



## Review – Kidney Cancer

# Update on the Medical Treatment of Metastatic Renal Cell Carcinoma

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### Abstract

**Context:** Metastatic renal cell carcinoma (mRCC) has long been treated only by immunotherapy with good results only in a small population of patients. In recent years, major improvements in treatment possibilities have occurred with the advent of anti-angiogenic drugs. In the past 2 yr, pivotal phase III trials have confirmed this major breakthrough by increasing the progression-free survival rates and/or overall survival rates provided by sunitinib, sorafenib, and bevacizumab, and more recently by the mTOR (mammalian target of rapamycin) inhibitors temsirolimus and everolimus.

**Objective:** To update the previous review on smart drugs published in the European Journal in 2006 (Patard JJ, et al. Understanding the importance of smart drugs in renal cell carcinoma. *Eur Urol* 2006; 49:633–43).

**Evidence acquisition:** Critical review of published literature 2006–2008 (PubMed website search words: renal cell carcinoma and/or targeted therapy and prospective trials) and more recent meeting abstracts (American Society of Clinical Oncology 2007). Quality assessment included prospective phase I–III trials and critical evaluations with low numbers of patients, retrospective analyses, and slide presentations of meeting abstracts.

**Evidence synthesis:** This review presents the current situation and provides more recent data on sequential treatment, the association of targeted drugs, and the treatment of non-clear-cell histologies.

**Conclusions:** Treatment of mRCC with targeted therapy centers on at least two major pathways: angiogenesis and mTOR involving inhibiting drugs that may be used alone, in combination, or sequentially.

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## 1. Introduction

Renal cell carcinoma (RCC) accounts for 2% of all cancers [1]. In Europe, 40 000 patients are diagnosed with RCC each year, leading to 20 000 deaths [2].

One-third of patients are initially diagnosed with locally invasive or stage IV disease [3]. In 25% of patients having surgical resection for localised disease with a curative intent, recurrence occurs [4]. The prognosis for patients with distant disease is poor, with a 5-yr survival rate of  $\leq 10\%$  [5].

A major breakthrough has recently occurred in the knowledge of the genetics and transduction pathways involved in RCC [6]. Novel targeted therapies directed against angiogenesis and the mammalian target of rapamycin (mTOR) pathway are revolutionizing the treatment of metastatic RCC (mRCC).

This state-of-the-art review covers the key molecular pathways and provides the latest data likely to modify current practice [6].

## 2. Methods

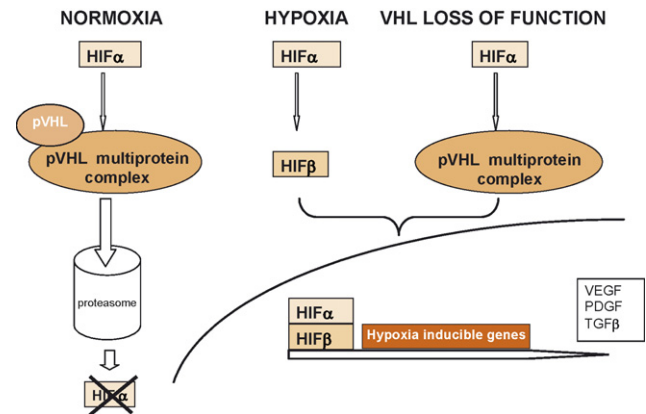
### 2.1. Key molecular pathways for therapeutic input

A major breakthrough was obtained with recognition of the importance of the hypoxia-driven pathway involving HIF (hypoxia-inducible factor) and related knowledge on angiogenesis with VEGF (vascular endothelial growth factor). Furthermore, new insights on resistant events or escape over time in the control of HIF/VEGF pathway have led to considering alternative pathways. The mTOR pathway seems to be an important primary or alternative pathway in RCC.

### 2.2. Hypoxia-induced pathway (Fig. 1)

Like other deprivation factors, hypoxia may affect cell growth. In normoxia, the alpha subunit of HIF (HIF $\alpha$ ) is hydroxylated by a pVHL (von Hippel-Lindau protein) complex unit and degraded through the proteasome [7]. So far, there has been no activation of the subsequent transcriptional events leading to the production of growth factors induced by hypoxia [8].

On the other hand, during hypoxia, HIF hydroxylation is inhibited. Depending on the level of oxygen deprivation, there is accumulation of unhydroxylated HIF, which no longer binds to pVHL. HIF $\alpha$  is therefore stabilised by dimerisation with the constitutively expressed HIF1 $\beta$  subunit and translocates to the nucleus. The HIF1 $\alpha$  and HIF1 $\beta$  complex binds to hypoxia-inducible gene promoters, including the main factor genes implicated in angiogenesis, pH regulation, glucose transport, glycolysis, cell cycle, homing and apoptosis [9]. In circumstances where HIF1 $\alpha$  accumulates, it reaches a level of detection in primary tumours and in metastatic sites.



**Fig. 1 – Hypoxia-induced pathway.** In normoxia, the subunit alpha of HIF $\alpha$  is hydroxylated before binding to the pVHL complex and is degraded through the proteasome. During hypoxia, HIF hydroxylation is inhibited, resulting in accumulation of unhydroxylated HIF, which no longer binds to pVHL. HIF $\alpha$  is therefore stabilised by dimerisation with HIF1 $\beta$  and translocates to the nucleus. Complexes HIF1 $\alpha$  and HIF1 $\beta$  bind to hypoxia-inducible gene promoters, including the main genes implicated in angiogenesis. There is an analogy in the consequence between hypoxia and VHL gene loss. HIF1 $\alpha$  $\beta$ : Hypoxia-inducible factor; pVHL: von Hippel-Lindau protein; pVHL multiprotein complex: pVHL + cullin 2 + elongins B,C + ubiquitin ligase complex components; VEGF: vascular endothelial growth factor; PDGF: platelet-derived growth factor; TGF $\beta$ : transforming growth factor.

### 2.3. Hypoxia-induced pathway and renal cell carcinoma (Fig. 1)

Clear-cell RCC is an example of the involvement of the HIF pathway in tumour proliferation and growth. Von Hippel-Lindau disease has been linked to the defection of the tumour suppressor gene VHL and a defective pVHL enabling the appearance of multiple tumours including RCC [10]. All patients with VHL disease and the majority of patients with sporadic RCC experience the loss or inactivation of both VHL gene alleles. The consequence of a defective pVHL is similar to that of hypoxia on HIF stabilization. Genetic events leading to the inactivation of the VHL suppressor gene are known to induce accumulation of HIF-1 $\alpha$  in the absence of hypoxia [11]. This activates the genes induced by the accumulation of HIF1 $\alpha$  and HIF1 $\beta$ , with the production of increasing levels of VEGF and PDGF (platelet-derived growth factor) [7]. The impact of pVHL in RCC growth has been shown in xenografts of RCC tumours with pVHL-defective tumour cells in mice, where introduction of pVHL abolished tumour growth [12]. Furthermore, by expressing an HIF variant or an HIF-derived peptide in RCC tumour cells, it was possible to avoid hydroxylation, and RCC tumours were able to grow in xenograft models in mice [13]. The involvement of HIF is at present considered mandatory for the onset of RCC.

Furthermore, even if expression of the HIF1 $\alpha$  protein is higher in clear-cell histology compared to non-clear-cell histology, a higher expression of HIF1 $\alpha$  has been associated

with a better outcome [14]. On the other hand, in sporadic RCC, the presence of *VHL* mutation is considered to be an independent predictive factor for better disease-free survival and survival in RCC treated by nephrectomy, but not in mRCC [15]. In some studies, *VHL* mutations were more frequent in small low-stage or low-grade tumours [16].

#### 2.4. Consequence of hypoxia-induced pathway involvement and renal cell carcinoma

In RCC as in many tumours, a critical breakthrough was made with the discovery of the link between the HIF pathway and angiogenesis.

VEGF production by induction of the HIF pathway is a recent discovery in RCC. VEGF acts by binding to the VEGF receptor (VEGFR1–3). VEGFR2 is the main receptor for inducing the effects of VEGF activation. Activation of the VEGFR2 signalling pathway leads to induction of metalloproteinases and increased vascular permeability, activation of endothelial cells leading to proliferation, and activation of anti-apoptotic events in endothelial cells and endothelial progenitor cells. Studies have shown that VEGF is overexpressed in RCC, which seems to be a prognostic factor for survival in patients with mRCC [17].

PDGF is another peptide produced by the HIF-dependent gene. PDGF targets vascular pericytes and facilitates the modelling of tumour vessels. TGF $\alpha$  (transforming growth factor alpha) is a ligand for EGFR (epidermal growth factor receptor) and activates the EGFR pathway. In RCC, altered expression of TGF $\alpha$  is associated with tumour development. The glucose transporter GLUT-1 is overexpressed in RCC and its implication in the development or RCC progression is suspected, where a low level of expression on tumour microarrays was associated with a trend for better survival in clear-cell and papillary tumours. Regulation of pH has been a special focus in RCC, showing that a decreased level of carbon anhydrase IX was correlated with a worse outcome in mRCC.

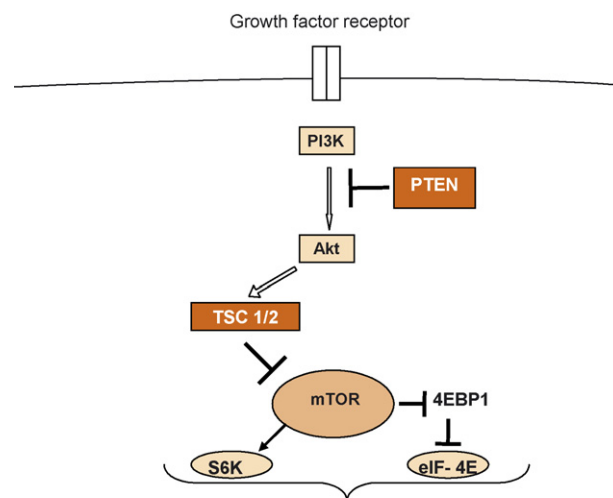
#### 2.5. Mammalian target of rapamycin pathway (Fig. 2)

The mTOR pathway is implicated in angiogenesis and in phosphatidylinositol 3-kinase (PI-3 kinase) pathway [18]; mTOR regulates the translation of 4EBP1 (eukaryotic translation initiation factor 4E binding protein) and S6K1 (ribosomal S6 kinase 1) [19]. The mTOR pathway is directly under the control of the PI-3 kinase pathway with downstream events but also acts in the regulation of this pathway. The mTOR is considered to promote angiogenesis in RCC by VEGF production and by facilitating proliferation of endothelial cells through serine/threonine kinase Akt activation and anti-apoptotic mechanisms.

PI-3 kinase stimulates the activation of Akt which inhibits the tuberous sclerosis complex TSC1 and TSC2 proteins from activating mTOR. Moreover, mTOR is able to inhibit the PI-3/Akt pathway.

The mTOR pathway has been reported to be more significantly altered in clear-cell RCC, high-grade tumours, and tumours with poor prognostic features [20].

The *PTEN* (phosphatase and tensin homolog deleted on chromosome Ten) tumour suppressor gene is frequently mutated or deleted in a wide variety of solid tumours, and



Gene transcription Cell growth Proliferation VEGF production

**Fig. 2 – The mTOR-induced pathway. Activation of mTOR results in the stimulation of the translational process, triggering the production of growth factors including VEGF (vascular endothelial growth factor). Control of mTOR activation is targeted within the PI3 kinase pathway. PI3K: phosphatidylinositol 3-kinase; mTOR: mammalian target of rapamycin; S6K: ribosomal S6 kinase; 4EBP1: eukaryotic translation initiation factor 4E binding protein; PTEN: phosphatase and tensin homolog deleted on chromosome ten; TSC: tuberous sclerosis complex.**

these cancers are generally more aggressive. PTEN negatively controls Akt activity. Exploration of protein expression of PTEN in renal carcinogenesis has shown that PTEN is highly expressed in normal renal tissue specimens while in RCC its expression is reduced to less than 10% compared with normal tissue [20].

#### 2.6. Epidermal growth factor receptor pathway

EGFR and its ligands, EGF and transforming growth factor-alpha (TGF- $\alpha$ ), are overexpressed in RCC. Analysis has shown an overexpression of EGFR in RCC. Adding EGF to RCC cell lines increases tumour invasion and motility. When EGFR pathway inhibitors are added to RCC tumour cell lines or given to mouse models, tumour angiogenesis is inhibited.

### 3. Vascular endothelial growth-factor inhibition

A tremendous step forward in the therapeutic management of mRCC has been achieved with anti-angiogenics [6]. These changes were incorporated into EAU guidelines in 2007 [21].

#### 3.1. Sunitinib (Table 1)

Sunitinib is an orally administered tyrosine kinase inhibitor of multiples targets especially VEGFR1,

**Table 1 – Medical treatment in advanced renal cell carcinoma phase II/phase III trials with anti-angiogenics, mTOR (mammalian target of rapamycin) inhibitors or EGFR (epidermal growth factor receptor) tyrosine kinase inhibitor**

Author	Trial design	Treatment	Patients n	Line of treatment	OR (%)	PFS (mo)	OS (mo)
Motzer [22,23]	Phase II	Sunitinib	63	≥First	40	8.7	16.4
			106	≥First	34	8.3	NR
Motzer [24]	Randomised phase III	Sunitinib vs IFN- $\alpha$	451	First	31 <sup>*</sup>	11 <sup>*</sup>	NR
			452		6	5	–
Yang [29]	Randomised phase II	Bevacizumab HD/LD vs placebo	39/37	≥Second	10/0	>4*/<4	–
			40		0	<4	–
Bukowski [31]	Randomised phase II	Bevacizumab/placebo vs Bevacizumab/erlotinib	53	First	13	8.5	NR
			51		14	9.9	20
Escudier [30]	Randomised phase III	Bevacizumab/IFN- $\alpha$ vs IFN- $\alpha$ /placebo	327	First	31 <sup>*</sup>	10.2 <sup>*</sup>	NR
			322		13	5.4	19.8
Escudier [32]	Randomised phase III	Sorafenib vs placebo	451	Second	2	5.5 <sup>*</sup>	NR
			452		0	2.8	14.7
Szczylik [34]	Randomised phase II	Sorafenib vs IFN- $\alpha$	97	First	5	5.7	–
			92		9	5.6	–
Hudes [37]	Randomised phase III	Temsirolimus vs IFN- $\alpha$ vs IFN- $\alpha$ /temsirolimus	209	First	8.6	3.7 <sup>**</sup>	10.9 <sup>*</sup>
			207		4.8	1.9	7.3
			210		8.1	3.7 <sup>*</sup>	8.4
Jac [39]	Phase II	Everolimus	41	≥First	32	>11.2	>24.2
Ravaud [40]	Randomised	Lapatinib	209	Second	1.4	3.7	11.4
	Phase III	vs hormonal therapy	207		0.5	3.7	10.5

OR: objective response rate; PFS: progression-free survival rate; OS: Overall survival rate; HD (high dose): 10 mg/kg; LD (low dose): 3 mg/kg. NR: Not remarkable.

\* $p < 0.001$ ; \*\* $p < 0.0001$ .

VEGFR2, VEGFR3 and PDGFR- $\alpha$  and PDGFR- $\beta$ . Two phase II studies in patients with cytokine-refractory mRCC showed an objective response rate (OR) >35% and a prolonged progression-free survival rate (PFS) compared with previous results [22,23]. A phase III trial comparing sunitinib with interferon alpha (IFN- $\alpha$ ) as first-line therapy was planned [24]. Seven hundred patients with mRCC were randomised to receive sunitinib at a dosage of 50 mg/d for 4 wk, every 6 wk, or IFN- $\alpha$ . The median PFS was 11 mo in the sunitinib group and 5 mo in the IFN- $\alpha$  group (hazard ratio [HR]: 0.42; 95% confidence interval [CI]: 0.32–0.54;  $p < 0.001$ ). The OR was 31% in the sunitinib group (95% CI: 26–36) and 6% for the IFN- $\alpha$  arm (95% CI: 4–9;  $p < 0.001$ ). No mature data on survival are available. Based on these results, sunitinib is now a new reference standard for first-line treatment of clear-cell mRCC [21,25].

An analysis of prognostic factors showed that the benefit of sunitinib extends across all prognostic risk-factor groups [26]. In patients with favourable, intermediate, and poor risk outcome the median PFSs were 14 mo, 9 mo, and 4 mo, respectively, with sunitinib, compared to 8 mo, 4 mo, and 1 mo, respectively, with IFN- $\alpha$ . Furthermore, in a retrospective analysis, sunitinib exposure measured by the steady-state area under the curve (and varied by 4-fold for a fixed dose) had an influence on efficacy [27].

The continuous administration of sunitinib at 37.5 mg/d has been assessed. Among 107 patients in a phase II trial, 21 patients (20%) and 56 patients (52%) had a partial response or a stable disease, respectively [28]. The median PFS was 36 wk. An ongoing trial is comparing the two schedules of administration of sunitinib.

### 3.2. Bevacizumab (Table 1)

Bevacizumab is a humanised monoclonal antibody that binds isoforms of VEGF-A. Bevacizumab was evaluated in patients refractory to immunotherapy and showed a gain in OR (10%) and in PFS compared to placebo at a dose of 10 mg/kg every 2 wk [29]. Therefore a double-blind phase III trial in 649 patients with mRCC received bevacizumab or placebo added to IFN- $\alpha$  [30]. PFS was significantly increased from 5.4 mo to 10.2 mo (HR: 0.63;  $p < 0.0001$ ) with addition of bevacizumab to IFN- $\alpha$  compared with IFN- $\alpha$  alone. The benefit of bevacizumab plus IFN- $\alpha$  was seen in patients with both good (12.9 mo vs 7.6 mo) and intermediate (10.2 mo vs 4.5 mo) prognoses, but was not detected in the group of poor-risk (2.2 mo vs 2.1 mo) patients. OR was 31% in the bevacizumab-plus-IFN- $\alpha$  group versus 13% ( $p < 0.0001$ ) in the placebo-plus-IFN- $\alpha$  group. No mature data are available on survival. The efficacy of first-line treatment with bevacizumab alone has also been evaluated in a randomised

phase II trial with OR of 13% and PFS of 8.5 mo [31]. Based on the results from the phase III trial, the combination of bevacizumab plus IFN- $\alpha$  has been considered as an additional option to first-line treatment because questions are still being raised about the benefit added by IFN- $\alpha$  and about the dosage of IFN- $\alpha$  to be combined.

### 3.3. Sorafenib (Table 1)

The activity of sorafenib was reported in a randomised discontinuation trial in patients having received at least one previous line of treatment, showing stabilization, and usually showing less than an objective response in 70% of the patients. This study was followed by a placebo-controlled phase III trial in patients in whom cytokine therapy had failed [32]. Sorafenib significantly prolonged PFS compared to placebo (24 wk vs 12 wk; HR: 0.44;  $p < 0.000001$ ). OR was only 2%. The gain was observed in all prognostic risk-factor groups. Patients were subsequently unblinded and 216 of the 452 patients receiving placebo crossed over to sorafenib. At the final analysis, overall survival (OS) for the intent-to-treat population did not differ significantly between sorafenib (17.8 mo) and placebo (15.2 mo) [33]. Sorafenib has also been investigated as a first-line treatment, and PFS did not differ between sorafenib and interferon alpha (5.7 mo vs 5.6 mo) [34]. A more intensive administration of sorafenib was tested with a pre-planned dose escalation: among 44 evaluable patients, 8 patients had a complete response, 14 patients had a partial response (PR), and 14 had stable disease  $\geq 3$  mo [35]. This study is compelling because the highest response rate described to date with sorafenib and a complete response rate never observed with anti-angiogenics, thereby justifying a similar ongoing multicentre study.

## 4. Mammalian target of rapamycin inhibition

### 4.1. Temsirolimus (Table 1)

Temsirolimus, an mTOR kinase inhibitor, is effective in patients with poor-risk mRCC [36,37]. In the pivotal phase III, patients with poor-risk mRCC were randomised to receive first-line treatment with temsirolimus or IFN- $\alpha$  alone or in combination. In the temsirolimus group, overall survival was 10.9 mo (95% CI: 8.6–12.7), which was significantly longer than in the IFN- $\alpha$  group (median: 7.3 mo; 95% CI: 6.1–8.9), with an HR of 0.73 (95% CI: 0.57–0.92;  $p < 0.0069$ ). However, OS in the combination group (median: 8.4 mo) was not significantly improved. The benefit of

temsirolimus on PFS and OS was more pronounced in patients with non-clear-cell histology tumours, but was not seen in the subpopulation of patients  $\geq 65$  yr old [38]. Based on these results, temsirolimus has been recommended as a first-line treatment in patients having at least three poor prognostic factors.

### 4.2. Everolimus

Everolimus (RAD001), an oral mTOR inhibitor, has shown activity in a phase II trial of patients with mRCC [39]. Patients with no more than one prior therapy received everolimus 10 mg/d. Twelve patients (23%) exhibited a partial response and 14 (38%) had stable disease. PFS was 11.2 mo. There are pending results from a phase III trial comparing everolimus to placebo after failure under anti-angiogenic therapy.

## 5. Epidermal growth-factor inhibition

### 5.1. Lapatinib

Lapatinib, a dual inhibitor of EGFR (ErbB-1) and ErbB-2 receptors, was compared with hormone treatment in a phase III trial after failure of first-line cytokine therapy [40]. Median time to progression (TTP) and median OS did not differ between the two groups. However, patients with high tumour EGFR expression showed a significantly longer OS (46.0 vs 37.9 wk; HR 0.69;  $p = 0.02$ ).

## 6. Toxicity

Knowledge of the toxicity of anti-angiogenics has largely increased in recent years and was the topic of a recent paper in European Urology [41]. There is still major concern about how these treatments should be administered in elderly patients, in patients with recent vascular events, or in those taking drugs that potentially interact with hepatic drug metabolism [42].

Less is known about the mTOR inhibitors, although there is a large body of literature on organ transplantation. They appear to be less toxic than anti-angiogenics.

## 7. Sequential treatment after one line of anti-angiogenics

At present, no validated treatment has resulted from randomised phase III trials. Nevertheless, most data

point toward the absence of cross-resistance between anti-angiogenics, so another anti-angiogenic may be used after the failure of a previous one while awaiting definitive results of a phase III trial.

### 7.1. Anti-angiogenics following sunitinib

A retrospective study demonstrated that sorafenib following sunitinib was only moderately efficient, with an impact frequently limited to stabilization [43]. In 22 patients progressing under sunitinib and then receiving sorafenib, one patient had PR and another stabilised.

### 7.2. Anti-angiogenics following bevacizumab

In a phase II trial, sunitinib was given to bevacizumab-refractory patients. Among 61 patients, 14 patients (23%) had a PR, and 36 (59%) had a stable disease [44]. Median PFS was 30.4 wk.

### 7.3. Anti-angiogenics following sorafenib

A retrospective study has shown that sunitinib following sorafenib may induce stabilisation or a PR [43]. In 68 patients progressing under sorafenib and receiving sunitinib, 10 patients (14.7%) had PR, and 34 (50%) had stable disease. More interestingly, among 10 patients who had progressed under sorafenib, 2 and 3 patients presented PR and stable disease, respectively.

## 8. Combination of targeted therapies

While anti-angiogenic therapy represents a breakthrough in the treatment of mRCC, most patients experience progression in <12 mo. Preclinical findings justify increasing the inhibition on the anti-angiogenic pathway in a direct way. Therefore, associations of drugs for vertical inhibition have been proposed associating monoclonal antibodies of the VEGF pathway or tyrosine kinase inhibitors of the VEGFR pathway or mTOR inhibitors. The other way to inhibit tumour cell growth is to inhibit multiple pathways involved in the process. To date, only angiogenesis and the mTOR pathway have been shown to be major pathways and to support the association of related drugs.

### 8.1. Anti-angiogenics and anti-angiogenics

The association of bevacizumab and sunitinib has been explored in a phase I study [45]. Nineteen

patients with mRCC received escalating doses of sunitinib from 25 mg/d to 50 mg/d with fixed-dose bevacizumab (10 mg/kg IV). Dose-limiting toxicity (DLT) was grade 4 haemorrhage in one patient in each of the higher doses and one fatal myocardial infarction at the highest dose. All levels of treatment induced a 37% PR. The recommended dose for a further phase II study was considered to be sunitinib and bevacizumab at the standard dose when given alone.

The association of bevacizumab and sorafenib has been explored in a phase I trial [46]. Sixteen patients were included for a dose escalation. Grade 3 proteinuria and uncontrolled grade 3 hypertension were DLT at the highest level, corresponding to the maximum tolerated dose (MTD), and the recommended dose was sorafenib at 200 mg twice daily (BID) and bevacizumab at 5 mg/kg.

### 8.2. Anti-angiogenics and interferon alpha

In phase I trials, patients received sunitinib or sorafenib and IFN- $\alpha$  with DLT which included fatigue and myelosuppression. Only inferior dosages of both sunitinib or sorafenib and IFN- $\alpha$ , compared to optimal dosages in monotherapy, were manageable.

Four phase II studies have evaluated the association of sorafenib and IFN- $\alpha$  at standard or low dosages with inconstant gain for the association.

### 8.3. Anti-angiogenics and other drugs

Anti-angiogenics have been combined with mTOR inhibitors to enhance the inhibition of angiogenesis while using the mTOR pathway involved in angiogenesis and/or to inhibit various pathways when using the larger spectrum of mTOR activity.

Temsirolimus and bevacizumab were associated without MTD to the standard dose of each drug in a phase I study [47]. During the phase I trial, up to a recommended weekly dosage of temsirolimus at 25 mg/kg IV and bevacizumab at a dosage of 10 mg/kg/2 wk, DLT encountered were grade 3 stomatitis and hypertriglyceridemia. Among 12 evaluable patients, 8 PR were reported.

Temsirolimus and sorafenib have been evaluated [48]. Patients were treated with escalating continuous oral doses of sorafenib (200 mg BID and 400 mg BID) and weekly IV temsirolimus (15 mg and 25 mg). Thirty-three evaluable patients showed DLT which included grade 3 hand-foot syndrome, mucositis, rash, thrombocytopenia, neutropenia, and creatinine-level elevation. The full recommended dosage

of both drugs appeared unachievable mainly owing to mucositis.

## 9. Predictive factors for efficacy of targeted drugs in metastatic renal cell carcinoma

The prognosis of patients with mRCC at the diagnosis of metastatic spread is usually based on the Memorial Sloan-Kettering Cancer Center (MSKCC) classification. However, little is known about how to identify the patients who have a fair chance of benefiting from “standard” anti-angiogenics. In this respect, the pivotal study using sunitinib as a first-line treatment showed that low haemoglobin ( $p = 0.004$ ), calcemia  $>10$  mg/ml ( $p = 0.001$ ), ECOG  $> 0$  ( $p = 0.0005$ ), more than one metastatic site ( $p = 0.0064$ ), and interval between diagnosis and treatment  $<1$  yr ( $p = 0.0002$ ) were independent adverse prognostic factors [26].

## 10. Non-clear-cell histology

To date, most mRCC patients included in trials have had a predominantly clear cell histology, and there is no available prospective data on other histologies, especially papillary (PRCC) and chromophobe (ChRCC) features. A multicentre retrospective study analysed 41 files of patients with PRCC and 12 with ChRCC [49]. Two patients with PRCC had PR and were treated with sunitinib. Twenty-seven (68%) patients had a stable disease  $\geq 3$  mo. PFS was 7.6 mo with a trend for better PFS with sunitinib than sorafenib (11.9 mo vs 5.1 mo). For patients with ChRCC, three patients (25%) had a response (two with sorafenib and one with sunitinib), and all the others had at least a stable disease  $\geq 3$  mo. PFS was 10.6 mo, and patients treated with sorafenib exhibited a trend toward more prolonged PFS (27.5 mo).

Another study evaluated the influence of histological subtype on the efficacy of temsirolimus as a first-line therapy [37]. In the phase III trial comparing temsirolimus to IFN- $\alpha$ , 18% were non-clear-cell RCC. PFS and overall survival rates were 7 mo and 11.6 mo, respectively, in PRCC patients, while they were 5.5 mo and 10.6 mo in clear-cell RCC patients.

## 11. Discussion

### 11.1. Impact of the update in practice

Recent findings have considerably clarified the first-line treatment for mRCC patients.

Only in specific circumstances should patients with a good performance status and only one site of metastasis be given immunotherapy. This represents fewer than 5% of the population of mRCC patients [4,21,50].

All other patients should be proposed anti-angiogenics based on the results of phase III trials, arguing for sunitinib as the standard treatment and bevacizumab plus IFN- $\alpha$  as an option.

For patients with poor MSKCC performance characteristics, temsirolimus has shown an advantage in survival rates. Sunitinib or sorafenib have shown some efficacy and therefore represent an optional treatment.

As second line of treatment, sorafenib is the drug of choice following immunotherapy, while sunitinib is an option, considering that immunotherapy still has a place for a selected population.

As a second line of treatment after an anti-angiogenic therapy, we recommend including patients in clinical trials because no drug has shown any benefit in prospective phase III trials. Nevertheless, another anti-angiogenic could be used in view of prospective phase II trials and retrospective reports. Data are pending on the role of mTOR inhibitors in this setting.

Moreover, information coming from clinical trials pointed out objective response rate, PFS, and/or OS. Whatever the gain in response rate, the impact of the drug on PFS or on OS is the most important goal. However, when a patient has symptoms due to the disease, which is not a rare event, there is concern for improvement of the symptoms as well as a gain in PFS or in OS. In such cases, the fact that some drugs provide an objective response rate of more than 30% could be useful.

## 12. Conclusions

The last couple of years have been especially promising for the treatment of mRCC with published phase III trials on sunitinib, sorafenib, temsirolimus, and bevacizumab, and preliminary data on sequential treatments and the association of targeted drugs. Major data are pending with regard to the ability of targeted-based therapy to induce a substantial subset of durable complete response, the impact of initial nephrectomy, what constitutes the optimal first-line therapy, and the impact on survival in the adjuvant setting.

Collaboration between urologists and medical oncologists will no doubt increase and become closer through their daily practice and in clinical trials focusing on the management of RCC.

**Author contributions:** Alain Ravaud had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Ravaud, Patard.

**Acquisition of data:** Ravaud, Culine, Fergelot, Bensalah.

**Analysis and interpretation of data:** Ravaud, Culine, Fergelot, Bensalah.

**Drafting of the manuscript:** Ravaud, Wallerand, Culine, Jean-Patard.

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### Editorial Comment on: Update on the Medical Treatment of Metastatic Renal Cell Carcinoma

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Advanced and metastatic renal cell cancer (RCC) is resistant to conventional chemotherapy, and long-term survival with immunotherapy is rare. Since the advent of the “smart drugs,” however, the treatment of advanced RCC has made progress [1].

In this paper, the authors give substantial attention to “major improvements,” “major breakthroughs,” and “especially promising data” [2]. The results obtained have indeed been considered “exciting” by medical oncologists. However, urological oncologists, who in Europe see most patients with RCC, are more cautious about the benefits of these new drugs on cancer-specific survival (increases in which amount to months and not years) and are more concerned about their initially underestimated toxicity.

The authors extensively report on treatment regimens, often those that have been previously published; yet they deal with the toxicity of angiogenics and mTOR inhibitors in only a few sentences. Let us remember that a poor tolerance of the drugs can necessitate dose adaptation, which sometimes equals suboptimal regimens. Sometimes treatments must be stopped, exposing patients to possible disease exacerbation. New toxicities have been recently reported such as in intracerebral haemorrhage [3] and direct cardiomyocyte toxicity [4]. The latter certainly needs further exploration. Considering the efficacy and toxicity of these drugs, the statement made by the authors that “all other patients should be proposed anti-angiogenics” is perhaps a bridge too far [5].

The interesting points of the paper are the sequential and combination strategies (with unavoidable increased toxicity). Disappointing in our knowledge is the lack of predictive factors of response. Further research is needed [6] and we have to reassess the prognostic systems that were designed in the era of immunotherapy.

Despite the results obtained with the small molecules, vaccination therapy is promising and needs to be further explored. Advanced RCC remains a challenge for organ-based specialists, but at least we have now medical treatments that we can discuss with our patients.

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### Editorial Comment on: Update on the Medical Treatment of Metastatic Renal Cell Carcinoma

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Medical treatment for metastatic renal cell carcinoma (RCC) is one of the hottest topics in urologic oncology. The data of a few recently published randomized controlled trials using sunitinib, sorafenib, and temsirolimus, as first- or second-line therapies in patients with metastatic RCC, has transformed the panorama of treatments for those patients (references 24, 32, and 37 in the text), and urologists and medical oncologists are witnessing an enormous increase in interest in

these so-called targeted therapies. To date, several molecules of proved or potential interest have been identified, including those inhibiting vascular endothelial growth factor (VEGF) (axitinib, bevacizumab, pazopanib, sunitinib, sorafenib), epidermal growth factor (EGF) (cetuximab, erlotinib, gefitinib, lapatinib, pazopanib), and the mTOR pathway (temsirolimus, everolimus) [1].

Prof. Ravaud and colleagues should be commended for their effort to summarize the fast-growing literature in the field in a review paper of great practical and educational usefulness [2].

The most recently released guidelines in the treatment of RCC recommended the use of the angiogenesis inhibitor drugs, although “the exact place of these new drugs is still open for discussion” [3]. Clearly, the revolution of the targeted therapies is just beginning, and several open questions have still to be addressed, including timing and role of surgery, role of tumour histologic subtype, optimal timing of treatment, patients’ selection for the either first- and second-line therapies, and so on [4,5]. Consequently, due to the large number of randomized controlled trials planned or already ongoing sponsored by the

different companies producing these new drugs, the literature in the field will be larger and larger, hopefully improving our patients’ chances of survival, as well as their quality of life.

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