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Review

Management of adverse events associated with the use of everolimus in patients with advanced renal cell carcinoma

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ABSTRACT

Purpose: In April 2009, an expert group of 11 physicians and clinical nurses met to discuss the management of selected adverse events associated with the use of everolimus for the treatment of metastatic renal cell carcinoma (mRCC). Everolimus is an orally administered inhibitor of the mammalian target of rapamycin that recently received approval from the European Medicines Agency for the treatment of advanced RCC that has progressed on or after treatment with vascular endothelial growth factor (VEGF)–targeted therapy, and from the United States Food and Drug Administration for treatment of advanced RCC after failure of sorafenib or sunitinib. Before the approval of everolimus, no standard therapy existed for the treatment of mRCC after failure of VEGF-targeted therapy. RECORD-1 (Renal Cell cancer treatment with Oral RAD001 given Daily) was the pivotal multicenter, phase III, randomised, double-blind, placebo-controlled trial of everolimus that led to approval for patients with disease progression on or after treatment with VEGF-targeted agents. Safety data from RECORD-1 were reviewed by these clinicians, all of whom had experience using everolimus in patients with mRCC. Adverse events discussed were non-infectious pneumonitis, infections, stomatitis and metabolic abnormalities.

Results: The outcome of this discussion is summarised here. Guidance for management of these adverse events is provided. Both clinicians and patients should be aware of the potential side-effects of everolimus and understand that these side-effects are manageable with standard care to optimise patient benefit.

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1. Introduction

Renal cell carcinoma (RCC) was diagnosed in approximately 58,240 individuals, and resulted in 13,040 deaths in the United States in 2010.[1] Estimates of RCC incidence and mortality in Europe over the same time period are 63,000 new cases and 26,000 deaths.[2] Approximately one-third of patients are initially diagnosed with metastatic disease,[3] and 20–30% of those with localised RCC who undergo surgery develop metastases.[4] Consequently, the development of effective therapies for advanced RCC has been the subject of intense study. Targeted therapies have been designed based on identification of the role of vascular endothelial growth factor (VEGF) in clear-cell RCC pathogenesis and have replaced cytokine monotherapy as the standard of care for advanced RCC. The VEGF receptor tyrosine kinase inhibitors (VEGFr-TKIs) sunitinib and sorafenib are now approved worldwide for the treatment of advanced RCC and sunitinib is recommended as a first-line therapy.[4,5] The combination of the anti-VEGF monoclonal antibody bevacizumab and interferon alpha (IFN-α) is also recommended as first-line therapy for metastatic disease.[4,5]

Although VEGF-targeted agents such as the VEGFr-TKIs and bevacizumab have demonstrated efficacy in mRCC, they rarely produce a complete or durable response and the disease eventually progresses.[6] Consequently, there is a need for an efficacious option for patients following failure of these agents. The mammalian target of rapamycin (mTOR) intracellular signalling pathway represents a viable target for the treatment of RCC. mTOR is a serine/threonine kinase located at a central point in several signalling cascades; abnormal functioning of the mTOR pathway is implicated in the pathogenesis of RCC and many other cancers.[7,8] The RECORD-1 (Renal Cell cancer treatment with Oral RAD001 given Daily) multicentre, phase III, randomised, double-blind, placebo-controlled clinical trial confirmed the potential of blocking mTOR in RCC.[9]

Based on the favourable results of this pivotal trial, the European Medicines Agency approved everolimus (Afinitor®, Novartis Pharmaceuticals, East Hanover, NJ), an orally administered mTOR inhibitor, for the treatment of advanced RCC that has progressed on or after treatment with VEGF-targeted therapy. Everolimus also has been approved by the US Food and Drug Administration for treatment of advanced RCC after failure of sorafenib or sunitinib. To date, no other agent has shown efficacy in VEGFr-TKI–refractory RCC; therefore, the findings of the RECORD-1 trial establish everolimus as an important treatment option for these patients. Given the potential for widespread usage of everolimus, there is a need for guidance from experienced clinicians regarding the appropriate management of everolimus-related adverse events (AEs). The dissemination of this information should ultimately allow patients to achieve maximum benefit from this therapy.

A meeting convened in April 2009 enabled a group of RECORD-1 investigators to discuss their views regarding the management of selected AEs associated with everolimus for the treatment of mRCC. The panel consensus regarding the most appropriate management approaches is discussed here.

2. RECORD-1 trial summary

The RECORD-1 trial compared everolimus with placebo in patients with clear cell mRCC who had disease progression during or within 6 months of treatment with sorafenib, sunitinib, or both. Prior treatment with cytokines or bevacizumab was permitted. Patients with HIV infection were excluded from the trial. Patients were randomised 2:1 to receive everolimus 10 mg/d ($n = 277$) plus best supportive care or placebo ($n = 139$) plus best supportive care (see Fig. 1).[9,10] Patients were stratified by Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic criteria (favourable, intermediate, or poor)[11] and number of prior VEGFr-TKI therapies (1 versus 2). The primary end-point was progression-free survival (PFS) by independent central radiology review. Tumour response was assessed at scheduled intervals using Response Evaluation Criteria in Solid Tumours v1.0.[12]

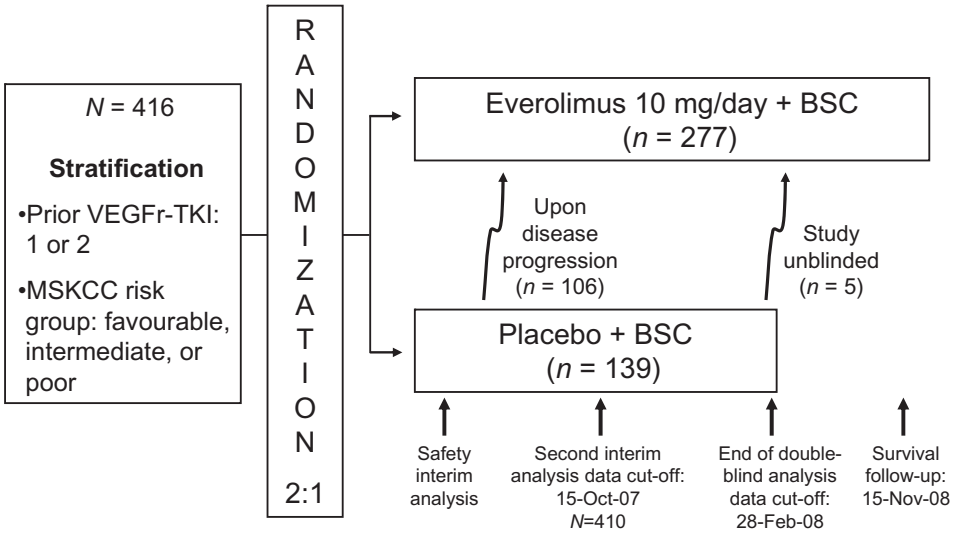

Fig. 1 – Design of the RECORD-1 trial. VEGFr-TKI, vascular endothelial growth factor receptor–tyrosine kinase inhibitor; MSKCC, Memorial Sloan-Kettering Cancer Center; BSC, best supportive care.

Data collected at the end of the double-blind phase of the trial demonstrated a median PFS of 4.9 months (95% confidence interval [CI], 4.0–5.5 months) with everolimus versus 1.9 months (95% CI, 1.8–1.9 months) with placebo (hazard ratio [HR] = 0.33; 95% CI, 0.25–0.43; $p < 0.001$) (see Fig. 2A).[10] Significant PFS prolongation by everolimus was achieved regardless of prior treatment and MSKCC risk status.[10]

Everolimus generally was well tolerated in RECORD-1, with a low incidence of grade 3/4 AEs. The most commonly reported AEs based on data from the end of the double-blind phase were stomatitis, asthenia, fatigue, rash, and diarrhoea and most were grade 1/2 in severity (see Table 1).[10] During the double-blind phase of the study, 4 deaths were reported in association with AEs: 3 were attributed to infection and 1 occurred in a patient with disease progression and everolimus-related grade 3 interstitial lung disease with acute respiratory failure.[10] Although the overall incidence of AEs was higher in patients receiving everolimus compared with placebo, the rate of Karnofsky Performance Status (KPS) deterioration was delayed significantly with everolimus compared

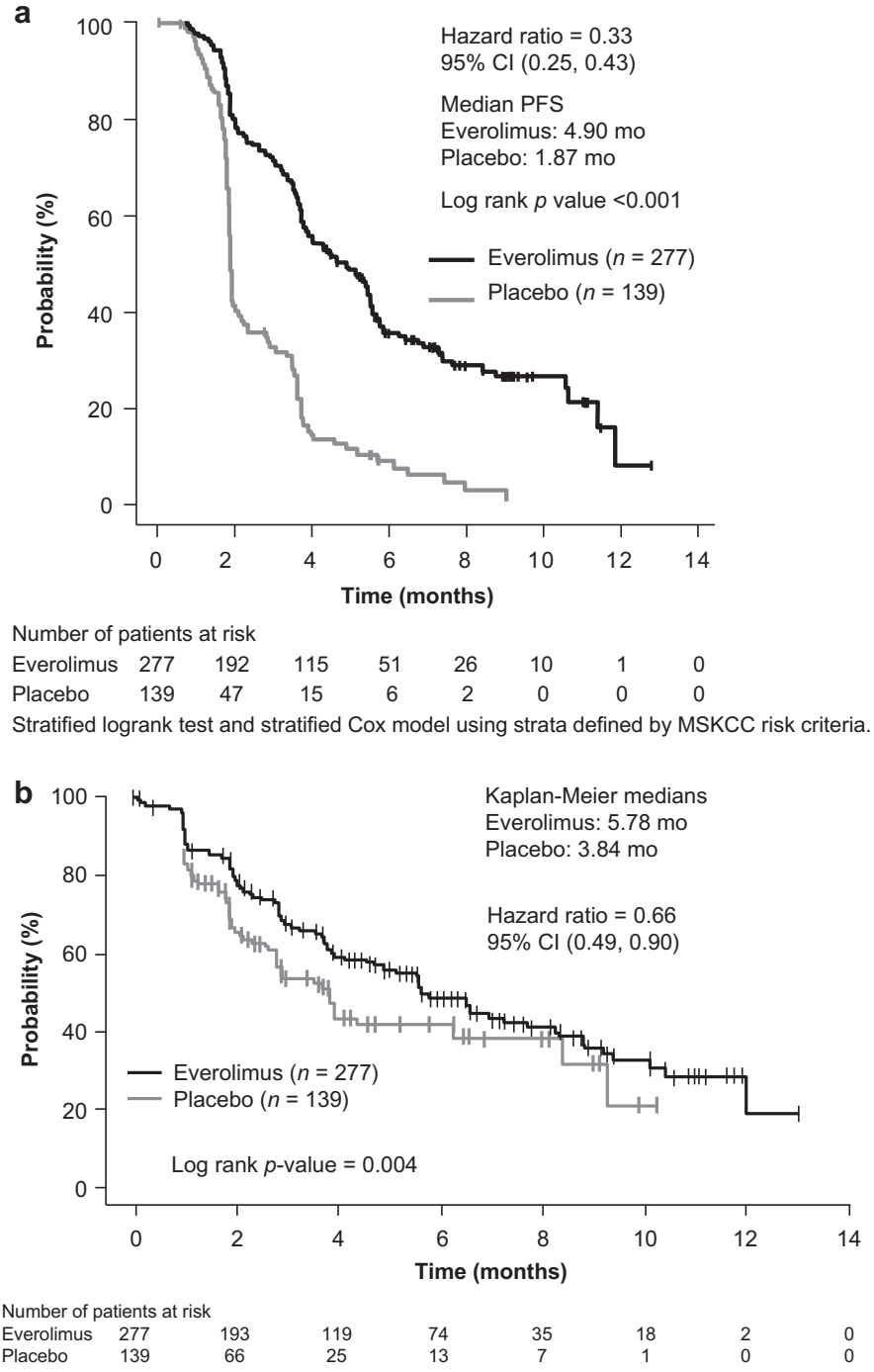

Fig. 2 – (a) Median progression-free survival (PFS) at end of double-blind treatment. (b) Time to definitive deterioration in Karnofsky Performance Status by 10%. Reprinted with permission from John Wiley and Sons.[10]

Table 1 – Incidence of selected treatment-related adverse events and metabolic abnormalities in RECORD-1 (end of double-blind phase).

	Everolimus 10 mg/d (n = 274)		Placebo (n = 137)	
	All grades (%)	Grade 3/Grade 4 (%)	All grades (%)	Grade 3/Grade 4 (%)
Adverse event				
Stomatitis	42	3/0	8	0/0
Asthenia	22	2/0	9	<1/0
Fatigue	23	3/0	17	<1/0
Rash	28	1/0	5	0/0
Diarrhoea	21	1/0	4	0/0
Nausea	18	<1/0	8	0/0
Mucosal inflammation	17	1/0	1	0/0
Oedema peripheral	13	<1/0	4	0/0
Infections (total)	13	2/2	2	0/0
Dyspnoea	10	2/0	3	0/0
Pneumonitis	14	4/0	0	0/0
Laboratory abnormality				
Haematology				
Anaemia	25	6/<1	4	<1/0
Lymphopenia	7	3/0	1	0/0
Thrombocytopenia	5	1/0	0	0/0
Chemistry				
Hypercholesterolaemia	18	3/0	2	0/0
Hypertriglyceridemia	15	1/0	2	0/0
Hyperglycaemia	8	4/0	<1	<1/0
Elevated creatinine	5	0/0	0	0/0

with placebo (see Fig. 2B). These findings highlight the need for effective interventions to manage everolimus-associated AEs so that patients can remain on effective therapy for as long as possible.

Panel members discussed their experience with selected AEs including non-infectious pneumonitis, infections, stomatitis, hyperglycaemia and hyperlipidemia (hypercholesterolaemia and hypertriglyceridemia), focusing on successful approaches to the management of these AEs. Summaries of their discussions are provided below, followed by consensus recommendations for general management.

2.1. *Non-infectious pneumonitis*

Non-infectious pneumonitis is a non-malignant infiltration of the lungs and is a class effect of rapamycin analogues such as everolimus and temsirolimus.[13,14] Limited evidence suggests that this drug-associated pneumonitis is immunologically mediated; biopsies, when performed, have shown organising pneumonia, granulomatous inflammation and lymphocytic infiltration/vasculitis and bronchoalveolar lavage may show lymphocytosis. Patients may be asymptomatic or have non-specific respiratory signs and symptoms, such as cough, dyspnoea, hypoxia, and, rarely, pleural effusion. Fever also may be present, making differential diagnosis even more difficult. The most common radiographic changes observed with mTOR inhibitor-associated pneumonitis are ground-glass opacities and focal consolidation, predominantly in the lower lobes.[14]

In the RECORD-1 trial, approximately 14% of patients in the everolimus group had a diagnosis consistent with non-infectious pneumonitis (grade 1, n = 9; grade 2, n = 18; grade 3, n = 10; grade 4, n = 0). This diagnosis was determined by routine X-rays performed every 2 months and confirmed in most cases by computed tomography (CT) scans; all were reviewed by a central radiology panel (see Fig. 3).[15] The typical onset for patients experiencing pneumonitis (any grade) occurred within 2–6 months of treatment initiation (see Fig. 4). Most cases of pneumonitis were manageable. Dose reductions were needed for 2 patients with grade 1 pneumonitis. Among 18 patients with grade 2 pneumonitis, corticosteroid therapy was initiated in 10 patients, the dose of everolimus was adjusted for 12 patients and everolimus was discontinued in 3 patients. Complete resolution of grade 2 pneumonitis occurred in 11 patients and one case improved to grade 1. No grade 2 cases progressed to grade 3. In patients with grade 3 pneumonitis, steroid therapy was initiated in 6 patients, the dose of everolimus was adjusted for 6 patients and everolimus was discontinued in 7 patients. Complete resolution of grade 3 pneumonitis occurred in 6 cases; 1 patient improved to grade 1 and in 1 patient, pneumonitis persisted. Two patients died of complications that may have been related to grade 3 pneumonitis: one death was related to recurrent candidal sepsis with acute respiratory distress and the other was related to progressive RCC with acute respiratory failure. Based on these findings, the everolimus prescribing information has been revised to indicate that non-infectious pneumonitis may be associated with a fatal outcome.[16]

2.1.1. *Panel recommendations*

In patients with baseline respiratory symptoms (cough, dyspnoea on exertion or at rest) or in patients with documented

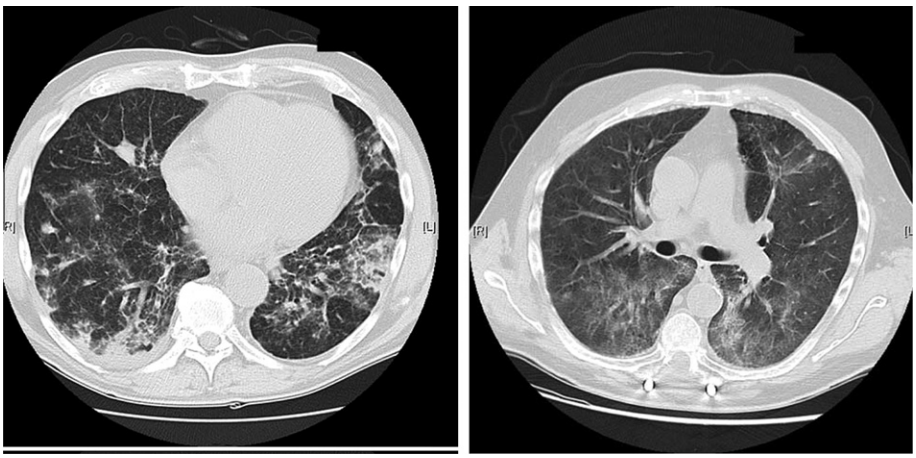

Fig. 3 – Radiographs illustrating the radiographic changes associated with everolimus from RECORD-1 patients. Left panel: bilateral ground glass opacities with mild reticular interstitial disease, predominantly in the lower lobes, in a 63-year-old man with metastatic renal cancer approximately 3 months after starting everolimus. Right panel: chest CT showing stable metastatic nodules but increased interstitial markings with septal thickening in 74-year-old man with metastatic renal cancer after approximately 4 months of treatment. Reprinted with permission of the American Thoracic Society.

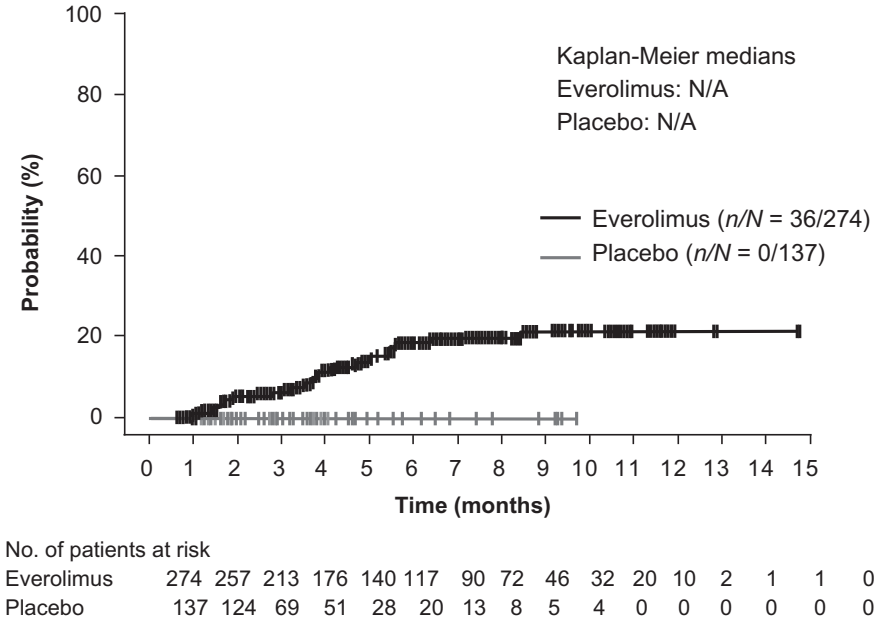

Fig. 4 – Time to diagnosis of pneumonitis in RECORD-1.

multiple lung metastases, a CT scan and lung function tests, including lung volumes, single breath transfer factor (T_L,CO) and arterial oxygen saturation should be performed before everolimus is initiated. In the event of a T_L,CO value lower than 40% of predicted, everolimus should be held until lung function tests have normalised.

In patients without evidence of compromised pulmonary function, pulmonary function tests and CT scans may be performed at the discretion of the treating physician. A diagnosis of non-infectious pneumonitis should be considered in patients who present with non-specific respiratory signs and symptoms. Broncho-alveolar lavage may be useful in these patients to rule out infection and to assess the lung inflammation profile. A temporary treatment interruption may be considered if symptoms are moderate or severe; following resolution of symptoms, everolimus may be reinitiated at a reduced dosage of 5 mg/d.

The presence of pleural effusions may complicate the diagnosis in patients with lung metastases, as they may result from disease progression or from the development of drug-related pneumonitis. In questionable cases, the panel recommends interruption of everolimus and initiation of corticosteroid treatment; pneumonitis that is not tumour-related should resolve with these interventions. Bronchoscopy with bronchoalveolar lavage and trans-bronchial biopsy may be considered to rule out non-drug-related causes and assess

Table 2 – Panel-recommended management strategies for selected everolimus-associated adverse events.

	Pneumonitis	Infections	Stomatitis	Metabolic Abnormalities

Considerations	• Obtain a history of any pulmonary conditions
	  ○ Consider PFTs at screening and baseline, particularly in patients with significant lung disease
	  ○ Use caution in patients with <20% diffusion capacity
	  ○ If TL,CO < 40% of predicted, repeat PFTs
	• Consider avoidance of everolimus in patients with significant pulmonary fibrosis or severe COPD; consider pulmonary consultation
	• In case of suspected pneumonitis, rule out Pneumocystis carinii infection, especially in patients with <200 CD4+ cells/μL
	• In case of suspected pneumonitis, consider the possibility of Legionella infection, especially in hospitalised patients
	• In case of fever, titration of infection biomarkers (e.g. procalcitonin) may help discriminate between infectious and non-infectious causes
	• In case of suspected pneumonitis, consider pulmonary consult for induced sputum culture or BAL
		• Use caution in patients with a history of prior infections (hepatitis, fungal, other opportunistic infections)
		• Consider evaluating the risk of infection on the basis of CD4+ cell absolute count (<200/μL) or percentage (<12%)
		• A basal evaluation of the antibody immune status is potentially useful (e.g. antibody status for Toxoplasma, CMV, HSV, EBV)
		• Investigate possible latent tuberculosis infection (especially in endemic countries or in migrants from these countries) through:
		  ○ Patient medical history
		  ○ Mantoux reaction
		  ○ QuantiFERON®-TB Gold test (in case of a positive or doubtful Mantoux test, or – if negative – in case of concomitant immunosuppression (e.g. CD4+ cells <200/μL)
		• Depending on the epidemiological setting, consider persistent bowel parasites (e.g. latent tropical strongyloides)
		• Patients with fungal infections are not recommended for everolimus therapy, though medical judgment should be exercised
		  ○ Patients should have complete resolution of fungal infection before initiation of everolimus
		• Recommend preventive therapy for hepatitis B infection to avoid reactivation (in both HBsAg-positive and HBcAb-positive patients)
			• Consider evaluation for herpes virus or fungal infections	• Optimal glycaemic and lipidemic control should be achieved prior to the start of everolimus therapy
				• Consider other possible causes of hyperlipidemia (hypothyroidism, nephrotic syndrome, drugs such as thiazides)
				• All patients should have a baseline lipid panel and hepatic function studies (fasting)

Patient education	• Increase awareness of potential risk • Advise regarding when to inform healthcare providers of complications	• Increase awareness of the potential risk • Advise regarding proper hygiene and when to inform healthcare providers of complications (e.g. fever)	• Advise patients to practise good oral hygiene • Advise patients to contact physician if >3 lesions, lesions last >3 d, or painful lesions interfere with daily life	• Increase awareness of the potential risk • Advise regarding when to inform healthcare providers of complications
Treatment recommendations	• See Table 3	• See Table 4	• See Table 5	• See Table 6
General points	• Consider the role of serial imaging for monitoring (assessing CT scans) • Perform serial PFTs as indicated by symptoms • Monitor via common radiographic findings • Consider diagnostics to determine underlying cause • Corticosteroid use is dependent on the clinical judgment of the treating physician	• Due to limited experience in patients with these specific infections, recommendations are difficult; consider consultation with an infectious diseases specialist	• Avoid alcohol- or peroxide-containing products for topical anaesthetic treatment	• Monitor liver function and muscle symptoms of hyperlipidemia

BAL, bronchoalveolar lavage; CMV, cytomegalovirus; COPD, Chronic obstructive pulmonary disease; CT, computed tomography; EBV, Epstein-Barr virus; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HSV, herpes simplex virus; IV, intravenous; PFTs, pulmonary function tests; T_L, CO, single breasth transfer factor.

the pattern and severity of lung injury in patients with grade 3 pneumonitis. Key recommendations for the management of pneumonitis are summarised in Table 2 and specific guidelines for dose modifications and interruptions are listed in Table 3.

2.2. *Infections*

The immunosuppressive properties of everolimus may predispose patients to opportunistic infections and reactivation of previous infections. Pneumonia and other bacterial infections and invasive fungal infections have been reported in patients treated with everolimus. In addition, the prevalence of hepatitis B surface antigen-positive subjects among cancer patients ranges between 5.3% (in Europe) and 12% (in China); in these patients, the frequency of clinical HBV reactivation ranged between 14% and 19%.[17,18] The clinical significance of HBV reactivation is associated with pre-chemotherapy liver function and relapse is associated with a mortality of 5–40%.[19]

In the RECORD-1 trial, the overall incidence of infections was 36.9% in the everolimus group and 18.2% in the placebo group; treatment-related infections occurred at a rate of 13% with everolimus and 2% with placebo. Everolimus-related infections included pneumonia, sepsis, and fungal infections; 2% were grade 3 and 2% were grade 4. Two of the four fungal infections involved reactivation of infection that occurred prior to everolimus. Some infections were severe, associated with respiratory failure, or had a fatal outcome. Two everolimus-related deaths were attributed to sepsis. Consequently, patient monitoring for symptoms and signs of infection must be vigilant and initiation of appropriate treatment must be prompt.

2.2.1. *Panel recommendations*

It is important to obtain a complete medical history before initiating everolimus therapy to identify patients at higher risk for developing infections. Patients starting on everolimus therapy should be provided with appropriate information regarding the potential risk of developing infections. Due to the potential for reactivation, patients with fungal infections should be comprehensively treated before the initiation of everolimus therapy. If an invasive systemic fungal infection is suspected, everolimus should be promptly discontinued and the patient treated with appropriate antifungal therapy. Similarly, patients with hepatitis B infection should be monitored for hepatitis B virus (HBV) DNA; the everolimus prescribing information was revised recently to communicate that fatal cases of HBV reactivation have occurred.[16] Lamivudine is a reasonable choice for antiviral prophylaxis; however, for patients who will be treated continuously (as in the case of patients with cancer) or for a long period of time, there is a high risk of developing resistance that may render second-line therapies ineffective. Therefore, according to recent guidelines,[20] the use of high-potency and high-genetic-barrier drugs such as entecavir or tenofovir could be considered to quickly suppress viremia while minimising progression of hepatic damage and the development of resistant viral mutants. Both tenofovir and entecavir doses should be adjusted in case of renal insufficiency. Tenofovir may cause electrolytic

disturbances, especially hypophosphatemia, as well as renal tubular acidosis.

Other endemic infections also may become problematic as more institutions gain experience with everolimus; constant vigilance based on local infectious disease patterns is warranted. Key recommendations for the management of infections are summarised in Table 2, and specific guidelines for dose modifications in response to infections are listed in Table 4.

2.3. *Stomatitis*

Stomatitis is an inflammation of the mucous membranes in the oral cavity, inner surface of the lips, or tongue that is associated with erythema, oedema, burning sensation and occasionally bleeding.[21] In RECORD-1, the incidence of stomatitis in the everolimus group was 42%, and 3% of cases were grade 3. The majority of patients had mild sores and most resolved within 3 d (see Fig. 5). Of the 120 everolimus-treated patients who developed stomatitis, 13 required dose modification or interruption, 49 required supportive therapies and 1 discontinued everolimus. Of the 11 patients with grade 3 stomatitis, 2 continued treatment without dose adjustment, 8 continued on a reduced dose and 1 discontinued. No cases of infection were diagnosed in conjunction with stomatitis. In patients who develop stomatitis, the onset tends to occur within the first 2 months of treatment (see Fig. 6).

2.3.1. *Panel recommendations*

Key recommendations for the management of everolimus-associated stomatitis are summarised in Table 2 and specific guidelines for dose modifications are listed in Table 5. Although experience with treating everolimus-associated stomatitis is limited, the efficacy of specific topical corticosteroids and mouthwashes in the treatment of chemotherapy-induced stomatitis has been reviewed extensively and may be applicable to patients treated with everolimus.[22,23] The panel advises good oral hygiene, treatment of anticipated infectious foci (e.g. periodontal diseases and granulomas), and avoidance of alcohol- or peroxide-containing products, as they may exacerbate the condition. These recommendations are consistent with those provided in evidence-based guidelines.[24] In addition, the panel recommends that patients should be evaluated for herpes and fungal infections, with institution of an antiviral agent (e.g. acyclovir) or antifungal agent (e.g. fluconazole) as appropriate. Special attention should be given to potential interactions between antifungal agents and everolimus; as such, mouthwashes containing an antifungal agent (e.g. nystatin) are preferred unless systemic treatment is required.

2.4. *Metabolic abnormalities*

Selected metabolic abnormalities that occurred at a higher frequency with everolimus in the pivotal trial are summarised in Table 1. Of these, the panel discussed hyperglycaemia,

Table 3 – Clinical management strategy: non-infectious pneumonitis.

Grade	Description	Treatment	Dose modification
1	Asymptomatic, radiographic findings only	• No intervention • Continue everolimus	• No change in dose
2	Symptomatic, not interfering with activities of daily living	Depending on severity of symptoms: • Consider everolimus dose interruption/reduction • Consult pulmonologist • Consider diagnostics to exclude infectious causes • Consider corticosteroids	• Restart at reduced dose when grade $\leqslant$1 and consider re-escalation • If no recovery to grade $\leqslant$1, discontinue everolimus
3	Symptomatic, interfering with activities of daily living, supplemental oxygen required	• Interrupt everolimus • Consult pulmonologist • Diagnostics to exclude infectious causes • Corticosteroids if infectious cause excluded (prednisone 20 mg/d PO or methyl-prednisolone 60 mg IV Q 6 h) • For impending respiratory distress: concomitant treatment with antibiotics and corticosteroids is recommended	• Hold treatment until recovery to grade 1; may restart within 2 weeks at a reduced dose (by 1 level) if evidence of clinical benefit
4	Life-threatening; ventilatory support indicated	• Interrupt everolimus • Consult pulmonologist • Diagnostics to exclude infectious causes • Corticosteroids if infectious cause excluded (prednisone 20 mg/d PO or methyl-prednisolone 60 mg IV Q 6 h) • For impending respiratory distress, concomitant treatment with antibiotics and corticosteroids is recommended	• Discontinue permanently

hypercholesterolaemia and hypertriglyceridemia. Abnormal serum glucose values were observed in 57% of patients who received everolimus and 25% of patients who received placebo; the incidence of hyperglycaemia in these groups was 8% and <1%, respectively. Most cases occurred in patients with abnormal fasting glucose levels before treatment. One new case of diabetes mellitus was reported during the trial.

Hypercholesterolaemia and hypertriglyceridemia were common with everolimus therapy; however, the incidence of grade 3 events was low and no grade 4 events were reported. Grade 3 hyperlipidemia was managed with standard medical interventions. The RECORD-1 protocol required discontinuation of everolimus for grade 4 hyperlipidemia.

2.4.1. *Panel recommendations*

The appearance of abnormal laboratory values can be managed routinely without treatment interruption. Intervention at the grade 2 level is recommended, with the extent of intervention dependent on the specific metabolic abnormality. Patients with underlying diabetes require careful monitoring and, potentially, modifications to their antihyperglycaemic regimen. The observation that hyperglycaemia occurred primarily in patients with abnormal pretreatment fasting glucose levels highlights the need for achievement of optimal glycaemic control before everolimus initiation. Periodic monitoring of fasting blood glucose levels during treatment also is recommended. The development of hyperglycaemia necessitates both immediate and long-term interventions to avoid a serious impact on overall health. In contrast, the development of hyperlipidemia generally does not immediately impact patient health but does require a long-term strategy for control. Notably, pharmacokinetic studies have not documented clinically significant interactions between everolimus and atorvastatin or pravastatin and simvastatin does not affect the clearance of everolimus.[16]

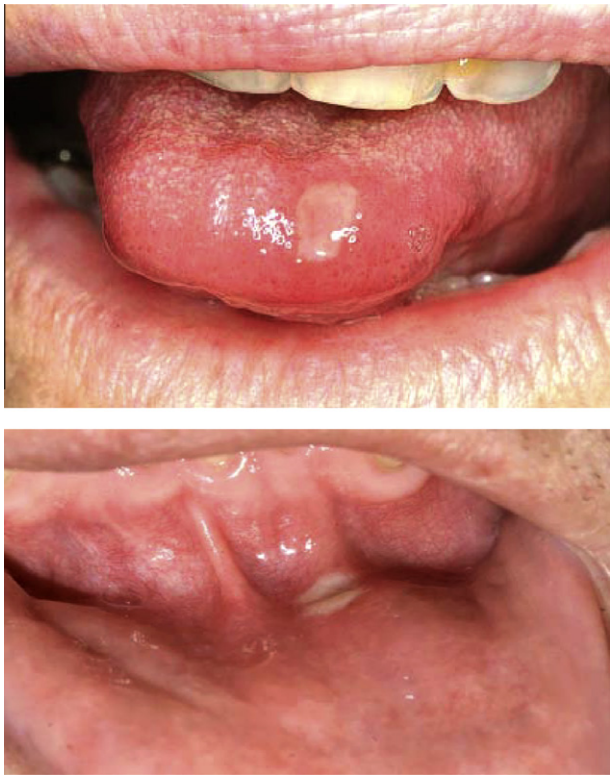

Fig. 5 – Representative cases of stomatitis in RECORD-1.

Table 4 – Clinical management strategy: infections.

Grade	Description	Treatment	Dose modifications
1	• None	• Provide adequate treatment of infection • Appropriate antibiotic use • Culture and be aware of the risk of atypical infections • Consider prophylaxis with entecavir or tenofovir in hepatitis B surface antigen-positive patients	• No change in dose
2	• Localised infection, with local intervention indicated	• Same as for Grade 1	• Maintain dose if tolerated • Hold dose if intolerable until recovery to grade ⩽1, then restart at same dose • If AE recurs at grade 2 level, hold dose until recovery to grade ⩽1, then restart at reduced dose • If dose held >21 d, discontinue treatment
3	• IV antibiotic, antifungal, or antiviral intervention indicated; interventional radiology or surgery indicated	• Same as for Grade 1	• Hold dose until recovery to grade ⩽1, then restart at reduced dose • If dose held >21 d, discontinue treatment
4	• Life-threatening consequences such as septic shock, hypotension, acidosis or necrosis	• Same as for Grade 1	• Discontinue everolimus

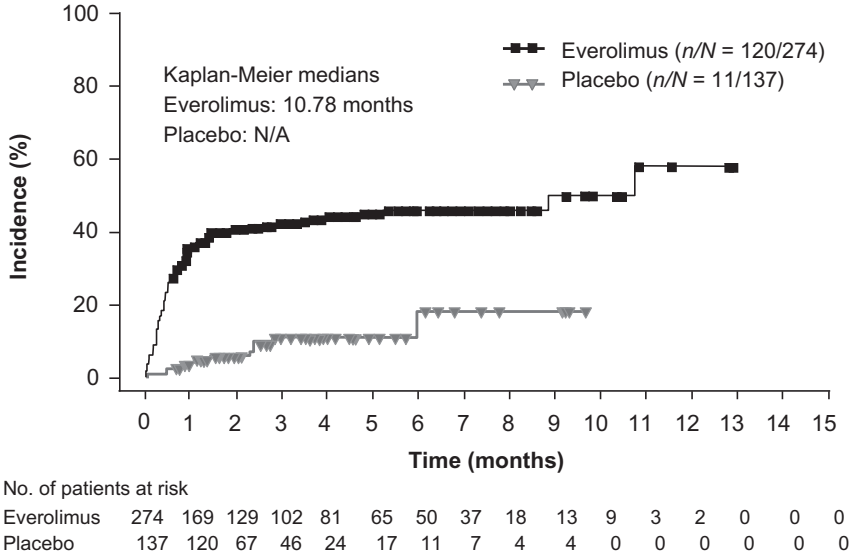

Fig. 6 – Time to diagnosis of stomatitis in RECORD-1 (includes stomatitis, oral mucositis and ulcer events).

Table 5 – Clinical management strategy: stomatitis.

Grade	Description	Treatment	Dose modification
1	• Minimal (normal diet)	• Non-alcoholic mouth wash or 0.9% salt water	• No change
2	• Symptomatic, but can eat and swallow modified diet	• Topical analgesic mouth treatments • Topical corticosteroids • Antiviral therapy if herpetic infection confirmed • Antifungal therapy (topical preferred) may be administered on a case-by-case basis • Avoid agents containing hydrogen peroxide, iodine and thyme derivatives	• Maintain dose if tolerable • Hold dose if intolerable until recovery to grade $\leqslant$1, then restart at same dose
3	• Symptomatic and unable to adequately aliment or hydrate orally	• Same as for Grade 2	• Hold dose until recovery to grade $\leqslant$1, then restart at reduced dose
4	• Symptoms associated with life-threatening consequences	• Same as for Grade 2	• Discontinue treatment

General recommendations are summarised in Table 2 and more specific guidelines are listed in Table 6. The panel recommends that clinicians refer to standard consensus guidelines for the management of these metabolic abnormalities. Guidelines supported by the American Diabetes Association and European Association for the Study of Diabetes recommend the achievement and maintenance of a normal glycaemic goal (haemoglobin A1C < 7%) through the institution of lifestyle interventions and/or metformin as initial therapy, with prompt addition or transition to new medications when target glycaemic goals are not achieved or sustained and the addition of insulin early in patients not meeting target glycaemic goals.[25] In patients with hyperlipidemia, numerous associations recommend that (1) dietary modifications be a component of a total lifestyle change aimed at weight loss and increased physical activity; (2) low-density lipoprotein cholesterol be the primary target of therapy; and (3) secondary targets include total cholesterol: high-density lipoprotein cholesterol (HDL-C) ratio and non-HDL-C levels.[26–28] Patients already treated with lipid-lowering agents should be advised that a higher dose may be required if everolimus treatment further increases lipid levels. Other potential causes of hyperlipidemia (e.g. hypothyroidism, nephrotic syndrome, drugs such as thiazides) should be investigated before starting everolimus. Serum triglyceride levels should be normalised before patients begin everolimus; statins may be effective in this regard if baseline triglyceride levels are $\leqslant$200 mg/dL. Omega fatty acids and niacin may be used as supplements to lower triglyceride levels. Treatment of hyperglycaemia also may lower triglyceride levels. Patients with very high triglyceride

Table 6 – Clinical management strategy: metabolic abnormalities.

Grade	Description	Treatment	Dose modification
1	• HG: >ULN – 160 mg/dL • HCE: >ULN – 300 mg/dL • HT: >ULN – 2.5 × ULN	• None	• No change
2	• HG: >160–250 mg/dL • HCE: >300–400 mg/dL • HT: >2.5–5.0 × ULN	• Treat hyperglycaemia according to the ADA and EASD consensus approach[25] • Treat hyperlipidemia according to standard guidelines[26–28] • Triglycerides ⩾500 mg/dL present risk of pancreatitis; treat urgently with fibrates	• Maintain dose if tolerable • Hold dose if intolerable until recovery to grade ⩽1, then restart at same dose[a]
3	• HG: >250–500 mg/dL • HCE: >400–500 mg/dL • HT: >5.0–10 × ULN	• Same as for Grade 2	• Hold dose until recovery to grade ⩽1, then restart at reduced dose or discontinue per clinical judgement
4	• HG: >500 mg/dL • HCE: >500 mg/dL • HT: >10 × ULN	• Same as for Grade 2	• Discontinue treatment

ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; HCE, hypercholesterolaemia; HG, hyperglycaemia; HT, hypertriglyceridemia.

levels (⩾500 mg/dL) are at risk for pancreatitis and should be treated urgently with fibrates.

2.5. *Dosing considerations*

Everolimus is recommended at a dose of 10 mg/d for the treatment of advanced RCC.[16] As everolimus is a substrate of the cytochrome p450 3A4 isoenzyme (CYP3A4) and a substrate and moderate inhibitor of the multidrug efflux pump P-glycoprotein (PgP),[16] absorption and elimination of everolimus may be influenced by products that affect CYP3A4 and/or PgP.[29] In a study of healthy subjects, the coadministration of rifampin, a CYP3A4 inducer, decreased the AUC of everolimus by an average of 63%.[30] Coadministration with strong inhibitors and inducers of CYP3A4 and/or PgP should be avoided during everolimus treatment.[16] However, if patients require treatment with a strong CYP3A4 inducer, clinicians may consider increasing the everolimus dose to 20 mg/d using 5-mg increments; this approach is predicted to allow adjustment of the AUC of everolimus to the range observed without inducers.[16]

3. Conclusions

Everolimus is an orally available mTOR inhibitor that is approved for the treatment of advanced RCC in patients whose disease has progressed on or after treatment with VEGF-targeted therapy. Before the approval of everolimus, no standard therapy existed for patients who failed treatment with VEGF-targeted therapy; thus, everolimus addresses an unmet need for an effective treatment option for this patient population. Significant prolongation of PFS and reduction in the risk of progression compared with placebo represent important clinical benefits of everolimus that emphasise the need to maintain patients on treatment. Everolimus is generally well tolerated and treatment-related AEs are manageable with proper pretreatment planning, careful on-treatment monitoring and prompt attention when they manifest. Patient education is critical for the rapid identification and reporting of potential AEs. Both clinicians and patients should be aware of potential side-effects of everolimus. Side-effects associated with everolimus are similar in type and severity to those occurring with other mTOR inhibitors,[31] suggesting that they are class effects of these targeted agents. As mTOR inhibitors are used more widely in RCC and other neoplastic diseases, appropriate management of these side-effects will be necessary to maximise patient benefit.

Conflict of interest statement

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REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010;**60**:277–300.
2. Ferlay J, Autier P, Boniol M, et al. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 2007;**18**:581–92.
3. Molina AM, Motzer RJ. Current algorithms and prognostic factors in the treatment of metastatic renal cell carcinoma. *Clin Genitourin Cancer* 2008;**6**:s7–s13.
4. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Kidney Cancer. V.2.2010.
5. Coppin C, Le L, Porzsolt F, Wilt T. Targeted therapy for advanced renal cell carcinoma. *Cochrane Database Syst Rev* 2008;**2**:CD006017.
6. Oudard S, Medioni J, Ayllon J, et al. Everolimus (RAD001): an mTOR inhibitor for the treatment of metastatic renal cell carcinoma. *Expert Rev Anticancer Ther* 2009;**9**:705–17.
7. Brugarolas J. Renal-cell carcinoma – molecular pathways and therapies. *N Engl J Med* 2007;**356**:185–7.
8. Thomas GV, Tran C, Mellinghoff IK, et al. Hypoxia-inducible factor determines sensitivity to inhibitors of mTOR in kidney cancer. *Nat Med* 2006;**12**:122–7.
9. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008;**372**:449–56.
10. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. *Cancer* 2010;**116**:4256–65.
11. Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. *J Clin Oncol* 2004;**22**:454–63.
12. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;**92**:205–16.
13. Cho D, Signoretti S, Regan M, Mier JW, Atkins MB. The role of mammalian target of rapamycin inhibitors in the treatment of advanced renal cancer. *Clin Cancer Res* 2007;**13**(2 Suppl): 758s–63s.
14. Duran I, Siu LL, Oza AM, et al. Characterisation of the lung toxicity of the cell cycle inhibitor temsirolimus. *Eur J Cancer* 2006;**42**:1875–80.
15. White DA, Camus P, Endo M, et al. Non-infectious pneumonitis after everolimus therapy for advanced renal cell carcinoma. *Am J Respir Crit Care Med* 2010;**182**:396–403.
16. Afinitor prescribing information. Basel, Switzerland: Novartis Pharma AG; 2010.
17. Alexopoulos CG, Vaslamatzis M, Hatzidimitriou G. Prevalence of hepatitis B virus marker positivity and evolution of hepatitis B virus profile, during chemotherapy, in patients with solid tumours. *Br J Cancer* 1999;**81**:69–74.
18. Yeo W, Chan PK, Zhong S, et al. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. *J Med Virol* 2000;**62**:299–307.
19. Marzano A, Angelucci E, Andreone P, et al. Prophylaxis and treatment of hepatitis B in immunocompromised patients. *Dig Liver Dis* 2007;**39**:397–408.
20. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B. *J Hepatol* 2009;**50**:227–42.
21. Köstler WJ, Hejna M, Wenzel W, Zielinski CC. Oral mucositis complicating chemotherapy and/or radiotherapy: options for prevention and treatment. *CA Cancer J Clin* 2001;**51**:290–315.
22. Stokman MA, Spijkervet FK, Boezen HM, et al. Preventive intervention possibilities in radiotherapy- and chemotherapy-induced oral mucositis: results of meta-analyses. *J Dent Res* 2006;**85**:690–700.
23. Potting CM, Uitterhoeve R, Op Reimer WS, Van Achterberg T. The effectiveness of commonly used mouthwashes for the prevention of chemotherapy-induced oral mucositis: a systematic review. *Eur J Cancer Care (Engl)* 2006;**15**:431–9.
24. Harris DJ, Eilers J, Harriman A, Cashavelly BJ, Maxwell C. Putting evidence into practice®: evidence-based interventions for management of oral mucositis. *Clin J Oncol Nurs Pract* 2007;**12**:141–52.
25. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care* 2009;**32**:193–203.
26. National Institutes of Health. National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Final report. <http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf>.
27. Genest J, Forhlich J, Fodor G, McPherson R. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: 2003 update. *CMAJ* 2003;**169**:1–10.
28. International task force for prevention of coronary heart disease. Treatment guidelines for dyslipidemia. <http://www.chd-taskforce.com/pdf/2004_06_09_zurich.pdf>.
29. Kirchner GI, Meier-Wiedenbach I, Manns MP. Clinical pharmacokinetics of everolimus. *Clin Pharmacokinet* 2004;**43**:83–95.
30. Kovarik JM, Hartmann S, Figueiredo J, et al. Effect of rifampin on apparent clearance of everolimus. *Ann Pharmacother* 2002;**36**:981–5.
31. Hutson TE, Figlin RA, Kuhn JG, Motzer RJ. Targeted therapies for metastatic renal cell carcinoma: an overview of toxicity and dosing strategies. *Oncologist* 2008;**13**:1084–96.