a randomised phase 2 trial comparing everolimus plus bevacizumab with bevacizumab plus interferon alfa (IFN-α) in patients with previously untreated mRCC [13]. RECORD-3 is an open-label, multicentre, phase 2 study comparing first-line everolimus followed by second-line sunitinib versus the opposite sequence (first-line sunitinib followed by second-line everolimus) in the treatment of patients with mRCC [14]. With its oral administration route, everolimus has the potential to be more acceptable to patients than temsirolimus, which requires weekly intravenous infusion. Everolimus has shown activity in patients with favourable, intermediate, and poor MSKCC risk whose disease had progressed on a VEGF-targeted therapy (sorafenib or sunitinib or both) [15], which helps to confirm the activity of mTOR inhibitors in mRCC.

#### 3.2.1. Treatment-naïve patients with favourable or intermediate prognosis

Sunitinib is a tyrosine kinase inhibitor (TKI) that acts mainly on the VEGF receptor (VEGFR) and platelet-derived growth factor receptor. In a phase 3 trial of sunitinib versus IFN-α in untreated patients with mRCC [16–18], sunitinib demonstrated significant improvements in objective response rate (ORR; independent review, 39% vs 8%; $p < 0.000001$) [17], median progression-free survival (PFS; 11 mo vs 5 mo; $p < 0.001$), and OS (26.4 mo vs 20.0 mo; hazard ratio [HR]: 0.808; $p = 0.036$; crossover data censored) [18]. These data have led to sunitinib being recommended as a first-line therapy for patients with mRCC [1,19–25] (Fig. 1).

Bevacizumab, a monoclonal antibody targeting VEGF directly, has shown efficacy in combination with IFN-α in two phase 3 trials in patients with previously untreated mRCC [26–29]. In the first of these studies, median PFS was 10.4 mo for bevacizumab plus IFN-α compared with 5.5 mo for IFN-α alone ($p < 0.0001$) [27]. No significant difference in OS was observed (23.3 mo vs 21.3 mo; $p = 0.1291$) [27]. Consistent results were seen in the second study, performed by the Cancer and Leukemia Group B, with median PFS of 8.4 mo and 4.9 mo, respectively ($p < 0.0001$) [28]. No significant difference in OS was observed (18.3 mo vs 17.4 mo; $p = 0.069$) [28]. The PFS benefits seen in these trials are similar to those obtained with sunitinib in patients with advanced RCC who were previously untreated [16] and

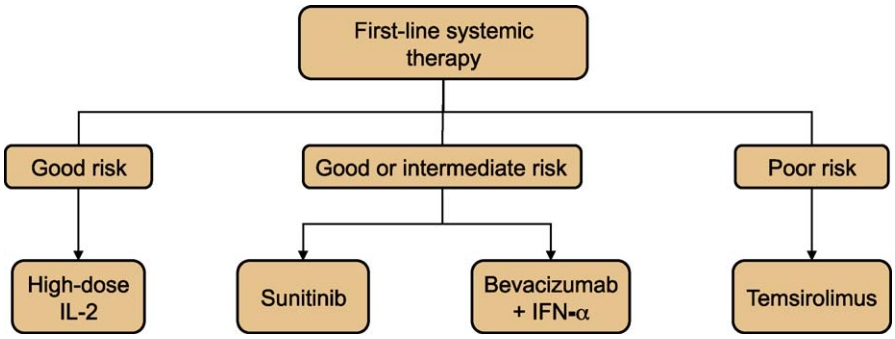


**Fig. 1 – Treatment schematic for patients with metastatic clear-cell renal cell carcinoma in the first-line setting based on the most recent European guidelines [19–21,23–25]. Cytokines, including high-dose interleukin-2 (IL-2), are recommended only for a specific subset of patients in European Organisation for Research and Treatment of Cancer Genitourinary (EORTC-GU) Group, United Kingdom consensus guidelines, French Urology Association (AFU), and European Society for Medical Oncology (ESMO) guidelines [20,21,23,24]. Sunitinib has shown efficacy across all patient risk groups and is therefore recommended as a potential alternative to temsirolimus by AFU, EORTC-GU and ESMO [21,23,24]. EORTC-GU and AFU guidelines also recommend sorafenib as an option for patients ineligible for treatment with other agents [21,23].**
**IFN-α = interferon alfa.**

suggest that bevacizumab plus IFN-α is another acceptable and effective therapy in the first-line setting [1,19–25] (Fig. 1).

#### 3.2.2. *Treatment-naïve patients with poor prognosis*

Temsirolimus is an intravenously administered inhibitor of mTOR. A randomised phase 3 trial compared monotherapy with temsirolimus versus IFN-α versus temsirolimus plus IFN-α as a first-line treatment in patients with mRCC and poor prognosis [30]. Patients were required to have at least three of six predictors of short survival according to a prognostic factor scheme modified from the MSKCC model [30]. Patients who received temsirolimus alone, compared with those who received IFN-α alone or the combination, had greater PFS (5.5 vs 3.1 vs 4.7 mo, respectively), OS (10.9 vs 7.3 vs 8.4 mo), and ORR (8.6% vs 4.8% vs 8.1%). The results of this trial justify mTOR as a target for cancer treatment, and recent European guidelines recommend that temsirolimus be considered as a first-line treatment in poor-risk patients [19–21,23–25] (Fig. 1).

### 3.3. *Cytokine-refractory patients*

Sorafenib is a small-molecule inhibitor of VEGFR and related receptors and also inhibits the intracellular signalling enzyme Raf kinase. In a placebo-controlled phase 3 trial involving patients with mRCC who had failed previous cytokine therapy, a PFS advantage for sorafenib of 5.5 mo versus 2.8 mo ($p < 0.001$) was observed [31,32]. Partial responses (PR) were reported as the best response in 10% of patients receiving sorafenib and in 2% of placebo recipients ($p < 0.001$). The disease control rate was higher for sorafenib than placebo (62% vs 37%; $p < 0.001$) [31]. An improved OS with sorafenib was observed after censoring placebo patients who had crossed over to sorafenib (17.8 mo vs 14.3 mo; $p = 0.0287$) [32]. Based on the results of this trial, sorafenib is recommended as a second-line agent in cytokine-refractory patients [1,19–25] (Fig. 2).

The efficacy of sunitinib in a total of 169 patients with mRCC who progressed on prior cytokine therapy was demonstrated in two phase 2 trials [33,34]. Across the two trials, PR was reported in 34–40% of patients, and a median PFS of 8.3–8.7 mo was observed [33,34]. Taken together, these data indicate that either sorafenib or sunitinib may be valid second-line treatment options for patients who have failed prior cytokine-based therapies, and this strategy is recommended by recent guidelines [1,19–25] (Fig. 2).

### 3.4. *Patients refractory to vascular endothelial growth factor–targeted therapy*

Substantial clinical benefit has been afforded by novel TKIs, including sunitinib and sorafenib, to patients with mRCC. However, the therapy is not curative, and there is a large unmet medical need for patients refractory to VEGF-targeted therapy. Appropriate second-line treatment

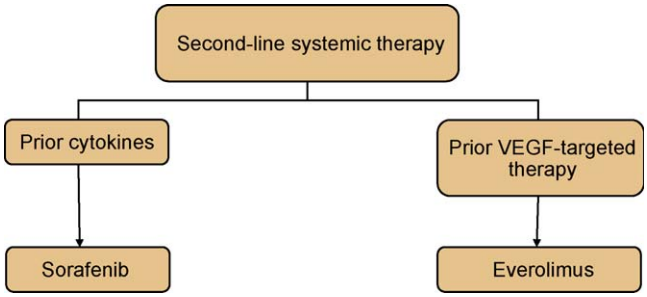


**Fig. 2 – Treatment schematic for patients with metastatic clear-cell renal cell carcinoma in the second-line setting based on the most recent European guidelines [19–21,23–25]. Sorafenib is currently the recommended first choice in patients refractory to cytokines [19–21,23–25], while sunitinib is recommended as an alternative option in this setting by the European Organisation for Research and Treatment of Cancer Genitourinary (EORTC-GU) Group, the European Society for Medical Oncology (ESMO), and the French Urology Association (AFU) [21,23,24]. The AFU also names bevacizumab plus interferon alfa as a possible alternative to sorafenib in this setting [21]. Everolimus is the recommended first-choice treatment in patients refractory to vascular endothelial growth factor (VEGF)–targeted therapy [19–21,23–25].**

**Table 1 – Recent guidelines for systemic treatment of metastatic clear-cell renal cell carcinoma [1,19–25]**

| Guidelines | First-line treatment | | Second-line treatment | |
|---|---|---|---|---|
| | Good or intermediate prognosis | Poor prognosis | Prior cytokine treatment | Prior VEGF-targeted therapy |
| European | | | | |
| ESMO [24] | Sunitinib or bevacizumab + IFN-α<br>Option: Cytokines*<br>(including high-dose IL-2) | Temsirolimus<br>Option: Sunitinib | Sorafenib<br>Option: Sunitinib | Everolimus |
| EAU [25] | Sunitinib or bevacizumab + IFN-α (grade A) | Temsirolimus (grade A) | Sorafenib (grade A) | Everolimus (grade A) |
| EORTC-GU [23] | Sunitinib (Level 1b) or bevacizumab + IFN-α (Level 1a) | Temsirolimus (level 1b) | Sorafenib (level 1b)<br>Option: Sunitinib | Everolimus (level 1b) |
| SOGUG [19] | Sunitinib or bevacizumab + IFN-α | Temsirolimus | Sorafenib | Everolimus |
| AFU [21] | Sunitinib or bevacizumab + IFN-α or cytokines*<br>Option: Sorafenib | Temsirolimus<br>Option: Sunitinib | Sorafenib<br>Option: Sunitinib<br>or bevacizumab + IFN-α | Everolimus |
| UK [20] | Sunitinib or bevacizumab + IFN-α or cytokines* | Temsirolimus | Sorafenib | Everolimus |
| North American | | | | |
| CCO [22] | Sunitinib or bevacizumab + IFN-α | Temsirolimus | Sorafenib | Everolimus |
| NCCN [1] | Sunitinib (category 1)<br>Bevacizumab + IFN-α (category 1)<br>Temsirolimus (category 1 for poor-prognosis; category 2B for selected patients of other risk groups)<br>High-dose IL-2* (selected patients, category 2A)<br>Sorafenib (selected patients, category 2A) | | Sorafenib or sunitinib (category 1)<br>Option: Temsirolimus (category 2A)<br>IFN-α or high-dose IL-2 or bevacizumab (category 2B)<br>Low-dose IL-2 ± IFN (category 3) | Everolimus (category 1)<br>Options: Sorafenib (category 2A)<br>Temsirolimus (category 2B)<br>Sunitinib (category 2A) |

VEGF = vascular endothelial growth factor; ESMO = European Society of Medical Oncology; INF-α = interferon alfa; IL-2 = interleukin-2; EAU = European Association of Urology; EORTC-GU = European Organisation for Research and Treatment of Cancer Genitourinary Group; SOGUG = Spanish Oncology Genitourinary Group; AFU = French Urology Association; CCO = Cancer Care Ontario; NCCN = National Comprehensive Cancer Network; mRCC = metastatic renal cell carcinoma.

* Cytokines are recommended only for selected patients with good prognosis.

The EAU classifies recommendations for the treatment of metastatic renal cell carcinoma as grades A–C, modified from grades of recommendation developed by the Oxford Centre for Evidence-Based Medicine [25,38].

The EORTC-GU classifies evidence based on levels (1–5) developed by the Oxford Centre for Evidence Based Medicine [23,38].

The NCCN gives recommendations based on evidence categories 1–3 [1].

approaches are required for these patients (Fig. 2). One possibility would be to switch to an agent with a different mechanism of action or molecular target—for example, an mTOR inhibitor such as everolimus—and this strategy is supported by data from the RECORD-1 trial [15].

In this phase 3 trial, patients receiving everolimus (10 mg once daily; $n = 272$) had significantly prolonged PFS versus those on placebo ($n = 138$; 4.0 mo vs 1.9 mo; HR: 0.30; $p < 0.0001$) [15]. The end of double-blind analysis from this trial indicated a further improvement in PFS with everolimus treatment (4.90 mo [$n = 277$] vs 1.87 mo [$n = 139$]; HR: 0.33; $p < 0.001$) [35]. PFS benefit following treatment with everolimus was maintained across patients with favourable ($n = 120$), intermediate ($n = 235$), or poor ($n = 61$) MSKCC risk. At the end of double-blind analysis, median OS was 14.78 mo in the everolimus group and 14.39 mo in the placebo group [36]. Crossover from placebo to the active treatment arm was allowed after disease progression, potentially confounding OS; 81% of placebo recipients who progressed crossed over to everolimus treatment.

### 3.5. *Guidelines for the treatment of metastatic renal cell carcinoma*

Recent European and American guidelines that have provided algorithms for first- and second-line treatment options in mRCC are the European Organisation for Research and Treatment of Cancer Genitourinary Group (EORTC-GU) [23]; the European Association of Urology (EAU) [25]; the Spanish Oncology Genitourinary Group (SOGUG) [19]; the European Society for Medical Oncology (ESMO) [24]; the French Urology Association (AFU) [21]; UK consensus guidelines [20]; Cancer Care Ontario (CCO; Canada) [22], and the National Comprehensive Cancer Network (NCCN; United States) [1] (Table 1). Based on efficacy and safety results, sunitinib monotherapy and bevacizumab in combination with IFN-α may be considered first-line treatment options in patients with metastatic or unresectable clear-cell RCC and favourable or intermediate prognosis according to MSKCC criteria [1,19–25]. In the second-line setting, sorafenib treatment is recommended for patients with mRCC refractory to cytokines, and everolimus treatment is recommended for patients refractory to VEGF-targeted therapy [1,19–25]. Recommendations for the treatment of clear-cell mRCC from the most recent European guidelines (EAU, EORTC-GU, ESMO, SOGUG, AFU, and UK guidelines) are summarised in Figs. 1 and 2 [19–21,23–25].

Some guidelines also suggest alternative agents. Cytokines (including high-dose interleukin-2 [IL-2]) are named as an option for first-line treatment of selected patients with mRCC with good prognosis in the EORTC-GU, ESMO,

AFU, and UK guidelines [20,21,23,24]. Furthermore, sunitinib is suggested as a possible alternative to temsirolimus as first-line treatment in patients with poor prognosis and also as an alternative to sorafenib as a second-line treatment after cytokines [21,23,24]. For patients previously treated with bevacizumab, treatment with sunitinib appears effective in a proportion of cases and is acknowledged in the EORTC-GU guidelines [23,37]. For patients refractory to mTOR inhibitors, the EAU suggests enrolment in a clinical trial [25].

The NCCN proposes a number of options for first- and second-line systemic treatment for relapse or stage IV and medically or surgically unresectable clear-cell RCC based on evidence categories from 1 to 3 [1]. In addition to the preferred treatment based on category 1 evidence outlined above (Figs. 1 and 2, Table 1), the NCCN also suggests alternative options for selected patients in the first-line setting, such as high-dose IL-2 or sorafenib (both category 2A), temsirolimus (category 2B), enrolment in a clinical trial, or best supportive care. In the second-line setting, everolimus is the only recommended treatment supported by category 1 evidence; other options suggested by the NCCN include sorafenib (category 2B following TKI), sunitinib (category 2A following TKI), temsirolimus (category 2A following cytokine therapy and category 2B following TKI), IFN-α (category 2B), high-dose IL-2 (category 2B), bevacizumab (category 2B), low-dose IL-2 with or without IFN-α (category 3), enrolment in a clinical trial, or best supportive care.

For patients with non–clear-cell histology, suggested agents include temsirolimus, sorafenib, and sunitinib (NCCN, EORTC-GU, UK guidelines, and ESMO) [1,20,23,24]. The NCCN also includes chemotherapy or best supportive care as options [1], whereas the EORTC-GU also suggests bevacizumab plus IFN-α (good or intermediate risk) or high-dose IL-2 (sufficiently good performance status) as options in patients with non–clear cell RCC [23].

## 4. Conclusions

The increasing amount of evidence with targeted agents is helping to clarify the first- and second-line treatment approaches in patients with mRCC and different prognostic risk factors. Recent clinical studies form the basis for new treatment guidelines for mRCC. In particular, recent data from the phase 3 trials with temsirolimus and orally administered everolimus establish mTOR inhibitors as a valid therapeutic approach for mRCC in poor-risk patients and in those who have failed treatment with VEGF-targeted therapy. These agents are included as valid and recommended treatment options in recent European guidelines [19–21,23–25].

Although immunotherapy with high-dose IL-2 should still be considered for low-risk patients, this group represents a small proportion of the population of mRCC patients [9]. Therefore, the majority of patients should receive VEGF-targeted agents. In the first-line setting, sunitinib appears the most viable option for favourable- and intermediate-risk patients, with evidence also supporting bevacizumab (plus IFN-α), while temsirolimus should be considered for poor-risk patients [1,19–25]. Although sorafenib is not recommended for first-line therapy, it is currently the drug of choice in the second-line setting, following the results of the phase 3 trials in cytokine-refractory patients [1,19–25,31]. However, there is increasing evidence for the mTOR inhibitor everolimus as a therapeutic option after failure of VEGF-targeted therapy; in this second-line patient population, it is the only drug with evidence of efficacy from a large phase 3 trial.

The role of surgery in the management of patients with mRCC in the era of emerging effective systemic targeted therapies remains to be fully defined. Ongoing clinical studies are evaluating these novel agents in the adjuvant setting. It will be essential to continue to update treatment algorithms as further evidence on current targeted agents becomes available, especially their sequential use and possible combinations. The resulting optimal use of these agents will help improve clinical benefits and tailor treatment regimens for each individual patient.

## Conflicts of interest

Dr. Patard is a consultant for Baxter, Bayer, Pfizer, Wilex, and Wyeth. The author did not receive an honorarium or consultancy fee for writing this manuscript.

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