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mTOR inhibitors in advanced renal cell carcinomas: From biology to clinical practice

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Abstract

To date, oral everolimus is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with vascular endothelial growth factor-targeted therapy, and intravenous temsirolimus for the first-line treatment of patients with poor prognosis metastatic renal cell carcinoma. However, some factors could guide the treatment choice aiming to individualize a treatment plan. Besides the crucial issue of treatment efficacy, other factors are to be considered such as disease status, histological subtype, extent of the disease, patient-specific factors, and agent-specific factors. All of these considerations have to stay in the frame of guideline recommendations which represent evidence-based medicine. The purpose of this article is to summarize the main pharmacological and pharmacokinetic characteristics of mTOR inhibitors, and to define targeted populations according to prognostic indexes.

Keywords: Temsirolimus; Everolimus; Kidney cancer; mTOR inhibitors

1. Introduction

In 2008, about 88,400 new cases of renal cell carcinoma (RCC) occurred in Europe, making it the 10th most common cancer [1]. During last decades, this incidence has constantly increased. At the time of diagnosis, more than 10% of RCC are metastatic [1]. For a long time, metastatic RCC (mRCC) has been considered as resistant to the majority of treatments resulting in a poor outcome. Since 2006, the better knowledge of the biological mechanism of RCC led to the development of novel agents targeting hypoxia inducible factor (HIF)/vascular endothelial growth factor (VEGF) pathways, as well as mammalian target of rapamycin (mTOR) pathway that are both involved in renal cell carcinogenesis. These new agents include tyrosine kinase inhibitors (TKI) targeting the VEGF receptors (VEGF-R) (axitinib, pazopanib, sorafenib, sunitinib, tivozanib); monoclonal antibodies directed against the VEGF (bevacizumab); and mTOR inhibitors (everolimus, temsirolimus) [2].

Angiogenesis is the main pathway playing an important role in invasion and dissemination of RCC. Angiogenesis is mediated by numerous pro-angiogenic factors, including the VEGF considered as the cornerstone of this process [3], and the deletion of the von Hippel Lindau (VHL) gene is the most common genomic event in clear-cell carcinomas, which represents 75% of RCCs [4,5]. mTOR is a highly conserved serine–threonine kinase and a key regulatory protein in cancer that recognizes stress signals via the phosphoinositide 3-kinase (PI3K)–Akt pathway. The activation of the PI3K/Akt/mTOR pathway is crucial for proliferation and survival of numerous malignancies including RCC. Signals from growth factor receptors activate PI3K, resulting in Akt activation and, finally, activation of the centrally located downstream mTOR (Fig. 1). It has been demonstrated that

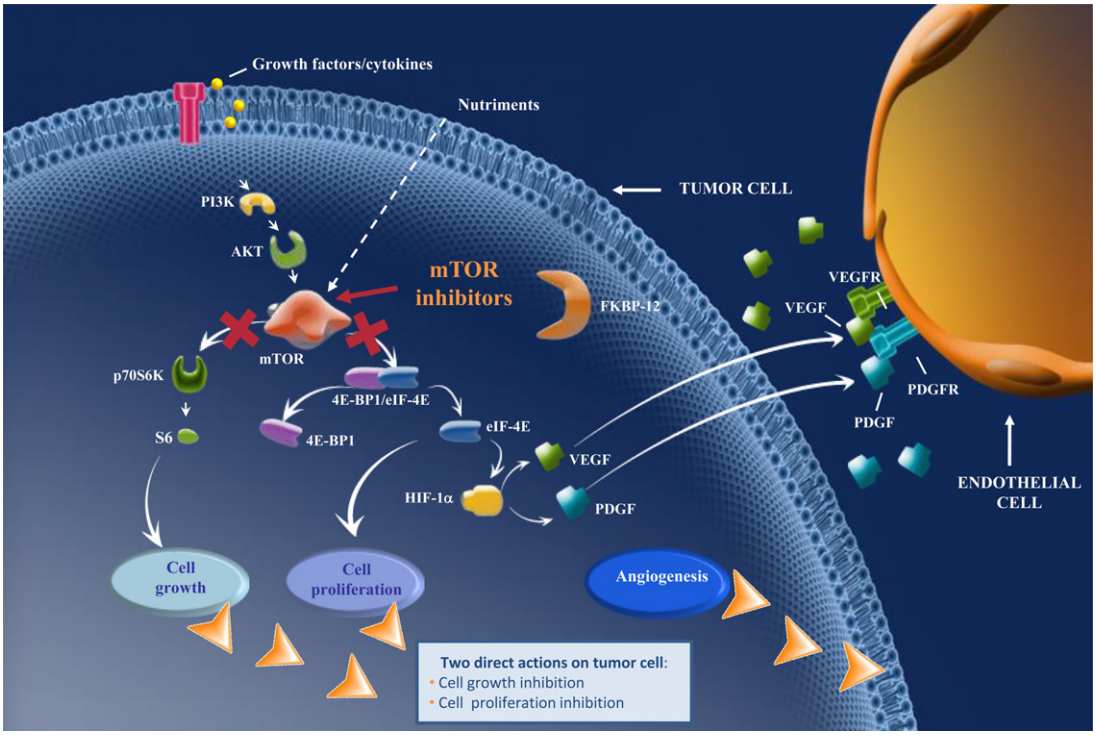

Fig. 1. Action of mTOR inhibitors on PI3K/Akt/mTOR signaling pathway.

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Akt, mTOR, and p70S6K1 are phosphorylated (activated) in most cancer types. These data suggest that mTOR might be a promising target in cancer treatment [6,7]. Several arguments highlight an important role of mTOR as element participating in the pro-mitogen transduction of the signal: mTOR and PI3K proteins are essential for the activity of VEGF on proliferation, survival and migration of endothelial cells [8]. The blocking of this pathway would prevent the action of VEGF and consequently the cell proliferation. The mTOR protein regulates the expression of the HIF1-α and HIF2-α, thus linking the mTOR pathway to angiogenesis [9]. The mTOR inhibitors, by decreasing the expression of the HIF, act on the tumor angiogenesis. Direct signs of activation increased by the Akt/mTOR/p70S6K1 pathway were observed in RCC [10].

To date, everolimus and temsirolimus are both registered for the treatment of mRCC. According to the REnal Cell Cancer Treatment with Oral Rad001 (RECORD-1) pivotal study, oral everolimus is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy [11,12]. As regards temsirolimus, the Global Advanced Renal Cell Carcinoma (ARCC) pivotal study demonstrated the superiority of intravenous (IV) temsirolimus over interferon alpha (IFN-α) for the first-line treatment of patients with poor prognosis mRCC [13].

The purpose of this article is to summarize the main pharmacological and pharmacokinetic characteristics of mTOR inhibitors, to define targeted populations according to prognostic indexes, to refine indications according to the results of the studies as well as patient's profile such as histological characteristics, safety and comorbidities. In terms of future directions, some topics such as mechanisms of resistance, predictive factors of response to mTOR inhibitors and, thereby, clinical trials to conduct require to go further.

2. Biological action and pharmacokinetic characteristics

2.1. Biological action: the mTOR signaling network

The mTOR signaling pathway was first identified during studies exploring the immunosuppressive activity of an agent called rapamycin. Rapamycin, also named sirolimus, was originally identified as a natural antifungal antibiotic isolated from the bacteria *Streptomyces hygroscopicus* in the 1970s [14,15]. Due to its ability to potently inhibit T-cell function, rapamycin was initially mainly used as an immunosuppressant in recipients of solid organ transplantation [16], but subsequently was found to be an attractive candidate for application in oncology due to its antitumor activity, including preclinical models for RCC [17,18]. Several analogs of rapamycin, including everolimus and temsirolimus, have been developed to improve solubility and bioavailability. They share the same mechanism of action and have been successfully applied in the treatment of various solid malignancies [19].

Rapamycin and its analogs do not directly inhibit the mTOR kinase. mTOR inhibitors functions in a manner similar to rapamycin but with an improved pharmaceutical profile. They bind with high affinity to the FK binding protein 12 (FKBP-12), an abundant intracellular immunophilin [20]. Interaction of the mTOR inhibitors–FKBP-12 complex with mTOR inhibits its kinase activity, resulting in decreased phosphorylation of the mTOR-regulated translational controllers p70 ribosomal protein S6 kinase 1 (p70S6K1) and 4E-binding protein-1 (4EBP-1) [21,22]. Ultimately, mTOR inhibitors inhibits the synthesis of various proteins that have important roles in the cell cycle and tumorigenesis, such as cyclin D1, HIF, and VEGF [17,23]. The resulting complex potently inhibits the kinase activity of mTORC1, but has no suppressive effects on mTORC2 (Fig. 2) [23,24].

2.2. mTOR inhibitors: pharmacokinetic characteristics and clinical implications

Temsirolimus (Torisel; Pfizer, New York, NY, USA) is a water-soluble prodrug of rapamycin rapidly metabolized to sirolimus through de-esterification at position C43; both are potent binders of FKBP-12, and each forms an inhibitory complex with subsequent suppression of mTORC1 activity [25]. However, because of its intrinsic mTOR inhibitory activity, temsirolimus is not considered as a prodrug [20]. Temsirolimus is available as a concentrate for solution for IV injections (25 mg/mL). The recommended dose for RCCs treatment is 25 mg weekly [13].

Everolimus (Afinitor; Novartis, Basel, Switzerland) is an orally bioavailable hydroxyethyl ether derivate of rapamycin and, unlike temsirolimus, is not converted to sirolimus in vivo [25]. Everolimus is available as oral tablets of 1.5 mg, 5 mg and 10 mg. The daily recommended dose is 10 mg, either with or without food [11]. Respective pharmacokinetic characteristics of temsirolimus and everolimus are summarized in Table 1 [11,13,26–32].

2.2.1. Drug interactions

Temsirolimus. Temsirolimus and its primary metabolite, sirolimus, are metabolized by the cytochrome P450 (CYP) 3A4 pathway [28]. Potential drug interactions for temsirolimus exist with agents that modulate CYP3A4 activity. If a concomitant strong CYP3A4 inhibitor is necessary, a temsirolimus dose reduction to 12.5 mg weekly should be considered, and the most common agents are listed in Table 2 [30]. In vitro studies showed that temsirolimus and sirolimus inhibit the CYP2D6. However, a single IV dose of 25 mg temsirolimus did not alter the disposition of desipramine, an antidepressant using the CYP2D6 metabolic pathway [33]. Therefore, no dose adaptation is recommended for concomitant treatment interfering with the CYP2D6 pathway.

Everolimus [27]. Everolimus is metabolized mainly in the gut and liver by CYP3A4, CYP3A5, CYP2C8, and the efflux

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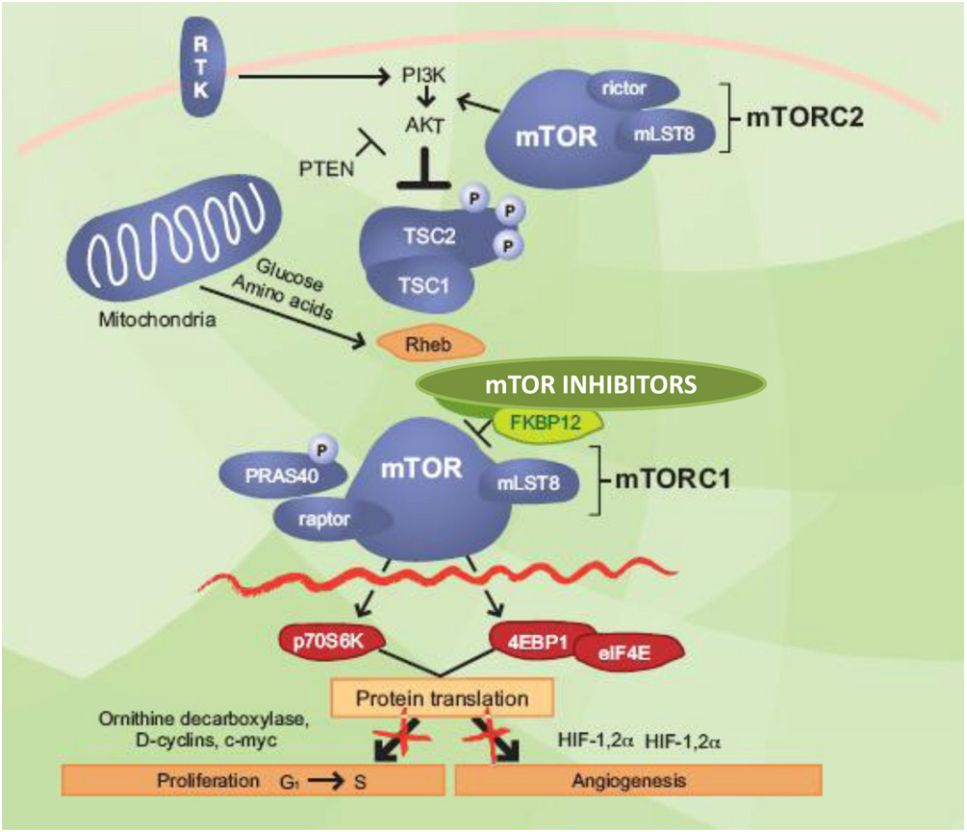

Fig. 2. Action of mTOR inhibitors on kinase activity of mTORC1 and mTORC2 [24].

transporter P-glycoprotein (PGP). Everolimus and four main metabolites, hydroxy-, dihydroxy-, and demethyl-everolimus and the ring-opened form of everolimus, were found in blood. Everolimus is, at the same time, a moderate inhibitor of PGP, a competitive inhibitor of CYP3A4, and a mixed inhibitor of CYP2D6 in vitro. Potent or moderately potent inhibitors of CYP3A4 will cause a pharmacokinetic interaction, resulting in higher C_{max} and AUC values for everolimus. Therefore, concomitant use of potent or moderately potent CYP3A4 inhibitors should be avoided (Table 2).

Table 1
Summary of pharmacokinetic features of temsirolimus and everolimus [11,13,26–32].

Pharmacokinetic parameters	Temsirolimus	Everolimus
Route of administration	IV	Oral
Recommended dose	25 mg weekly [13]	10 mg daily [11]
Absorption	Not applicable	Bioavailability of about 16% [26]; reduced by 50% with high-fat meal [27]
Protein binding	85% [28]	75% [27]
Metabolism	By CYP3A4 to active metabolite sirolimus [28]	By CYP3A4, CYP3A5, and CYP2C8 in four main metabolites, hydroxy-, dihydroxy-, and demethyl-everolimus and the ring-opened form of everolimus [27]
Plasmatic peak	0.5–2.0 h [28]	1.2–2.0 h [27]
Elimination		
Terminal half-life	13 h [28]	26–38 h [29]
In the feces	78% [20]	98% [27]
In the urine	4.6% [20]	2% [27]
Drug interactions	50% dose reduction (i.e. 12.5 mg weekly) if concurrent strong inhibitors of CYP3A4 [30]	With CYP3A4, CYP3A5, and CYP2C8 inducers/inhibitors [27]
Dose adjustment		
Age	No [20]	No [29]
Hepatic impairment	Not studied if moderate or severe hepatic impairment	50% dose reduction (i.e. 5 mg daily) if significant hepatic impairment [31]
Renal impairment	No [32]	No [29] but not studied if concurrent hemodialysis

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Table 2
Common CYP3A4 inhibitors interacting with mTOR inhibitors.

Strong interaction	Moderate interaction	Weak interaction
Protease inhibitors (e.g. ritonavir)	Aprepitant	Cimetidine
Some macrolides antibiotics • Clarithromycin • Telithromycin	Some macrolide antibiotics • Erythromycin	Buprenorphine
Chloramphenicol	Some calcium channel blockers • Verapamil • Diltiazem	
Some azole antifungals • Itraconazole	Some azole antifungals • Fluconazole Bergamottin (constituent of grapefruit)	

2.2.2. *Comorbidities: modulations of mTOR inhibitor therapy according to different circumstances*

Age. Efficacy and dosing of temsirolimus and everolimus are independent of age [20,29]. No dose reduction is required in elderly patients.

Hepatic impairment. A higher incidence of thrombocytopenia was noted in patients with mild hepatic impairment treated with temsirolimus [28]. Moderate and severe hepatic impairment have not been studied in treatment with temsirolimus. The dosage of everolimus should be reduced by half in patients with significant hepatic impairment [31]. A liver monitoring should be considered to adapt the dose of mTOR inhibitors. The mTOR inhibitors have an immunosuppressive effect, which predispose patients to viral infections including reactivation of hepatitis B/C virus. A systemic screening of hepatitis B/C is therefore required before starting an mTOR inhibitor.

Renal impairment. Concurrent hemodialysis did not show any influence on temsirolimus and sirolimus pharmacokinetics, excluding the need for temsirolimus dose adjustments for renal impairment [32]. Only 2% of everolimus is eliminated in the urine; therefore, renal impairment is not expected to influence drug exposure [29]. No dosage adjustment of everolimus is recommended in patients with renal impairment. However, the impact of concurrent hemodialysis has not been studied.

3. Who to treat?

Temsirolimus is indicated for the first-line treatment of patients with poor prognosis mRCC whereas oral everolimus is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy [11–13]. Today, how can we define a poor prognosis in the era of antiangiogenic therapy, and, thereby, identify patients eligible for temsirolimus as first-line treatment of mRCC?

At the beginning of the 21st century, when immunotherapy was the cornerstone of mRCC treatments, a prognostic classification as defined by the Memorial Sloan-Kettering Cancer Center (MSKCC) identified three prognostic subgroups (good, intermediate, and poor) according to the following risk factors: Karnofsky general status < 80%, absence of prior nephrectomy, disease-free interval < 1 year, hemoglobin < lower limit of normal, lactate dehydrogenase (LDH) > 1.5× upper limit of normal, and corrected serum calcemia > 10 mg/dL [34]. A patient with zero risk factors has a favorable risk, a patient with one or two risk factors has an intermediate risk, and a patient with more risk factors has a poor risk for survival. In France, a simplified classification has been proposed by the Groupe Français d'Immunothérapie: a good prognosis was defined as a PS = 0 and a unique metastatic site; a poor prognosis was defined as PS ≥ 1, or liver metastases associated with at least another metastatic site and a disease-free interval < 1 year; the other patients are considered as having an intermediate prognosis [35].

At the era of targeted therapy, besides previous factors (PS, disease-free survival and corrected calcemia for sunitinib [36]), retrospective analyses, taking into account TKIs and bevacizumab, have highlighted new factors such as neutrophils (>4.5 × 10^9/L) and platelets (>300 × 10^9/L) [37,38]. More recently, the International Kidney Cancer Working Group developed a model using a dataset of 645 patients treated with TKIs [39]. Factors contributing to the prognostic index included Karnofsky PS, number of metastatic sites, disease-free interval, pretreatment hemoglobin, white blood count, LDH, alkaline phosphatase, and serum calcium. Median survival in the low, intermediate and poor risk groups was 26.9 months, 11.5 months, and 4.2 months, respectively.

In routine practice, the choice of physicians for a first-line treatment is usually influenced by the patient's PS, and disease symptoms instead of using validated prognostic factors. The response rate to mTOR inhibitors in first- and second-line remains low when compared to TKIs. Therefore, symptomatic patients with a good PS are currently treated with TKI to increase the achievement of a clinical response, even if the patient belongs to a poor prognosis group. On the other hand, patients with a poor PS are usually treated with temsirolimus as first-line treatment, regardless of other prognostic factors or symptoms because of the favorable toxicity profile. The choice between mTOR inhibitors and TKI as first-line treatment, as well as in second-line, is nowadays based on clinicians experience more than on evidence-based medicine [40]. Currently, no data from large randomized prospective trials are available comparing TKI and mTOR inhibitors in first-line treatment. Results of large randomized clinical trials are expected in the future such as the comparison of everolimus and sunitinib in first-line treatment. Besides, other factors are to be considered: histological

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subtype; patient-specific factors such as comorbidities, age, adherence to therapy, tolerability and quality of life (QoL); agent-specific factors taking into account drug availability, route of administration, pharmacokinetics, drug interactions, and cost of treatment. All of these considerations have to stay in the frame of guideline recommendations which represent evidence-based medicine.

4. What are the teachings from clinical data?

4.1. Pivotal studies

4.1.1. Temsirolimus

Promising results in phase I studies led to a dedicated phase II trial in heavily pretreated mRCC, showing an overall response rate (ORR) of 7%, a median progression-free survival (PFS) of 5.8 months, and a median overall survival (OS) of 15 months [41]. Although efficacy results were comparable among the three tested doses (25, 75 or 250 mg weekly), dose reductions and treatment discontinuations were more frequent at higher doses. A subgroup analysis by MSKCC risk group demonstrated greater than twofold survival differences between good or intermediate versus poor-risk patients at each. Compared with historical data for IFN-α, treatment benefit was most striking for the poor-risk population. Thereby, the subsequent phase III studies were designed for poor-risk mRCC patients at a weekly dose of 25 mg.

The Global Advanced Renal Cell Carcinoma (ARCC) multicenter, randomized phase III trial, conducted between 2003 and 2005, compared temsirolimus to IFN-α, or the combination, in advanced RCC [13]. Eligibility criteria allowed all histologic subtypes, but required participants to be previously untreated, and to belong to the poor prognostic subset of patients according to the MSKCC criteria, as abovementioned [34]. Overall, 626 patients were randomized to one of three arms: temsirolimus 25 mg intravenously (IV) once weekly, IFN-α 3 million units subcutaneously three times per week (escalated to 18 million units three times per week, if tolerated), or a combination of temsirolimus 15 mg IV weekly and IFN 3 million units (escalated to 6 million units three times per week). The primary endpoint was OS compared between temsirolimus, IFN-α and their combination. Efficacy in the intent-to-treat population revealed superior OS for temsirolimus over IFN-α ($p = 0.008$) but no improved OS for the combination over IFN-α alone ($p = 0.70$) (Table 3). The PFS was significantly improved in patients receiving temsirolimus ($p < 0.001$), although no significant difference was reported in terms of ORR (Table 3). In prespecified exploratory subgroup analyses, the superior survival benefit of temsirolimus was greatest for patients less than 65 years of age ($p = 0.02$) and for those with elevated LDH ($p = 0.008$). Based on this study, temsirolimus received FDA approval for the first-line treatment of poor prognosis, advanced RCC.

Table 3
Temsirolimus in first-line treatment of poor-prognosis mRCC patients: efficacy results of ARCC phase III trial [13].

Efficacy criteria	IFN-α	Temsirolimus	Temsirolimus-IFN-α
Number of patients	207	209	210
Response, %			
ORR[a]	4.8	8.6	8.1
Clinical benefit[b]	15.5	32.1	28.1
Median PFS, months[c]	1.9	3.8	3.7
Median OS, months	7.3	10.9	8.4

IFN-α, interferon alpha; ORR, overall response rate; PFS, progression-free survival; OS, overall survival.

[a] No significant differences among the three arms.

[b] Objective response or stable disease ≥6 months. The clinical benefit was significantly higher for patients receiving temsirolimus and the temsirolimus-IFN-α combination than in the IFN-α arm ($p < 0.001$ and $p = 0.002$, respectively).

[c] PFS was significantly longer in patients receiving temsirolimus ($p < 0.001$).

Table 4
Everolimus after failure of VEGF-targeted therapy in mRCC patients: final efficacy results, by independent central review of RECORD-1 phase III trial [12].

Efficacy criteria	Everolimus	Placebo	HR (95% CI)	*p*
Number of patients	277	139		
Response, %				
PR	1.8	0		
Median PFS, months	4.9	1.9	0.33 (0.25–0.43)	<0.001
Median OS, months	14.8	14.4	0.87 (0.65–1.15)	0.162

HR, hazard ratio; CI, confidence interval; PR, partial response; PFS, progression-free survival; OS, overall survival.

4.1.2. Everolimus

In phase I trial, a clinical efficacy was seen for several mRCC patients [29]. Subsequently, a single-arm phase II trial enrolled 41 mRCC patients with one or no prior regimen to be treated on everolimus 10 mg daily [42]. The trial reported a median PFS and OS of 11.2 and 22.1 months, respectively; ORR was 14%, and 70% of patients had a clinical benefit.

Subsequently, a multicenter, international, placebo-controlled phase III trial was conducted to investigate everolimus in patients who progressed on cytokines, sunitinib, sorafenib, or both TKIs [11]. The RECORD-1 trial assigned 416 patients with advanced RCC to either everolimus 10 mg daily or placebo by 2:1 randomization, both in conjunction with best supportive care. All subjects had clear-cell RCC that had progressed on or within 6 months after the end of therapy with TKIs. Updated results of RECORD-1 showed that the median PFS was significantly longer for patients receiving everolimus (4.9 months versus 1.9 months) with a hazard ratio (HR) of 0.33 (95% confidence interval [95% CI], 0.25–0.43; $p < 0.001$; Table 4) [12]. Partial responses were seen in 1.8% of patients receiving everolimus, none with placebo. The 10-month PFS was 25%. Benefit was seen in all MSKCC-risk groups regardless of prior therapy. A post hoc exploratory OS analysis to correct for bias introduced by crossover from placebo to everolimus after progression showed that survival time with everolimus was

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estimated at 1.9-fold longer than for placebo if no crossover occurred.

The RECORD-1 trial leads to the approval of everolimus as a standard second-line treatment of mRCC after failure to TKI. Nevertheless, recent data from the AXIS trial leads to the approval of axitinib, a new TKI, in second-line treatment after sunitinib failure [43]. In the AXIS trial, patients were stratified according to PS and type of previous treatment and then randomly assigned to either axitinib (5 mg twice daily) or sorafenib (400 mg twice daily). Axitinib resulted in significantly longer PFS compared with sorafenib. These recent data published by Rini et al. on axitinib questioned on the best second-line treatment and the best sequence between TKI–TKI–mTOR inhibitor versus TKI–mTOR inhibitor–TKI [43]. The only available head-to-head trial comparing an mTOR inhibitor, temsirolimus, and a TKI, sorafenib, in second-line treatment after sunitinib failure is the INTORSECT trial. Results from the trial were recently reported and show no superiority of temsirolimus over sorafenib [44]. The question of the best second-line treatment remains unanswered. An argument to use an mTOR in second-line treatment is probably the subgroup analysis of patients enrolled in the RECORD-1 trial. This analysis evaluated the effect of everolimus on survival in patients who had received one or two prior TKIs [45]. Patients in all stratified subgroups derived significant clinical benefit from everolimus treatment, including those previously treated with either one or two TKIs. However, there was a trend toward a longer PFS in patients treated with one prior TKI compared with two TKIs. Given the number of available molecules for the treatment of mRCC, the optimal sequence has to be explored with larger databases and prospective studies.

The usefulness of everolimus single-agent in the first-line setting is being investigated in the RECORD-3 trial, an international multicenter phase II trial randomizing treatment-naive patients with advanced RCC. Patients are randomized to receive everolimus or sunitinib until disease progression; upon progression, patients will cross over to second-line treatment with the opposite drug until the second occurrence of progression. The primary endpoint will assess PFS after first-line treatment. Overall efficacy of both sequences will be compared based on the time from start of the sequence to progression after second-line therapy, or death. Finally, the Poortor study is currently ongoing to evaluate everolimus in poor prognosis mRCC.

4.2. Histologic subtypes

Clear cell carcinoma represents, by far, the most common histology in mRCC. Most of the non-clear cell histologies are papillary or chromophobe tumors. There are no phase III data available to determine which should be the standard of care in these specific histologies.

The ARCC study included patients with both conventional and non-clear cell histologies. Patients with histologies other than clear cell RCC accounted for 17% and 18% in the temsirolimus and IFN-α group, respectively. An unplanned secondary analysis for this patient subset was undertaken and suggested superior median OS and PFS for temsirolimus versus IFN-α with a HR of 0.49 (95% CI, 0.29–0.85) and 0.38 (95% CI, 0.23–0.62), respectively [46]. Whereas median OS was shorter in non-clear cell histologies compared with conventional RCC, the benefit of temsirolimus appeared more pronounced with non-clear cell or indeterminate primary cell types. This may be because IFN has fewer efficacies in this group [47].

As regards second-line treatment with everolimus, the REACT (RAD001 Expanded Access Clinical Trial in RCC) study showed that ORR was similar for non-clear cell mRCC than in the overall study population with 1.3% of partial response versus 1.7%, and 49.3% of clinical benefit versus 51.6% [48].

Even if temsirolimus is sometimes considered as the best option in non-clear cell histology, retrospective analyses have demonstrated activity of sunitinib and sorafenib in papillary and chromophobe histologies [49]. However, the response of papillary forms remains low compared with the general mRCC population receiving a first-line TKI treatment as only 4.8% of them achieved a response with a median PFS of 7.6 months. The SUPAP trial evaluating sunitinib in type I and II papillary RCC showed that response rate was lower than in clear cell tumors [50].

Prospective studies are ongoing to determine whether mTOR inhibition is more active that VEGF inhibition in non-clear cell histologies. For instance, the multicenter phase II RAPTOR trial is currently ongoing to evaluate the efficacy and safety of everolimus single-agent in treatment-naive patients with advanced papillary RCC [51]. The ongoing ESPEN trial was designed to compare everolimus and sunitinib in patients with non-clear cell renal carcinoma and patients were stratified for papillary or other non-clear cell subtypes.

4.3. After failure of mTOR inhibitors: resistance and re-challenge

4.3.1. Re-challenge: lack of data

After failure of a first-line treatment with temsirolimus, it is usual to prescribe a TKI as second-line treatment. Of concerns, is it relevant to prescribe everolimus as third-line therapy? To date, this question has been weakly addressed. Recently, a retrospective analysis involving 12 patients investigated the efficacy of everolimus after temsirolimus failure and conversely [52]. Despite the small size of this study, results suggested that responders to everolimus as first-line treatment could not benefit from a re-challenge with temsirolimus whereas patients who were not responders to first-line temsirolimus could still respond to everolimus.

4.3.2. Resistance to mTOR inhibitors

One could hypothesize that the mechanism of resistance is incomplete between molecules having a similar mechanism

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of action. Several mechanisms of resistance have been mentioned to explain primary or secondary failures to mTOR inhibitors: mutations in FKBP-12, PI3K/Akt pathway activation, increases in ERK/MAPK signaling, activation of PIM kinases, functional status of PP2A phosphatases and PDK1 activity, altered expression levels of eIF4E and 4E-BP1, dysregulation of $p27^{Kip1}$ levels, oxidative stress, modulation of apoptotic regulators, enhanced angiogenesis, and stimulation of autophagy [53]. Importantly, classical mTOR inhibitors inhibit only mTORC1 and not mTORC2, whereas the latter is responsible for Akt/protein kinase B (PKB) activation via a positive-feedback loop. Activation of insulin-growth factor receptor and Akt/PKB results in activation of both PI3K pathway and antiapoptotic signaling.

To overcome this problem, a dual inhibition of PI3K and mTORC1/mTORC2 signaling is currently investigated for several malignancies, especially breast cancer and mRCC. In addition, other strategies to downregulate mTOR signaling, such as the antidiabetic metformine [54], are being pursued in clinical trials [55].

Translational research becomes more and more essential in mRCC to identify new mechanism of resistance, new targets, as well as predictive factors of response. In the future, these findings should facilitate the tailoring of treatments in mRCC.

4.4. Place of treatment combinations

Combining targeted treatments for renal cell carcinoma has been suggested as a possible method to improve treatment efficacy. Despite the improvements in survival with targeted treatment, most patients eventually become resistant to treatment and ultimately die from the disease. Better treatment strategies are thus needed. A potential benefit from combinations of the newly approved drugs has been suggested on the biological rationale that they have different targets or different mechanisms of action aimed at different malignant processes.

As a consequence, phase I trials have assessed the tolerance of combination therapies, but because of dose-limiting toxicities, some combinations, such as temsirolimus and sunitinib [56], bevacizumab and sunitinib [57], and everolimus and sunitinib had to be stopped early [58]. Nevertheless, the combination of bevacizumab with an mTOR inhibitor, either temsirolimus or everolimus, was tolerable at the maximum doses available on label and showed good response rates in phase 1–2 trials [59–61]. The randomized phase II trial TORAVA explored the efficacy and feasibility of a temsirolimus–bevacizumab combination [62]. Unfortunately, as previously experienced with other combinations, the toxicity of the temsirolimus and bevacizumab combination (mainly fatigue, proteinuria, hypertension, and skin disorders) was much higher than anticipated and limited treatment continuation over time. Clinical activity was low compared with the benefit expected from sequential use of each targeted therapy. Recently, the results of the INTORACT trial were presented showing that the bevacizumab-temsirolimus combination was not superior to the bevacizumab–interferon combination as first-line treatment of mRCC [63]. Safety data were consistent with known profiles of these agents without unacceptable toxicities. In the same way, the RECORD-2 trial did not demonstrate any difference between bevacizumab–everolimus and bevacizumab–interferon [64].

To date, sequential strategies remain the standard of care. This strategy provides indication that multiple lines of treatment may extend survival although the optimal sequence is still unknown [65]. New treatment used in combination or sequentially have potential to provide a better patient outcome. The results from ongoing or planned trials will help shape future therapy.

5. The safety as referee

If efficacy data resulting from numerous randomized trials provided arguments for the selection of a first-line treatment, safety and characteristics of patients remain a crucial point for treatment choice. Sequential treatments represent an opportunity to improve the PFS. However, sequential treatments highlight the need for treating and preventing drug-related toxicities in order to maintain compliance and QoL.

5.1. Safety

Among adverse effects, some are common to all mTOR inhibitors such as fatigue, anorexia, diarrhea and anemia, whereas others are more specific of a class or of a molecule.

5.1.1. A class-specific effect of mTOR inhibitors: interstitial pneumonitis

As regards mTOR inhibitors, the predominant class-effect toxicity is the occurrence of non-specific interstitial pneumonitis. Although this is often asymptomatic or only presents with mild dyspnea and/or cough, it can be life-threatening in extent. Physiopathology of pulmonary toxicity is not fully elucidated. This event involves about 35% of the patients receiving a mTOR inhibitor, and appears after 3–4 months of treatment [12,13]. The clinical presentation is either a non-infectious pneumonitis that could be the result of a direct toxicity on pneumocytes, of an endothelial dysfunction or of an immunoallergic mechanism; or an infectious pneumonitis, knowing that both forms are not excluded each other.

In the ARCC trial, temsirolimus-related interstitial pneumonitis paid limited attention as four cases (2%) of patients of the temsirolimus arm developed this event [13]. However, a subsequent independent, blinded review in the temsirolimus group revealed all grades drug-induced pneumonitis in 29% of the patients versus 6% in the IFN-α group ($p < 0.0001$) [66]. Most (60%) occurred within the first 8 weeks of treatment, and only 31% were symptomatic. Monitoring and managing temsirolimus-related interstitial pneumonitis is presented in Table 5 [67].

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Table 5
Monitoring and managing side-effects associated with temsirolimus treatment [67].

Monitoring	Management
Pulmonary function tests; chest X-ray or CT scan	Asymptomatic patients with only radiologic changes would not require specific therapies or drug interruptions
Surveillance is warranted based on phase II data	Patients with radiologic changes with few clinical symptoms may require temporary treatment interruption
Appropriate diagnostic tests to exclude opportunistic infection (differential diagnosis: aspergillosis)	Patients with increasing clinical symptoms in conjunction with a decrease in diffusing capacity of the lung to carbon monoxide measurement on pulmonary function tests may require drug discontinuation and high doses of steroids Patients with underlying pulmonary pathologies and any clinical or radiologic change after temsirolimus treatment may require drug discontinuation and tests to rule out infectious complications

CT, computed tomography.
Adapted from: Bellmunt et al. [67].

Table 6
Management of everolimus-associated non-infectious pneumonitis [68].

Severity	Definition	Intervention	Imaging or further diagnostic workup
Grade 1	Radiographic changes with few or no symptoms	• Continue without dose adjustment, maintain close clinical follow-up[a]	• Obtain chest CT scan, PFT • Repeat CT scan or CXR every 2 cycles until back to baseline
Grade 2	Moderate symptoms	• Reduce dose to 5 mg/d until ≤grade 1 • Consider interruption if symptoms troublesome to patient • Discontinue treatment if no improvement in ≥3 weeks • Consider corticosteroid, if above is ineffective[b]	• Obtain chest CT scan, PFT • Repeat every cycle until return to baseline • In appropriate clinical setting, rule out causes, such as infection (bronchoscopy), PE, or cardiac cause
Grade 3	Severe symptoms	• Interrupt everolimus until ≤grade 1 • Initiate corticosteroids[c] – High-dose IV methylprednisolone for respiratory distress – Lower dose in less severe cases • Upon resolution of toxicity, consider reinitiating everolimus at attenuated dose	• Obtain CT chest, PFT • Repeat every cycle until return to baseline • Bronchoscopy • Consider workup for other causes (e.g., PE, cardiac)
Grade 4	Life-threatening	• Discontinue everolimus permanently • Initiate corticosteroids[c] • Do not restart	• Obtain chest CT scan, PFT • Repeat every cycle until return to baseline • Bronchoscopy • Consider workup for other causes (e.g., PE, cardiac)

CXR, chest radiograph; PE, pulmonary embolism; PFT, pulmonary function test.
Adapted from: White et al. [68].
[a] Except if findings extensive or baseline pneumonitis worsening. In either case, consider interruption or dose modification.
[b] Prior to initiation of corticosteroids, exclude infectious process, cardiac cause, or pulmonary embolism, if appropriate.
[c] Infectious cause or pulmonary embolism should be excluded if either suggested by clinical presentation; however, this should not delay initiation of steroids.

In the RECORD-1 trial, the incidence of all grades non-infectious pneumonitis was 13.5% (3.6% grade 3, none grade 4) with a median time to occurrence of 15 weeks [12]. Clinical pneumonitis was fully reversible in 54% of cases. This trial contained a prospective, independent monitoring of patients for pneumonitis that was reported separately [68]. On blinded review of serial images obtained with the study, baseline radiographic abnormalities were present in 17% of all patients, in 24% of those who went on to develop clinical pneumonitis, and in 50% of those with subsequent grade 3 pneumonitis. New or worsening radiographic changes suggestive of pneumonitis were detected in 53.9% of patients on everolimus, which included 38.9% of patients without clinical suspicion for pneumonitis. Based on their observations, the investigators issued specific management guidelines (Table 6) [68].

Recently, a review was designed to develop a decision tree for use in routine clinical practice (Fig. 3) [69]. A key recommendation was the subdivision of grade 2 pneumonitis into grade 2a and 2b, where grade 2a is closer to grade 1 and grade 2b to grade 3. This subdivision takes into account the nature and severity of clinical symptoms potentially related to

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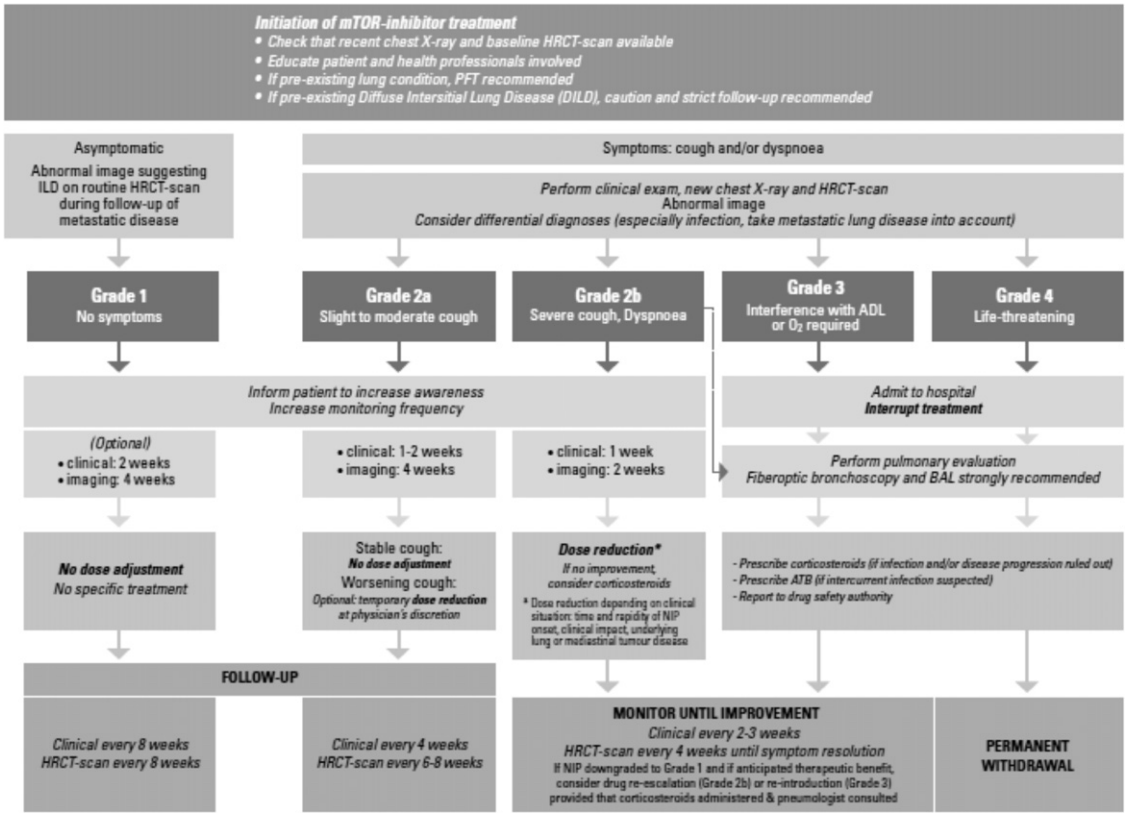

Fig. 3. Decision-tree for the management of mTOR inhibitor-associated pneumonitis in patients with mRCC [69]. PFT: pulmonary function tests; ILD: interstitial lung disease; ADL: activities of daily living; BAL: bronchoalveolar lavage; ATB: antibiotics.
Adapted from: Albiges et al. [69].

pneumonitis, either the onset of new symptoms or the worsening of existing symptoms, and thus determines the type and frequency of follow-up. It also helps to identify a subgroup of patients in whom treatment, if effective, may be continued without dose adjustment.

5.1.2. *Incidence-differentiated common toxicities*

Besides interstitial pneumonitis, other toxicities are common to both mTOR inhibitors with different levels of incidence: stomatitis, hyperglycemia, hypercholesterolemia, hypertriglyceridemia, hypophosphatemia, anemia, cutaneous toxicity. The incidence of major adverse effects is summarized in Table 7 [12,13].

Stomatitis. The results of pivotal trials confirm what is observed in routine practices, i.e. a higher incidence of all-grade stomatitis with everolimus compared with temsirolimus (44% versus 20%), even if grade 3–4 stomatitis remain rare [12,13]. Topical therapy is recommended; however, alcohol- or peroxide-containing mouthwashes should be avoided.

Hyperglycemia. The attenuating effects of the PI3K/Akt/mTOR cascade on insulin signaling have been established, and mTOR has been implicated in insulin resistance [70–72]. As expected, clinical trials of mTOR inhibitors highlighted an impact on glucose metabolism. The incidence of hyperglycemia are more frequent with everolimus than with temsirolimus (57% versus 26%), whereas the incidence of grade 3–4 hyperglycemia is close between both mTOR inhibitors (15% versus 11%, respectively) [12,13]. Physicians should adhere to good clinical practice, which includes adequate glucose control before initiation of mTOR-directed treatment, education of patients on the symptoms of hyperglycemia, and intermittent monitoring of fasting glucose levels.

Table 7
Incidence of major side-effects with mTOR inhibitors [12,13].

Side-effect, %	Temsirolimus [13]		Everolimus [12]	
	All grade	Grade 3–4	All grade	Grade 3–4
Number of patients	208	274		
Stomatitis	20	1	44	4
Hyperglycemia	26	11	57	15
Hypercholesterolemia	24	1	77	4
Hypertriglyceridemia	27	3	73	<1
Hypophosphatemia	6	NR	37	6
Anemia	45	20	92	13
Cutaneous toxicity	47	4	29	1
Diarrhea	27	1	30	1
Anorexia	32	3	25	1

NR, not reported.

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Hyperlipidemia. Effects of lipid metabolism can be explained through the roles of mTOR in cell metabolism [73]. Recent studies suggest that the TOR signaling network controls fat metabolism. In particular, mTORC1 appears to play an important role in adipogenesis as rapamycin treatment prevents adipocyte differentiation and, thus, lipid accumulation. The mechanism by which mTOR controls adipogenesis is poorly understood. In the pivotal phase III trials [12,13], temsirolimus caused hypercholesterolemia and hypertriglyceridemia in 24% and 27% of patients, respectively; the reported incidence was higher for everolimus as cholesterol and triglycerides were elevated in 77%, and 73% of patients, respectively. As for the management of hyperglycemia, no standardized guidance has been issued. Physicians should ascertain adequate levels prior to starting treatments and monitor patients for the development of hyperlipidemia.

Hypophosphatemia. Mild hypophosphatemia has been reported in 6% of patients using temsirolimus and 37% (6% of grade 3–4) for patients using everolimus in pivotal phase III trials [12,13]. Severely low levels can impair neurologic and myocardial function and should be replenished.

Anemia. The incidence of all-grade anemia is higher with everolimus than with temsirolimus (45% versus 92%), whereas the incidence of grade 3–4 anemia is close between both mTOR inhibitors (13% versus 20%, respectively) [12,13].

Cutaneous toxicity. Whereas hand-foot syndrome is a class-type toxic effects of TKIs [36,74], this event is not associated with mTOR inhibitors, reflecting the distinct targeted mechanisms. The mTOR inhibitor-associated cutaneous toxicity consists of rash, acneiform dermatitis, pruritus, ungueal toxicity and lower limb edema [75]. Contrarily to the majority of other drug-related toxicities, the cutaneous toxicity is more frequent with temsirolimus than with everolimus (47% versus 29%) [12,13]. The management of cutaneous side effects should be based on fragrance-free moisturizer lotion, and, if necessary, on topical corticosteroids.

Infections. The mTOR inhibitors were initially mainly used as an immunosuppressant in recipients of solid organ transplantation because of their ability to potently inhibit T-cell function [16]. So, these immunosuppressive properties of mTOR inhibitors may predispose RCC patients to infections with opportunistic pathogens as well as to bacterial, viral or fungal infections. Systemic bacterial infections as pneumonia, invasive fungal infections including candidiasis or invasive aspergillosis or viral infections such as reactivation of hepatitis B/C virus, have been described with mTOR inhibitors treatment. Some of these infections have been severe (e.g. leading to respiratory failure) and occasionally fatal. Clinicians should be aware of the increased risk of infection with mTOR inhibitors and be vigilant for any symptoms and clinical signs of infection. Pre-existing infections should therefore be treated appropriately before starting treatment with mTOR inhibitors. If a severe infection occurs during mTOR inhibitors administration, the treatment should be discontinued temporarily or permanently. *Other toxicities* – Other toxicities consist mainly in hypersensitivity, gastro intestinal disorders (anorexia, diarrhea, nausea/vomiting) as described in Table 7.

5.2. Route of administration: oral or intravenous

Numerous factors guide the therapeutic choice between temsirolimus and everolimus and first of all, the therapeutic indication between first- and second-line. Besides this imperative, the choice could depend on multiple criteria among which transport considerations have to be taken into account. Indeed, the IV treatment requires a weekly coming to the hospital, contrarily to the oral treatment. In contrast, oral treatment needs a high degree of adherence and compliance. So, it is widely accepted that several patients become non-compliant to oral treatment for several reasons, including side effects. The available evidence reveals that patient adherence to oral antineoplastic agents is variable and not easily predicted. Adherence rates ranging from less than 20% to 100% have been reported [76]. Thereby, each prescriber has to work with his patient to find the just balance between the therapeutic imperatives and the best option according to the potent compliance of each patient.

However, all these considerations highlight the risk of deviance from the indications of each molecule in the respect of their registration. In first-line treatment for poor prognosis mRCC patients, the treatment choice is between IV temsirolimus and oral sunitinib. This question is currently addressed by a study conducted by the Central European Society for Anticancer Drug Research that is now completed. In second-line treatment, the ongoing INTORSECT trial compares IV temsirolimus to oral sorafenib after failure of first-line sunitinib.

6. Conclusions

Guidelines for the treatment of mRCC are rapidly evolving to incorporate the new targeted therapies that have been approved by US and European regulatory authorities. The National Comprehensive Cancer Network (NCCN) guidelines were revised as of October 2009 (version 2.2010) and the European Association of Urology (EAU) were updated in April 2010 [77]. Interestingly, the NCCN guidelines take into account the histologic subtype as a discretionary factor for the choice of a first-line treatment. However, the crucial question of the third-line treatment is not addressed in those recommendations although in the RECORD-1 trial, the majority of patients had received everolimus as third- or fourth-line treatment [11,12]. During the last European Society of Medical Oncology (ESMO) congress, new guidelines were presented that addressed the issue of third-line therapy as well as first- and second-line treatments (Fig. 4) [78].

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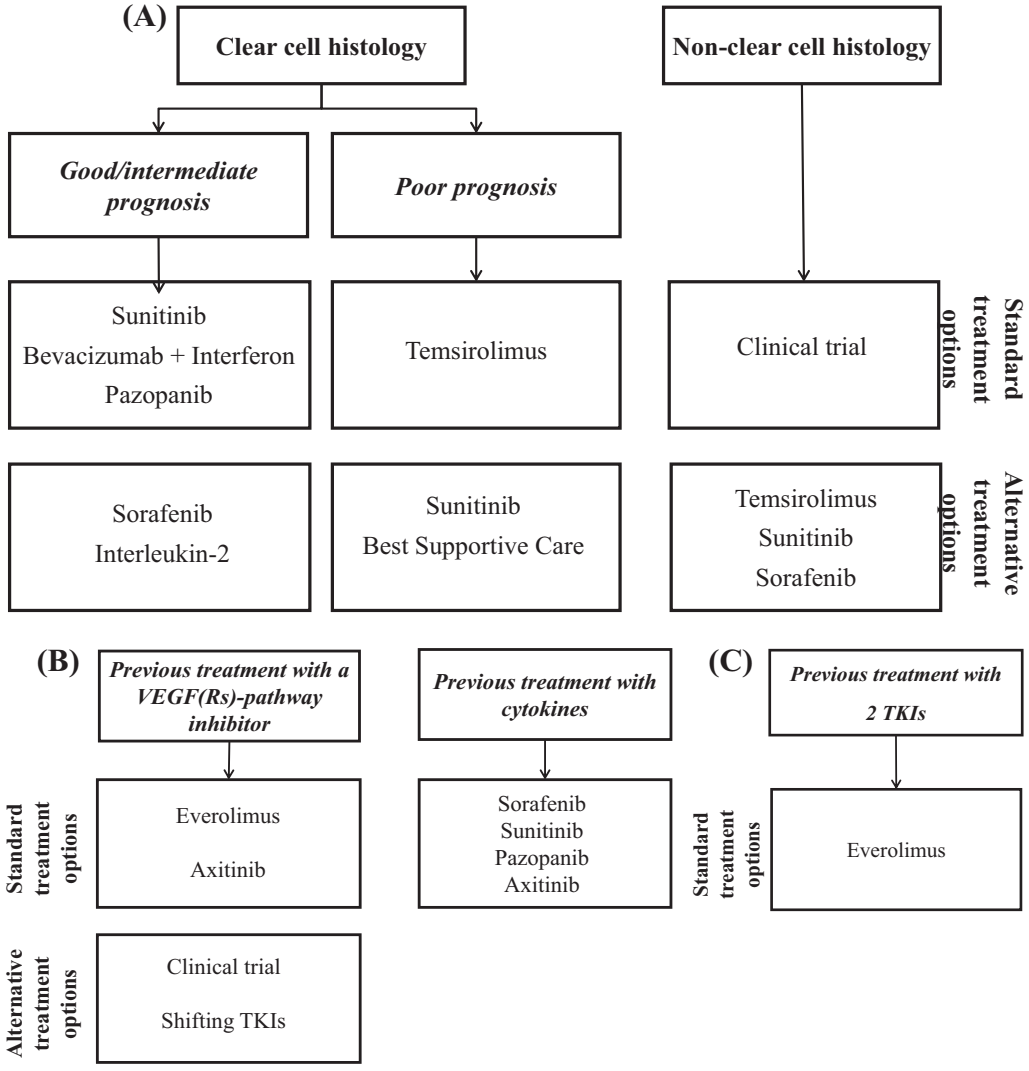

Fig. 4. Summary of ESMO guidelines and recommendations in metastatic renal cell carcinoma for first- (A), second- (B), and third-line treatment (C) [78].

Unfortunately, some important data are still missing to refine the choice of first-line treatment and subsequent strategies: (**1**) temsirolimus has not been tested irrespective of risk subgroups; (**2**) temsirolimus has not been compared directly neither to TKIs nor to everolimus in first-line treatment; (**3**) no data are yet available regarding everolimus in first-line treatment; (**4**) the efficacy of mRCC-indicated targeted therapies remains unclear according to histologic subtypes; (**5**) the therapeutic sequences, and the re-challenge with a same-class molecule are poorly documented; (**6**) predictive factors of response to mTOR inhibitors are warranted to tailor the treatment plan; (**7**) the compliance to oral targeted therapies is not described; (**8**) the impact of hemodialysis, which is not a rare circumstance in RCC patients, is poorly studied. If we could have all or any of those results, the choice between one of both mTOR inhibitors could articulate around advantages and drawbacks of each, and according to the profile of every patient.

Reviewers

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Conflict of interest statement

Philippe Barthélémy received honoraria from Novartis, Pfizer, Roche; *Benjamin Hoch* was an advisor for Sanofi-Aventis and Pfizer; *Christine Chevreau* was an advisor for Pfizer, Novartis, and Bayer Healthcare; *Florence Joly* was an advisor for Pfizer, Novartis, Sanofi-Aventis, Roche and Janssen; *Brigitte Laguerre* received honoraria from Pfizer

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