

# Horizon Scanning in Oncology

Everolimus (Afinitor<sup>®</sup>) for  
advanced/ meta-  
static kidney cancer



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# 1 Drug description

## Generic/Brand name:

Everolimus (RAD-001)/Afinitor®

## Developer/Company:

Novartis

## Description:

Everolimus is an oral inhibitor of the mammalian target of rapamycin (mTOR), a serine-threonin kinase. Mechanisms of action include the inhibition of the mTor kinase whose pleiotropic activity is up-regulated in many human cancers, the reduction of vascular endothelial growth factor (VEGF) expression and the inhibition of hypoxia inducible factor (HIF-1) expression. Ultimately, cell proliferation, angiogenesis and glucose up-take are slowed down and therefore, further growth of cancer cells is reduced or stopped [1, 2].

There are 5 mg and 10 mg tablets for oral administration. The usual dose is 10 mg once daily, but dose reduction to 5 mg might become necessary for the management of adverse effects. Maximum daily dose should not exceed 20 mg and treatment should be continued as long as clinical benefits can be observed and as long as toxicity remains acceptable [1].

**everolimus, an oral mTOR inhibitor, reduces or stops growth of cancer cells**

**daily dose is 10mg**

**treatment should be continued as long as clinical benefits can be observed**

# 2 Indication

Everolimus (Afinitor®) is indicated for the treatment of patients with metastatic or advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

**for advanced or metastatic renal cell carcinoma**

# 3 Burden of disease

Renal cell cancer (RCC), with about 90% the most common type of kidney cancer [3], is newly diagnosed in about 40,000 patients each year in Europe and can be held accountable for an estimated annual 20,000 deaths [4].

Associated risk factors are smoking and obesity, as well as genetic abnormalities [3]. Median age of RCC diagnosis is at 65 years [3] with more men than women being affected [5].

**renal cell carcinoma is the most common type of kidney cancer**

three risk-groups are distinguished

Risk stratification is important for choosing the most appropriate therapy. The most common model to predict short survival is the Memorial Sloan-Kettering Cancer Centre or *Motzer* criteria (MSKCC) which are based on risk-factors or predictors, such as high blood levels of lactate dehydrogenase and calcium, anaemia, time of less than a year from diagnosis to the need for systemic treatment and low performance status (Karnofsky performance status <80%). Depending on the number of risk factors three groups can be stratified: a good, intermediate or poor risk-group [3].

depending on the staging 5-year survival rates range from 23% to 64%

Staging of renal cancer depends on the tumour grade, local extent of the tumour, presence of metastases in the regional lymph nodes or metastatic disease. In contrast to localized tumours with a high probability of cure (stage I/II), more advanced forms with either metastases in the regional lymph nodes (stage III) or with distant metastases (stage IV) of kidney cancer are linked to poor outcomes. Estimated average 5-year survival rate for patients ranges from 23% (stage IV) to 64% (stage III) [3].

25% -30% of patients are diagnosed when tumour has metastasised  
an estimated 300 patients per year are affected in Austria

Due to the often asymptomatic course of the disease, about 25% to 30% of patients are diagnosed when the tumour has already metastasised [6, 7]. Applying this estimate to the Austrian context (with an overall incidence of 1209 renal cancer cases in 2006 [8]) - results in about 300 patients per year. 20% to 30% of patients with previously localized tumours relapse one to two years after surgery [3].

## 4 Current treatment

treatment options include  
surgery,  
cytokines,  
monoclonal antibodies,  
kinase inhibitors,  
mTOR inhibitors

For stage III RCC, primary treatment consists of radical nephrectomy with or without lymph node dissection. For stage IV cancers, surgery is also an option and might include nephrectomy and/or metastasectomy.

In addition to best supportive care, options for first- and second-line therapy for patients who relapse or with stage IV RCC and medically or surgically unresectable cancer are

- ✿ cytokines (interferon- $\alpha$ , high-dose interleukin-2)
- ✿ monoclonal anti-VEGF antibodies (bevacizumab)
- ✿ multi kinase inhibitors with activity including the downstream signalling of the vascular endothelial growth factor receptor (VEGFR) (sorafenib, sunitinib)
- ✿ mTor inhibitors (temsirolimus) [3].

Until recently, cytokines were the only available systemic treatment options for metastatic RCC but were limited to patients with a good risk profile and were accompanied by substantial treatment related morbidity [6, 9]. This has changed with the availability of other treatments such as targeted therapies using multi kinase or mTOR inhibitors.

The EMEA approved sunitinib, sorafenib for patients who have failed prior interferon- $\alpha$  or interleukin-2 therapy [10], bevacizumab in combination with interferon- $\alpha$  and finally, temsirolimus as first-line treatment for patients with advanced RCC and poor prognosis (according to MSKCC) [10].

## 5 Current regulatory status

Orphan drug designation was granted by European Medicines Agency (EMA) in June 2007. In May 2009, the Committee for Medicinal Products for Human Use adopted a positive opinion to recommend marketing authorisation for everolimus for

- ❖ patients with advanced renal cell carcinoma whose disease has progressed on or after treatment with VEGF-targeted therapy [2].

The final EU market authorization was granted in August 2009 [11, 12].

The United States Food and Drug Administration (FDA) granted approval for everolimus for

- ❖ the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib in March 2009 [1].

Everolimus (Certican®) is also approved for the prevention of transplant rejection [13].

**approved by the EMA and the FDA for advanced renal cell carcinoma which has progressed after VEGF-targeted therapy**

## 6 Evidence

Two studies evaluating everolimus were identified. One phase III trial allocated RCC patients, in whom previous therapies - mainly sunitinib or sorafenib - have failed, to either everolimus or placebo therapy. Improved progression free survival was observed for the active treatment group (4.0 months) in comparison to the control group (1.9 months). No difference was found for overall survival or quality of life.

The single arm phase II trial included 37 patients with one previous therapy and metastatic RCC for the analysis. Median overall survival was 22.1 months, and median progression-free survival was 11.2 months.

The majority of side-effects were of grade 1 or grade 2 in both studies.

**one phase III trial and one phase II trial were identified**

### 6.1 Efficacy and safety - phase III studies

Reference	NCT00410124, published [14]
Sponsor	Novartis Oncology
Country	Australia, Canada, Europe, Japan, USA
Design	Multi-centre, double-blind, randomised phase III trial, crossover to everolimus if disease progression was observed in placebo group
Participants characteristics	410 pts <sup>1</sup> (I 272 vs C 138), median age: I 61 years (range: 27 – 85 years) vs C 60 years (range: 29 – 79 years)

<sup>1</sup> pts= Patients,

Treatments	<b>Intervention:</b> oral 10 mg everolimus/day in a 28 day cycle and best supportive care <b>Control:</b> placebo and best supportive care <b>Treatment duration:</b> until disease progression, unacceptable toxicity, death, discontinuation for any other reason.
In-/exclusion criteria	<b>Inclusion:</b> adults with metastatic renal cell carcinoma with clear-cell component, progression on or within 6 months of stopping treatment with sunitib and/or sorafenib, or previous therapy with bevacizumab, IL-2, IF- $\alpha$ ; Karnofsky-performance status score $\geq$ 70% <b>Exclusion:</b> previous treatment with mTOR inhibitor, untreated CNS metastases, uncontrolled medical conditions (diabetes, unstable angina pectoris, symptomatic congestive heart failure, recent myocardial infarction)
Follow-up	Scheduled recruitment period of 16 months and an additional follow-up of 5 months, but trial was terminated after second interim analysis because criteria for positive study were met
Outcomes	<b>Primary:</b> progression-free survival <b>Secondary:</b> safety, objective tumour response rate, overall survival, disease-related symptoms, quality-of-life
Key results	<b>Median progression free-survival</b> (blinded independent central review): I 4.0 months (95% CI <sup>2</sup> : 3.7, 5.5) vs C 1.9 months (95% CI: 1.8, 1.9), HR <sup>2</sup> = 0.30 (95% CI: 0.22, 0.40; p < 0.0001) <b>Objective tumour response:</b> I 3 pts (1%) vs C 0 pts (0%) <b>Overall survival:</b> HR = 0.83 (95% CI: 0.50, 1.37; p = 0.23) <b>Global health status/quality-of-life score:</b> HR = 1.02 (95% CI: 0.70, 1.50)
Adverse effects	<b>All grades:</b> stomatitis (all grades): I 40% vs C 11%, rash: I 25% vs C 4%, fatigue: I 20% vs C 16%, anaemia: I 91% vs C 76%, hypercholesterinaemia: I 76% vs C 32%, hyperglycaemia: I 50% vs C 23%, <b>Grade 3:</b> anaemia: I 9% vs C 5%; hyperglycaemia I 12% vs C 1%, lymphopenia I 14% vs C 5%, pneumonitis I 3% vs C 0% <b>Grade 4:</b> more often in everolimus group, always $\leq$ 1%
Commentary	Everolimus was associated with a reduction in the risk of progression or death compared with placebo in patients with metastatic renal cell carcinoma whose disease had progressed after treatment with VEGF-targeted therapies. Clinical resistance to VEGF inhibitors does not imply resistance to mTOR inhibitors.

<sup>2</sup> CI = Confidence Interval

<sup>3</sup> HR = Hazard Ratio

**everolimus in comparison to placebo prolonged progression-free survival by 2.1 months**  
**no differences for overall survival**  
**common adverse events mostly grade 1 or 2**  
**treatment discontinuation in 10% of intervention group due to toxicity**

This randomised phase III trial included 410 patients, mainly with favourable or intermediate risk features according to the MSKCC. 15% of patients in the intervention and placebo group were classified as being at poor risk. Improved progression-free survival was found for the everolimus group and was similar across all risk subgroups. Yet, no significant difference of overall survival was demonstrated between intervention and placebo group. According to the authors, this might be due to the fact that out of 98 patients who progressed in the placebo group, 79 were allowed to crossover to the everolimus group.

Adverse effects were more common in the everolimus group but were mostly of grade 1 or grade 2. Due to drug related toxicity, treatment discontinuation occurred in 28 patients (10%) in the intervention group in comparison to five patients (4%) in the placebo group. 5% in the everolimus group died within 28 days of their last dose (one might have been attributable to treat-



ment) and 4% in the control group.

The trial was stopped early as the criteria for a positive study ( $\geq 60\%$  of targeted 290 progression free events were observed) were met after the second interim analysis and the remaining patients in the placebo group were allowed to cross-over to the active treatment arm [15].

**cross-over was allowed**

## 6.2 Efficacy and safety - further studies

Another company sponsored, single-armed phase II study enrolled 41 patients with predominantly clear cell RCC and progressive metastatic disease with  $\leq 1$  prior therapy [16]. 10 mg everolimus were administered every day for 8 weeks or until disease progression. Patients were mostly at MSKCC intermediate risk (58.5%) or at good risk (36.6%). Additionally, 17% of the study population had not been treated previously with any systemic therapy. Based on the findings of 37 patients, median progression-free survival was 11.2 (95% CI: 1.7, 36.2) months; median overall survival was 22.1 (95% CI: 1.4, 36.4) months. Stable disease for  $\geq 3$  months was observed in 27 patients and for  $\geq 6$  months in 21 patients.

**uncontrolled trial showed median overall survival of 22.1 months**

Most common side effects were of grade 1 or 2, including anorexia (38%), nausea (38%), diarrhoea (31%), stomatitis (31%) and rash (26). Hematologic adverse effects of grade 3 were thrombocytopenia (7.7%), hyperglycaemia (7.7%) and hypercholesterolemia (5.1%).

**side-effects mainly grade 1 or 2**

Additionally, one previous horizon scanning report was identified [7].

## 7 Estimated costs

The manufacturer's price for one package Afinitor® 10 mg containing 30 tablets is € 3,600, yielding € 120 for one tablet daily [17]. These costs occur as long as clinical benefits can be observed and as long as toxicity remains acceptable. In the above mentioned phase III trial, median duration of treatment was 95 days for the everolimus group. Assuming the same treatment duration, costs additional to expenses for previous therapies would be € 11,400. But because the preferred sequence of the new therapies in RCC is unclear, some of these costs will be additive and others alternative to existing ones.

**one tablet Afinitor® 10mg costs EUR 120**

**these expenses are in addition to previous therapies**

## 8 Ongoing research

One ongoing phase III trial was found on Clinical trials.com:

[NCT00410124](#): The trial on which the presented results are based is still ongoing to assess the secondary endpoint of overall survival [18].

ongoing studies assess everolimus as first-line therapy

However, plenty phase I and phase II trials were identified. Research topics include everolimus as first-line therapy for patients with metastatic kidney cancer, in combination with other drugs, such as bevacizumab or sorafenib, or for a broad range of other cancer types [19].

## 9 Commentary - English

no other standard treatment option when targeted therapies have failed

The two studies presented in this report showed improved progression-free survival in patients with metastatic RCC treated with everolimus as second line therapy. Since no other standard treatment exists for patients, in whom previous targeted therapies have failed, everolimus provides a treatment option for those patients [15, 18]. Consequently, the drug was approved by the EMEA and the FDA for the treatment of patients with advanced/metastatic RCC after treatment failure of sunitinib and/or sorafenib.

everolimus in comparison to placebo led only to a modest difference in progression-free survival

Progression-free survival, the primary outcome of the phase III trial, was 4.0 months (95% CI: 3.7, 5.5) in the everolimus group and 1.9 months (95% CI: 1.8, 1.9) in the placebo group (HR = 0.30), leading to a modest difference of 2.1 months. As confirmed objective tumour response was seen in only 1% of the everolimus group and in 0% of the placebo group, the advantage in progression-free survival is mainly the result of disease stabilisation.

no improvements in overall survival or quality-of-life instead of placebo controlled trial, comparison to another mTOR inhibitor might have been better

No improvements for the intervention group were observed either with regards to quality-of-life scores or to overall survival. The most frequent observed adverse effects were of grade 1 or grade 2.

Unequivocally, everolimus is “the first and only agent with established clinical benefit for the treatment of patients with RCC after tyrosine kinase inhibitor therapy [15]”. Nevertheless, improvements in overall survival for everolimus are still missing. The authors argue that results might have been confounded by reasons that patients were allowed to cross-over to the active treatment arm for ethical reasons. Therefore, it remains questionable if a placebo controlled trial was an appropriate study design. Temsirolimus, like everolimus an mTOR inhibitor, has demonstrated improved overall survival in comparison to another active agent (IF- $\alpha$ ) for, admittedly, previously untreated RCC patients [4, 9]. Hence, the direct head-to-head comparison of both mTOR inhibitors would have been a better way to determine the real benefit of everolimus.

many treatment options for advanced renal cell cancer

Until recently, treatment options for advanced/metastatic RCC were quite limited. This has changed with the availability of a number of new drugs such as sunitinib, sorafenib or temsirolimus. Hence, the remaining challenge is the identification of the most effective drugs with the least side effects for the treatment of RCC, as well as the determination of the best sequence or combination of these new therapies. Everolimus might offer advantages over other drugs in terms of oral application and acceptable side-effects, but its value for the treatment of RCC has not been established yet.

real value of everolimus not yet established

Because the principle of mTOR inhibition applies to a broad range of malignancies (multiple clinical trials ongoing) there is a relevant potential for off-label use of Everolimus.

## 10 Commentary - German

Eine Phase III Studie zeigte bei PatientInnen mit metastasiertem Nierenzellkarzinom (RCC), die mit Everolimus als Zweitlinien-Therapie behandelt worden waren, längeres progressionsfreies Überleben (PFS) im Vergleich zu Placebo. Da bisher keine Standardtherapie für mit „Targeted therapies“ vorbehandelten PatientInnen existiert, stellt Everolimus erstmals eine Therapieoption für diese Personen dar [15, 18]. Daher wurde Everolimus sowohl von der EMEA als auch von der FDA zur Behandlung von metastasiertem/fortgeschrittenem RCC nach Therapieversagen von Sunitinib und/oder Sorafenib zugelassen.

PFS, der primäre Endpunkt der Phase III Studie, war 4.0 Monate (95% CI: 3.7, 5.5) in der Everolimusgruppe und 1.9 Monate (95% CI: 1.8, 1.9) in der Placebogruppe (HR= 0.30), wodurch sich eine Differenz von 2.1 Monaten ergab. Da eine bestätigte objektive Tumorresponse in 1% der Everolimusgruppe und in 0% der Placebogruppe beobachtet worden war, ist das verlängerte PFS damit hauptsächlich auf eine Stabilisierung der Erkrankung zurückzuführen.

Keine Unterschiede wurden für den aktiven Behandlungsarm in Bezug auf Lebensqualität oder Gesamtüberleben gefunden. Die am häufigsten beobachteten unerwünschten Nebenwirkungen waren Grad 1 oder Grad 2.

Zweifellos ist „Everolimus das erste und einzige Medikament mit bewiesenem klinischem Nutzen zur Behandlung von PatientInnen mit RCC nach einer Therapie mit Tyrosin-Kinase-Inhibitoren“ [15], trotz allem ist der Nachweis eines verlängerten Gesamtüberlebens nach wie vor ausständig. Die Autoren der Phase III Studie argumentieren, dass dies möglicherweise durch das Cross-over Design der Studie bedingt ist, weil aufgrund ethischer Überlegungen PatientInnen der Placebogruppe zur aktiven Therapie überwechseln durften. Fragwürdig ist daher, ob eine Placebo-kontrollierte Studie tatsächlich das beste Studiendesign war. Für Temsirolimus, wie Everolimus auch ein mTOR Inhibitor, zeigte eine Studie ein verlängertes Gesamtüberleben im Vergleich zu einem anderen, aktiven Medikament (IF- $\alpha$ ) - allerdings für noch unbehandelte PatientInnen [4, 9]. Der direkte Vergleich der beiden mTOR Inhibitoren wäre daher möglicherweise ein besserer Weg gewesen, um den tatsächlichen Nutzen von Everolimus zu bestimmen.

Bis vor kurzem waren die Behandlungsmöglichkeiten für metastasiertes/fortgeschrittenes RCC eingeschränkt. Durch die Verfügbarkeit neuer Medikamente wie Sorafenib, Sunitinib oder Temsirolimus stehen nun aber zahlreiche Therapien zur Verfügung. Die verbleibende Herausforderung ist nun, sowohl die effektivsten und nebenwirkungsärmsten Medikamente zu identifizieren, als auch die beste Therapieabfolge zu bestimmen. Everolimus bietet aufgrund seiner einfachen Verabreichungsform und der akzeptablen Nebenwirkungen zweifellos einige Vorteile gegenüber anderen Therapien, allerdings ist der endgültige Stellenwert von Everolimus in der Behandlung des RCC noch nicht bewiesen.

Da das Prinzip der mTOR Inhibition bei sehr vielen Malignomen potentiell wirksam sein könnte (viele klinische Studien anhängig), besteht ein relevantes Potential des off-label Gebrauchs dieser Substanz.

**keine Standardtherapie für mit „Targeted therapies“ vorbehandelte PatientInnen**

**nur geringe Differenz in progressionsfreiem Überleben zwischen Everolimus und Placebo**

**keine Unterschiede bei Gesamtüberleben und Lebensqualität**

**statt Placebo kontrollierte Studie, wäre Vergleich mit anderem mTOR Inhibitor besseres Studiendesign gewesen**

**zahlreiche neue Medikamente zur Behandlung von fortgeschrittenem Nierenzellkarzinom**

**Stellenwert von Everolimus noch nicht bewiesen**

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