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# Trial blazing information on anticancer immunosuppresent Everolimus

**Balasubramanian J**✉

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**Author Affiliation:**
[1]Shield Health Care Pvt Ltd, Chennai-600095, India
[2]Periyar Maniammai University, Thanjavur-613403, Tamilnadu, India, E-mail: jvbalpharm@yahoo.co.in

✉**Correspondence to:**
Periyar maniammai University, Thanjavur-613403, Tamilnadu, India, E-mail: jvbalpharm@yahoo.co.in

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## 1. INTRODUCTION

Anticancer, or antineoplastic, drugs are used to treat malignancies, or cancerous growths. Drug therapy may be used alone, or in combination with other treatments such as surgery or radiation therapy. Suppression of the immune system and its ability to fight infection, immunosuppressant may result from certain diseases, such as AIDS or lymphoma, or from certain drugs, such as some of those used to treat cancer. Immunosuppression may also be deliberately induced with drugs, as in preparation for bone marrow or other organ transplantation, to prevent the rejection of a transplant. Initially, anti-cancer drugs were thought to be immunosuppressive based on their anti-proliferative and cytotoxic actions, which also determine their antitumor effects. Nevertheless, as early as the 1960s it became apparent that some of these agents can exert curative effects in experimental tumor models owing to the cooperation of host defenses against the tumor. It was concluded, therefore, that these agents can be at least permissive in their action such that antitumor host defenses can be activated, not unlike what happens in anti-infection therapies. As more information became available, this early simplistic assumption had to be modified to include the notion that at least some of these agents under certain conditions can directly or indirectly stimulate immune responses.

Anti-proliferative and cytotoxic agents are widely used alone and in combination among themselves and/or with different modalities of treatment in attempts to design effective anti-cancer therapies. In most cases, drug regimens involve the use of the agents at or near the maximum tolerated dose (MTD) with the aim of eradicating the greatest possible number of neoplastic cells. At present, however, it is becoming increasingly clear that several of these agents, in addition to their antitumor action, also affect host phenomena such as angiogenesis and immune responses and that some of these effects may have therapeutic potential.

## 2. EVEROLIMUS

Everolimus (RAD-001) is the 40-O-(2-hydroxyethyl) derivatives of sirolimus and works similarly to sirolimus as an inhibitor of mammalian target of rapamycin (mTOR). It is currently used as an immunosuppressant to prevent rejection of organ transplants and treatment of renal cell cancer. Much research has also been conducted on everolimus and other mTOR inhibitors for use in a number of cancers.



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**2.1. Indications**

- Advanced kidney cancer
- Prevention of organ rejection after renal transplant
- Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) in patients who are not suitable for surgical intervention.
- Progressive or metastatic pancreatic neuroendocrine tumors not surgically removable.
- Breast cancer in post-menopausal women with advanced hormone-receptor positive, HER2-negative type cancer, in conjunction with exemestane.
- Drug – eluting stent.

## 3. CHEMISTRY

Everolimus (previously known by the research code RAD-001) is a relatively large 'small molecule' drug (Molecular Weight of 958.2 g.mol-1), lipophilic, orally absorbed and has a low plasma binding of ~74%. Everolimus is primarily metabolized CYP3A4 routes, with known metabolites being essentially inactive as mTor inhibitors; these are largely excreted in the feces. Everolimus has a long mean elimination half-life of ~30 hours. Typical dosage is 10 mg (equivalent to ca. 10.4umol) once a day. The full prescribing information can be found here. The structure (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.04,9]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone) contains a macrolide ring (a large macrocyclic ester), often a characteristic of natural products. In fact, with the complex size, high number of defined stereocenters Everolimus is very 'natural product like', of striking functional group interest is the presence of the unusual alpha-keto amide functionality (the two adjacent carbonyls and the amide from the six membered piperidine ring - this has unusual conformational and reactivity properties, and is associated with the conformation required for cis- to trans-isomerisation for a proline containing peptide.

Everolimus is chemcially very similar to the natural product drug Rapamycin (in fact one chemical name for Everolimus is 42-O-(2-hydroxyethyl)-Rapamycin). Confusingly Rapamycin is also known by the USAN Sirolimus. Sirolimus was originally identified as an active component of a soil isolate from Easter Island, eventually the source of this molecule was found to be the bacteria Streptomyces hygroscopicus. A further member of the family is the drug Tacrolimus (USAN) (also know by the research code FK-506) which was isolated from a Japanese soil sample, and is made by the bacteria Streptomyces tsukubaensis. Of course, due to the other functions of Rapamycin (suppression of the immune system) drugs of this class may not actually be that useful for the extension of life.

## 4. PHARMACOLOGY

**4.1. Mechanism of Action**

Everolimus inhibits antigenic and interleukin (IL-2 and IL-15) stimulated activation and proliferation of T and B lymphocytes. In cells, everolimus binds to a cytoplasmic protein, the FK506 Binding Protein- 12 (FKBP-12), to form an immunosuppressive complex (everolimus: FKBP-12) that binds to and inhibits the mammalian Target of Rapamycin (mTOR), a key regulatory kinase. In the presence of everolimus phosphorylation of p70 S6 ribosomal protein kinase (p70S6K), a substrate of mTOR, is inhibited. Consequently, phosphorylation of the ribosomal S6 protein and subsequent protein synthesis and cell proliferation are inhibited. The everolimus: FKBP-12 complex has no effect on calcineurin activity. In rats and non-human primate models, everolimus effectively reduces kidney allograft rejection resulting in prolonged graft survival.

**4.2. Pharmacokinetics**

Everolimus pharmacokinetics has been characterized after oral administration of single and multiple doses to adult kidney transplant patients, hepatically-impaired patients, and healthy subjects.

***4.2.1. Absorption***

After oral dosing, peak everolimus concentrations occur 1 to 2 h post dose. Over the dose range of 0.5 mg to 2 mg twice daily, everolimus Cmax and AUC are dose proportional in transplant patients at steady-state.



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*4.2.2. Distribution*

The blood -to-plasma ratio of everolimus is concentration dependent ranging from 17% to 73% over the range of 5 ng/mL to 5000 ng/mL. Plasma protein binding is approximately 74% in healthy subjects and in patients with moderate hepatic impairment. The apparent distribution volume associated with the terminal phase (Vz/F) from a single-dose pharmacokinetic study in maintenance kidney transplant patients is 342 to 107 L (range 128 to 589 L).

*4.2.3. Metabolism*

Everolimus is a substrate of CYP3A4 and P-glycoprotein. The main metabolic pathways identified in man were monohydroxylations and O-dealkylations. Two main metabolites were formed by hydrolysis of the cyclic lactone. Everolimus was the main circulating component in blood. None of the main metabolites contribute significantly to the immunosuppressive activity of everolimus.

*4.2.4. Excretion*

After a single dose of radiolabeled everolimus was given to transplant patients receiving cyclosporine, the majority (80%) of radioactivity was recovered from the feces and only a minor amount (5%) was excreted in urine. Parent drug was not detected in urine and feces.

*4.2.5. Pharmacokinetics of the immunosuppressant Everolimus in maintenance of Renal transplant*

The novel macrocyclic immunosuppressant everolimus has been approved for use in renal and heart transplantation. The objective of this randomized, double-blind, placebo-controlled, dose-escalating Phase 1 study was to evaluate the pharmacokinetic profile of different dosing regimens of everolimus. Fifty-four subjects were randomized for 4-weeks treatment with everolimus (n = 44) or placebo (n = 10). Steady state was reached by day 4 of multiple dosing with evidence for dose- proportionality over the dose range tested. Systemic accumulation was 1.6- to 2.2- fold with multiple dosing. Steady-state predose trough concentrations were well correlated with AUC ($r = 0.87$, $p < 0.001$). Within -subject coefficients of variation for the tablet formulation ranged from 10-19% and between-subject coefficients from 34-60% for Cmax and AUC. There was no effect of common demographic parameters (age, sex, weight) on variability in steady-state exposure. These results support the clinical use of everolimus in renal transplantation.

## 5. CLINICAL TRIAL INFORMATIONS

**5.1. Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer**

Resistance to endocrine therapy in breast cancer is associated with activation of the mammalian target of rapamycin (mTOR) intracellular signaling pathway. In early studies, the mTOR inhibitor everolimus added to endocrine therapy showed antitumor activity. Everolimus combined with an aromatase inhibitor improved progression-free survival in patients with hormone-receptor–positive advanced breast cancer previously treated with nonsteroidal aromatase inhibitors.

**5.2. Everolimus in HR-Positive Advanced Breast Cancer**

In their study on the use of everolimus in postmenopausal women with hormone-receptor (HR)–positive advanced breast cancer, Baselga et al. (Feb. 9 issue)1 report that median progression-free survival in patients receiving everolimus was 6.9 months according to radiologic assessment by local investigators and 10.6 months according to central assessment. Patients who discontinued one or both study drugs (one group received exemestane alone, and the other exemestane in combination with everolimus) for reasons other than disease progression were required to continue the same schedule of radiologic assessment until progression occurred. It would be helpful to know whether the difference in progression-free survival as determined by central review could be attributed to the continuation of radiologic assessments beyond the discontinuation of the study treatment for reasons other than progression and at a time in which patients may have been given alternative forms of therapy. Of relevance to this question is the fact that only 37% of patients discontinued treatment because of disease progression in the group receiving combination therapy as compared with 66% of patients in the group receiving exemestane only. It is possible that the progression-free survival of 10.6 months reported with central analysis may therefore be an overestimation of the benefit of everolimus. Consequently, the progression-free survival of 6.9 months may more accurately reflect the true benefit achieved and should be used as the reference for future trial designs.



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**5.3. Everolimus in kidney cancer**

This phase III trial is studying everolimus to see how well it works in treating patients with kidney cancer who have full surgical resection. Patients must have histologically or cytologically confirmed renal cell carcinoma (clear cell or non-clear cell allowed, collecting duct or medullary carcinoma excluded). Patients must be considered pathologically either intermediate high risk or very high risk. Patients must not have history of distant metastases but can have microvascular invasion of the renal vein of any grade or stage (as long as M0). Patients must have undergone a full surgical resection (radical nephrectomy or partial nephrectomy) including removal of all clinically positive nodes. Surgical margins must be negative. Patient must not have any evidence of residual or metastatic RCC on scans after nephrectomy.

**5.4. Kidney cancer patients find hope in Everolimus**

Renal cell carcinoma, or metastatic kidney cancer, like other cancers, is believed to be caused by the abnormal functioning of signaling pathways in cells. Both the overproduction of VEGF factor and the von Hippel-Lindau tumour suppressor gene have been associated in particular with renal cancer. Previously, the outlook for a patient with metastatic kidney cancer was bleak. Now, some drugs have been successful to help control the receptor for VEGF, but an alternative is needed for the patients who do not respond.

Everolimus, a derivative of rapomycin, affects an important intracellular signaling pathway regulating proliferation, growth, cellular metabolism, and angiogenesis. To test everolimus' efficacy, Dr. Robert Motzer, of Memorial Sloan-Kettering Cancer Center, New York, USA, and colleagues performed a randomized, controlled phase III trial in patients whose metastatic kidney cancer had continued to progress despite treatment with sunitinib, sorafenib, or both. These patients were randomly assigned in a 2:1 ratio: 272 patients to receive 10 mg of everolimus once daily, or 138 patients with a placeblo. This treatment, in tandem with high quality supportive care, was examined in terms of progression-free survival, with the study ending after 290 progression events occurred. It was found that there was a significant difference in efficacy, which favored the group that was administered everolimus. The ethical implications of this progression, as it did not allow the placebo patients access to the drug, led to the trial's termination after 191 progression events. Progression events were observed in 37% (101 of 272) of patients in the everolimus group and 65% (90 of 138) of the placebo group.

Further analysis indicated that patients administered everolimus were less than one third as likely to experience disease progression. The median length of progression free survival time was 4 months in the medicated group, approximately twice that of the placebo. There were some adverse events, including stomatitis, rash, and fatigue, which were more common in the everolimus group, but were mostly mild or moderate in severity. Pneumotitis was also observed in 22 patients on everolimus, of whom eight had a severity grade 3. In conclusion, the authors have high hopes for everolimus. "On the basis of the results of this trial, we believe that everolimus should now be considered as the standard-of-care in patients with metastatic renal cell carcinoma whose disease has progressed after treatment with VEGF-targeted therapies."

**5.5. Final-phase trial underway for Everolimus in gastric cancer**

Fifty-four patients were enrolled in the trial, which was conducted at multiple Japanese institutions including the Osaka Medical College in Osaka, the National Cancer Center Hospital in Tokyo, and the Tochigi Cancer Center in Tochigi. Oral everolimus (10 mg) was administered daily. Results in 53 patients showed a disease control rate of 56%, a median progression- free survival of 2.7 months, and a median overall survival of 10.1 months. Grade 3 adverse events occurred in 20 patients and included anemia, fatigue, and stomatitis. Grade 4 adverse events, such as lymphopenia and hemorrhage, occurred in eight patients.

**5.6. Multicenter phase II study of everolimus in patients with previously treated metastatic gastric cancer: Main results**

These results showed that RAD001 monotherapy was generally well tolerated with promising activity in pts with previously treated MGC. These results support further evaluation of RAD001 in MGC.

**5.7. Everolimus a promising treatment for advanced gastric cancer**

NEW YORK (Reuters Health) - Everolimus may help control previously treated metastatic gastric cancer, according to a report in the March 15th Journal of Clinical Oncology. "There are very limited treatment options for patients who progress despite the standard treatment for this aggressive cancer," lead author Dr. Toshihiko Doi from National Cancer Center Hospital East, Chiba, Japan, told Reuters Health in an email. "The results from this study demonstrate that everolimus has the potential to provide an effective new option for these patients." In a single-arm phase II study, Dr. Doi and colleagues tested the safety and efficacy of everolimus monotherapy in 53 patients whose gastric cancer had progressed despite one or two prior chemotherapy regimens (with at least one containing fluorouracil or platinum derivatives, taxanes, or irinotecan). Patients received 10 mg/day orally until



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progression, unacceptable toxicity, or study discontinuation for any other reason. Twenty-eight of 50 patients (56.0%) in the per protocol analysis and 29 of 53 in the full analysis (54.7%) achieved some period of progression-free survival (median, 2.7 months). There were no complete responses. Nearly half the patients (45%) had a decrease in tumor size, with the maximum best change reaching a 34% decrease in sum of longest diameters when compared with baseline. The proportion of patients with stable disease (56.0%) and progressive disease (44.0%) was similar in the second-line and third-line treatment subgroups. The median overall survival was 10.1 months.

**5.8. Multicenter Phase II Study of Everolimus in Patients with Previously Treated Metastatic Gastric Cancer**

Everolimus, an oral inhibitor of the mammalian target of rapamycin, has shown antitumor activity in gastric cancer in preclinical and phase I studies. This phase II study evaluated the efficacy and safety of everolimus in pretreated patients with advanced gastric cancer. Everolimus monotherapy resulted in a promising DCR in patients with previously treated advanced gastric cancer. Adverse events are consistent with the reported safety profile of everolimus. These results warrant further evaluation in patients with advanced gastric cancer.

**5.9. Everolimus Improves Progression-Free Survival for Patients with Rare Pancreatic Cancer**

Everolimus, an immunosupressant agent used to prevent rejection of organ transplants, also has anti-angiogenic properties. It inhibits the mTOR protein, a central regulator of tumor cell division and blood vessel growth in cancer cells. The once-daily oral therapy was approved in March 2009 for advanced renal cell carcinoma, and is currently being tested in a host of other disease sites, including lymphomas, breast, skin, gastric, liver, colon and prostate cancers.

**5.10. Everolimus Improves Progression-Free Survival for Patients with rare pancreatic cancer, study finds**

In an international Phase III randomized study, everolimus, an inhibitor of the mammalian target of rapamycin (mTOR), has shown to dramatically improve progression-free survival for patients with advanced pancreatic neuroendocrine tumors (pNET), according to researchers from The University of Texas MD Anderson Cancer Center. The international double-blind trial, RADIANT-3, enrolled 410 patients with advanced, low or intermediate grade pNET. Patients were randomized to receive either 10 milligrams of everolimus or placebo. The primary endpoint was progression-free survival. Median exposure to everolimus was 38 weeks, compared to 16 weeks on placebo. At progression, patients were unblinded, and those randomized to placebo were offered open-label everolimus. The researchers found that everolimus was associated with a 65 percent reduction in the risk of progression and an increase in median progression -free survival of more than six months, from 4.6 to 11 months. Eighteen-month progression-free survival was 34 percent for those in the everolimus arm, compared to 9 percent for the placebo.

**5.11. Everolimus and immunosaprasent**

Everolimus is a novel immunosuppressive agent related to sirolimus. It is a proliferation signal inhibitor with an improved pharmacokinetic profile and bioavailability compared with sirolimus. Everolimus has been shown to be as effective as mycophenolate mofetil in reducing acute rejection in renal transplantation. In cardiac transplant recipients, it is superior to azathioprine in reducing acute rejection and cardiac allograft vasculopathy. Its use is also associated with a decrease in cytomegalovirus infection. However, co-administration with calcineurin inhibitors requires careful dose adjustment to prevent renal toxicity. Antiproliferative effects of everolimus may abrogate the increased risk of malignancy seen in solid organ transplantation.

**5.12. Drug-eluting stent**

The first successful trials were of sirolimus-eluting stents. A clinical trial in 2002 led to approval of the sirolimus-eluting Cypher stent in Europe in 2002. After a larger pivotal trial (one designed for the purpose of achieving FDA approval), published in 2003, the device received FDA approval and was released in the U.S. in 2003. Soon thereafter, a series of trials of paclitaxel-eluting stents led to FDA approval of the Taxus stent in 2004. The Xience V everolimus eluting stent was approved by the FDA in July 2008 and has been available in Europe and other international markets since late 2006. It is an investigational device in Japan.

## 6. SUMMARY

The steady state pharmacokinetic profiles of everolimus showed dose-proportionality across the dose range studied, and variability was low. Everolimus concentrations accumulated 1.6- to 2.2-fold with multiple dosing and reached steady state by day 4 of once-



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and twice-daily administration. Everolimus is a medication with a suppressive effect on the immune system. This medication is used in the management of transplant patients to prevent organ rejection, and can also be prescribed to people with certain types of kidney cancer. It may be used for off-label purposes beyond these approved uses. This drug works by suppressing the activation of enzymes involved in immune processes. In the case of transplant rejection, there is a concern that the patient's body could identify the donor organ as foreign and dangerous and start attacking it. Consequently, anti-rejection drugs are prescribed. In kidney cancers, everolimus appears to extend life for certain types of cells, while making it harder for others to survive, thereby helping in cancer treatment.



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