

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

ERSTEINE
(Everolimus Tablets)

COMPOSITION

ERSTEINE 5

Each Uncoated Tablet contains:

Everolimus 5mg

Excipients q.s.

ERSTEINE 10

Each Uncoated Tablet contains:

Everolimus 10mg

Excipients q.s.

INDICATION

Everolimus is indicated for the treatment of advance renal cell carcinoma

DOSE AND METHOD OF ADMINISTRATION

The recommended dose of Everolimus Tablets are 5mg and 10mg, to be taken once daily at the same time every day. Administer either consistently with food or consistently without food. Everolimus Tablets should be swallowed whole with a glass of water. Do not break or crush tablets.

Continue treatment until disease progression or unacceptable toxicity occurs.

Dose Modifications in renal cell carcinoma:

Management of severe or intolerable adverse reactions may require temporary dose interruption (with or without a dose reduction of Everolimus therapy) or discontinuation. If dose reduction is required, the suggested dose is approximately 50% lower than the daily dose previously administered.

Recommendations for dose reduction, interruption or discontinuation of Everolimus in the management of adverse reactions. General management recommendations are also provided as applicable. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Hepatic Impairment

Hepatic impairment will increase the exposure to everolimus. Dose adjustments are recommended:

- Mild hepatic impairment (Child-Pugh class A) – The recommended dose is 7.5 mg daily; the dose may be decreased to 5 mg if not well tolerated.

- Moderate hepatic impairment (Child-Pugh class B) – The recommended dose is 5 mg daily; the dose may be decreased to 2.5 mg if not well tolerated.
- Severe hepatic impairment (Child-Pugh class C) – If the desired benefit outweighs the risk, a dose of 2.5 mg daily may be used but must not be exceeded.

Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment.

CYP3A4/P-glycoprotein (PgP) Inhibitors

Avoid the use of strong CYP3A4/PgP inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole).

Use caution when co-administered with moderate CYP3A4/PgP inhibitors (e.g., amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem). If patients require co-administration of a moderate CYP3A4 /PgP inhibitor, reduce the Everolimus dose to 2.5 mg daily. The reduced dose of Everolimus is predicted to adjust the area under the curve (AUC) to the range observed without inhibitors. An Everolimus dose increase from 2.5 mg to 5 mg may be considered based on patient tolerance. If the moderate inhibitor is discontinued, a washout period of approximately 2 to 3 days should be allowed before the Everolimus dose is increased. If the moderate inhibitor is discontinued, the Everolimus dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor.

Grapefruit, grapefruit juice, and other foods that are known to inhibit cytochrome P450 and PgP activity may increase everolimus exposures and should be avoided during treatment.

Strong CYP3A4/PgP Inducers

Avoid the use of concomitant strong CYP3A4/PgP inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital). If patients require co-administration of a strong CYP3A4/PgP inducer, consider doubling the daily dose of Everolimus using increments of 5 mg or less. This dose of Everolimus is predicted, based on pharmacokinetic data, to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4/PgP inducers. If the strong inducer is discontinued, consider a washout period of 3 to 5 days, before the everolimus dose is returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer.

St. John's Wort (*Hypericum perforatum*) may decrease everolimus exposure unpredictably and should be avoided.

CONTRAINDICATIONS

Hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including everolimus. Non-infectious pneumonitis (including interstitial lung disease) has been frequently reported in patients taking Afinitor. Some cases were severe and on rare occasions, a fatal outcome was observed. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnoea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Opportunistic infections such as pneumocystis jirovecii (carinii) pneumonia (PJP, PCP) should be ruled out in the differential diagnosis of non-infectious pneumonitis (see

“Infections” below). Patients should be advised to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue Afinitor therapy without dose adjustments. If symptoms are moderate (Grade 2) or severe (Grade 3) the use of corticosteroids may be indicated until clinical symptoms resolve.

For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for pneumocystis jirovecii (carinii) pneumonia (PJP, PCP) may be considered.

Infections

Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens. Localised and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections such as aspergillosis, candidiasis or pneumocystis jirovecii (carinii) pneumonia (PJP, PCP) and viral infections including reactivation of hepatitis B virus, have been described in patients taking Afinitor. Some of these infections have been severe (e.g. leading to sepsis, respiratory or hepatic failure) and occasionally fatal.

Physicians and patients should be aware of the increased risk of infection with Afinitor. Pre-existing infections should be treated appropriately and should have resolved fully before starting treatment with Afinitor. While taking Afinitor, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of Afinitor.

If a diagnosis of invasive systemic fungal infection is made, the Afinitor treatment should be promptly and permanently discontinued and the patient treated with appropriate antifungal therapy.

Cases of pneumocystis jirovecii (carinii) pneumonia (PJP, PCP), some with fatal outcome, have been reported in patients who received everolimus. PJP/PCP may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP/PCP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnoea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus.

Concomitant use of angiotensin-converting enzyme (ACE) inhibitors

Patients taking concomitant ACE inhibitor (e.g. ramipril) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment).

Oral ulceration

Mouth ulcers, stomatitis and oral mucositis have been observed in patients treated with Afinitor. In such cases topical treatments are recommended, but mouthwashes containing alcohol, peroxide, iodine and thyme derivatives should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed.

Renal failure events

Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with Afinitor. Renal function should be monitored particularly where patients have additional risk factors that may further impair renal function.

Laboratory tests and monitoring

Renal function

Elevations of serum creatinine, usually mild, and proteinuria have been reported. Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein or serum creatinine, is recommended prior to the start of Afinitor therapy and periodically thereafter.

Blood glucose

Hyperglycaemia has been reported. Monitoring of fasting serum glucose is recommended prior to the start of Afinitor therapy and periodically thereafter. More frequent monitoring is recommended when Afinitor is co-administered with other medicinal products that may induce hyperglycaemia. When possible optimal glycaemic control should be achieved before starting a patient on Afinitor.

Blood lipids

Dyslipidaemia (including hypercholesterolaemia and hypertriglyceridaemia) has been reported. Monitoring of blood cholesterol and triglycerides prior to the start of Afinitor therapy and periodically thereafter, as well as management with appropriate medical therapy, is recommended.

Haematological parameters

Decreased haemoglobin, lymphocytes, neutrophils and platelets have been reported. Monitoring of complete blood count is recommended prior to the start of Afinitor therapy and periodically thereafter.

Functional carcinoid tumours

In a randomised, double-blind, multi-centre trial in patients with functional carcinoid tumours, Afinitor plus depot octreotide was compared to placebo plus depot octreotide. The study did not meet the primary efficacy endpoint (progression-free-survival [PFS]) and the overall survival (OS) interim analysis numerically favoured the placebo plus depot

octreotide arm. Therefore, the safety and efficacy of Afinitor in patients with functional carcinoid tumours have not been established.

Prognostic factors in neuroendocrine tumours of gastrointestinal or lung origin

In patients with non-functional gastrointestinal or lung neuroendocrine tumours and good prognostic baseline factors, e.g. ileum as primary tumour origin and normal chromogranin A values or without bone involvement, an individual benefit-risk assessment should be performed prior to the start of Afinitor therapy. A limited evidence of PFS benefit was reported in the subgroup of patients with ileum as primary tumour origin.

Interactions

Co-administration with inhibitors and inducers of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a *moderate* CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, dose adjustments of Afinitor can be taken into consideration based on predicted AUC.

Concomitant treatment with *potent* CYP3A4 inhibitors result in dramatically increased plasma concentrations of everolimus. There are currently not sufficient data to allow dosing recommendations in this situation. Hence, concomitant treatment of Afinitor and *potent* inhibitors is not recommended.

Caution should be exercised when Afinitor is taken in combination with orally administered CYP3A4 substrates with a narrow therapeutic index due to the potential for drug interactions. If Afinitor is taken with orally administered CYP3A4 substrates with a narrow therapeutic index (e.g. pimozide, terfenadine, astemizole, cisapride, quinidine or ergot alkaloid derivatives), the patient should be monitored for undesirable effects described in the product information of the orally administered CYP3A4 substrate.

Hepatic impairment

Exposure to everolimus was increased in patients with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment.

Afinitor is only recommended for use in patients with severe hepatic impairment (Child-Pugh C) if the potential benefit outweighs the risk.

No clinical safety or efficacy data are currently available to support dose adjustment recommendations for the management of adverse reactions in patients with hepatic impairment.

Vaccinations

The use of live vaccines should be avoided during treatment with Afinitor.

Wound healing complications

Impaired wound healing is a class effect of rapamycin derivatives, including everolimus. Caution should therefore be exercised with the use of Afinitor in the peri-surgical period.

DRUG INTERACTION

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of PgP. Therefore, absorption and subsequent elimination of everolimus may be influenced by products that affect CYP3A4 and/or PgP. *In vitro*, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

Known and theoretical interactions with selected inhibitors and inducers of CYP3A4 and PgP are listed in Table 2 below.

CYP3A4 and PgP inhibitors increasing everolimus concentrations

Substances that are inhibitors of CYP3A4 or PgP may increase everolimus blood concentrations by decreasing metabolism or the efflux of everolimus from intestinal cells.

CYP3A4 and PgP inducers decreasing everolimus concentrations

Substances that are inducers of CYP3A4 or PgP may decrease everolimus blood concentrations by increasing metabolism or the efflux of everolimus from intestinal cells.

Table 2 Effects of other active substances on everolimus

Active substance by interaction	Interaction – Change in Everolimus AUC/C _{max} Geometric mean ratio (observed range)	Recommendations concerning co-administration
Potent CYP3A4/PgP inhibitors		
Ketoconazole	AUC ↑15.3-fold (range 11.2-22.5) C _{max} ↑4.1-fold (range 2.6-7.0)	Concomitant treatment of Afinitor and potent inhibitors is not recommended.
Itraconazole, posaconazole, voriconazole	Not studied. Large increase in everolimus concentration is expected.	
Telithromycin, clarithromycin		
Nefazodone		
Ritonavir, atazanavir, saquinavir, darunavir, indinavir, nelfinavir		
Moderate CYP3A4/PgP inhibitors		
Erythromycin	AUC ↑4.4-fold (range 2.0-12.6) C _{max} ↑2.0-fold	Use caution when co-administration of moderate CYP3A4 inhibitors or PgP inhibitors cannot be avoided. If

	(range 0.9-3.5)		patients require co-administration of a moderate CYP3A4 or Pgp inhibitor, dose reduction to 5 mg daily or 2.5 mg daily may be considered. However, there are no clinical data with this dose adjustment. Due to between subject variability the recommended dose adjustments may not be optimal in all individuals, therefore close monitoring of side effects is recommended. If the moderate inhibitor is discontinued, consider a washout period of at least 2 to 3 days (average elimination time for most commonly used moderate inhibitors) before the Afinitor dose is returned to the dose used prior to initiation of the co-administration.
Imatinib	AUC ↑ 3.7-fold C _{max} ↑ 2.2-fold		
Verapamil	AUC ↑3.5-fold (range 2.2-6.3) C _{max} ↑2.3-fold (range 1.3-3.8)		
Ciclosporin oral	AUC ↑2.7-fold (range 1.5-4.7) C _{max} ↑1.8-fold (range 1.3-2.6)		
Fluconazole	Not studied. Increased exposure expected.		
Diltiazem			
Dronedarone	Not studied. Increased exposure expected.		
Amprenavir, fosamprenavir	Not studied. Increased exposure expected.		
Grapefruit juice or other food affecting CYP3A4/Pgp	Not studied. Increased exposure expected (the effect varies widely).		Combination should be avoided.
Potent and moderate CYP3A4 inducers			
Rifampicin	AUC ↓63% (range 0-80%) C _{max} ↓58% (range 10-70%)		Avoid the use of concomitant potent CYP3A4 inducers. If patients require co-administration of a potent CYP3A4 inducer, an Afinitor dose increase from 10 mg daily up to 20 mg daily should be considered using 5 mg increments or less applied on Day 4 and 8 following start of the inducer. This dose of Afinitor is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment. If treatment with the inducer is discontinued, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction), before the Afinitor dose is returned to the dose
Dexamethasone	Not studied. Decreased exposure expected.		
Carbamazepine, phenobarbital, phenytoin	Not studied. Decreased exposure expected.		
Efavirenz, nevirapine	Not studied. Decreased exposure expected.		

		used prior to initiation of the co-administration.
St John's Wort <i>(Hypericum perforatum)</i>	Not studied. Large decrease in exposure expected.	Preparations containing St John's Wort should not be used during treatment with everolimus

Agents whose plasma concentration may be altered by everolimus

Based on *in vitro* results, the systemic concentrations obtained after oral daily doses of 10 mg make inhibition of PgP, CYP3A4 and CYP2D6 unlikely. However, inhibition of CYP3A4 and PgP in the gut cannot be excluded. An interaction study in healthy subjects demonstrated that co-administration of an oral dose of midazolam, a sensitive CYP3A substrate probe, with everolimus resulted in a 25% increase in midazolam C_{max} and a 30% increase in midazolam $AUC_{(0-inf)}$. The effect is likely to be due to inhibition of intestinal CYP3A4 by everolimus. Hence everolimus may affect the bioavailability of orally co-administered CYP3A4 substrates. However, a clinically relevant effect on the exposure of systemically administered CYP3A4 substrates is not expected. Co-administration of everolimus and depot octreotide increased octreotide C_{min} with a geometric mean ratio (everolimus/placebo) of 1.47. A clinically significant effect on the efficacy response to everolimus in patients with advanced neuroendocrine tumours could not be established.

Co-administration of everolimus and exemestane increased exemestane C_{min} and C_{2h} by 45% and 64%, respectively. However, the corresponding oestradiol levels at steady state (4 weeks) were not different between the two treatment arms. No increase in adverse events related to exemestane was observed in patients with hormone receptor-positive advanced breast cancer receiving the combination. The increase in exemestane levels is unlikely to have an impact on efficacy or safety.

Concomitant use of angiotensin-converting enzyme (ACE) inhibitors

Patients taking concomitant ACE inhibitor (e.g. ramipril) therapy may be at increased risk for angioedema.

Vaccinations

The immune response to vaccination may be affected and, therefore, vaccination may be less effective during treatment with Afinitor. The use of live vaccines should be avoided during treatment with Afinitor. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG (Bacillus Calmette-Guérin), yellow fever, varicella, and TY21a typhoid vaccines.

FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential/Contraception in males and females

Women of childbearing potential must use a highly effective method of contraception (e.g. oral, injected, or implanted non-oestrogen-containing hormonal method of birth control, progesterone-based contraceptives, hysterectomy, tubal ligation, complete abstinence, barrier methods, intrauterine device [IUD], and/or female/male sterilisation) while receiving everolimus, and for up to 8 weeks after ending treatment. Male patients should not be prohibited from attempting to father children.

Pregnancy

There are no adequate data from the use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects including embryotoxicity and foetotoxicity. The potential risk for humans is unknown.

Everolimus is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether everolimus is excreted in breast milk. However, in rats, everolimus and/or its metabolites readily pass into the milk. Therefore, women taking everolimus should not breast-feed.

Fertility

The potential for everolimus to cause infertility in male and female patients is unknown, however amenorrhoea (secondary amenorrhoea and other menstrual irregularities) and associated luteinising hormone (LH)/follicle stimulating hormone (FSH) imbalance has been observed in female patients. Based on non-clinical findings, male and female fertility may be compromised by treatment with everolimus.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Afinitor may have a minor or moderate influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines if they experience fatigue during treatment with Afinitor.

UNDESIRABLE EFFECTS

Summary of the safety profile

The safety profile is based on pooled data from 2,672 patients treated with Afinitor in ten clinical studies, consisting of five randomised, double-blind, placebo controlled phase III studies and five open-label phase I and phase II studies, related to the approved indications.

The most common adverse reactions (incidence $\geq 1/10$) from the pooled safety data were (in decreasing order): stomatitis, rash, fatigue, diarrhoea, infections, nausea, decreased appetite, anaemia, dysgeusia, pneumonitis, oedema peripheral, hyperglycaemia, asthenia, pruritus, weight decreased, hypercholesterolaemia, epistaxis, cough and headache.

The most frequent Grade 3-4 adverse reactions (incidence $\geq 1/100$ to $< 1/10$) were stomatitis, anaemia, hyperglycaemia, infections, fatigue, diarrhoea, pneumonitis, asthenia, thrombocytopenia, neutropenia, dyspnoea, proteinuria, lymphopenia, haemorrhage, hypophosphataemia, rash, hypertension, pneumonia, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased and diabetes mellitus. The grades follow CTCAE Version 3.0 and 4.03.

Tabulated list of adverse reactions

Table 3 presents the frequency category of adverse reactions reported in the pooled analysis considered for the safety pooling. Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3 Adverse reactions reported in clinical studies

Infections and infestations	
Very common	Infections ^{a, *}
Blood and lymphatic system disorders	
Very common	Anaemia
Common	Thrombocytopenia, neutropenia, leukopenia, lymphopenia
Uncommon	Pancytopenia
Rare	Pure red cell aplasia
Immune system disorders	
Uncommon	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Decreased appetite, hyperglycaemia, hypercholesterolaemia
Common	Hypertriglyceridaemia, hypophosphataemia, diabetes mellitus, hyperlipidaemia, hypokalaemia, dehydration, hypocalcaemia
Psychiatric disorders	
Common	Insomnia
Nervous system disorders	
Very common	Dysgeusia, headache

Uncommon	Ageusia
Eye disorders	
Common	Eyelid oedema
Uncommon	Conjunctivitis
Cardiac disorders	
Uncommon	Congestive cardiac failure
Vascular disorders	
Common	Haemorrhage ^b , hypertension
Uncommon	Flushing, deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	
Very common	Pneumonitis ^c , epistaxis, cough
Common	Dyspnoea
Uncommon	Haemoptysis, pulmonary embolism
Rare	Acute respiratory distress syndrome
Gastrointestinal disorders	
Very common	Stomatitis ^d , diarrhoea, nausea
Common	Vomiting, dry mouth, abdominal pain, mucosal inflammation, oral pain, dyspepsia, dysphagia
Hepatobiliary disorders	
Common	Aspartate aminotransferase increased, alanine aminotransferase increased
Skin and subcutaneous tissue disorders	
Very common	Rash, pruritus
Common	Dry skin, nail disorders, mild alopecia, acne, erythema, onychoclasia, palmar-plantar erythrodysesthesia syndrome, skin exfoliation, skin lesion
Rare	Angioedema
Musculoskeletal and connective tissue disorders	
Common	Arthralgia
Renal and urinary disorders	
Common	Proteinuria*, blood creatinine increased, renal failure*
Uncommon	Increased daytime urination, acute renal failure*
Reproductive system and breast disorders	
Common	Menstruation irregular ^e
Uncommon	Amenorrhoea ^e
General disorders and administration site conditions	
Very common	Fatigue, asthenia, oedema peripheral

Common	Pyrexia
Uncommon	Non-cardiac chest pain, impaired wound healing
Investigations	
Very common	Weight decreased
<p>* See also subsection “Description of selected adverse reactions”</p> <p>^a Includes all reactions within the 'infections and infestations' system organ class including (common) pneumonia, urinary tract infection; (uncommon) bronchitis, herpes zoster, sepsis, abscess, and isolated cases of opportunistic infections [e.g. aspergillosis, candidiasis, pneumocystis jirovecii (carinii) pneumonia (PJP, PCP) and hepatitis B] and (rare) viral myocarditis</p> <p>^b Includes different bleeding events from different sites not listed individually</p> <p>^c Includes (common) pneumonitis, interstitial lung disease, lung infiltration and (rare) pulmonary alveolar haemorrhage, pulmonary toxicity, and alveolitis</p> <p>^d Includes (very common) stomatitis, (common) aphthous stomatitis, mouth and tongue ulceration and (uncommon) glossodynia, glossitis</p> <p>^e Frequency based upon number of women from 10 to 55 years of age in the pooled data</p>	

Description of selected adverse reactions

In clinical studies and post-marketing spontaneous reports, everolimus has been associated with serious cases of hepatitis B reactivation, including fatal outcome. Reactivation of infection is an expected event during periods of immunosuppression.

In clinical studies and post-marketing spontaneous reports, everolimus has been associated with renal failure events (including fatal outcome) and proteinuria. Monitoring of renal function is recommended.

In clinical studies and post-marketing spontaneous reports, everolimus has been associated with cases of amenorrhoea (secondary amenorrhoea and other menstrual irregularities).

In clinical studies and post-marketing spontaneous reports, everolimus has been associated with cases of pneumocystis jirovecii (carinii) pneumonia (PJP, PCP), some with fatal outcome.

In clinical trials and post-marketing spontaneous reports, angioedema has been reported with and without concomitant use of ACE inhibitors.

Elderly patients

In the safety pooling, 37% of the Afinitor-treated patients were ≥ 65 years of age. The number of patients with an adverse reaction leading to discontinuation of the medicinal product was higher in patients ≥ 65 years of age (20% vs. 13%). The most common adverse

reactions leading to discontinuation were pneumonitis (including interstitial lung disease), stomatitis, fatigue and dyspnoea.

OVERDOSE

Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been given with acceptable acute tolerability. General supportive measures should be initiated in all cases of overdose.

PHARMACOLOGICAL PROPERTIES

- **Pharmacodynamic properties**

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, protein kinase inhibitors, ATC code: L01XE10

Mechanism of action

Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor. mTOR is a key serine-threonine kinase, the activity of which is known to be upregulated in a number of human cancers. Everolimus binds to the intracellular protein FKBP-12, forming a complex that inhibits mTOR complex-1 (mTORC1) activity. Inhibition of the mTORC1 signalling pathway interferes with the translation and synthesis of proteins by reducing the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4EBP-1) that regulate proteins involved in the cell cycle, angiogenesis and glycolysis. S6K1 is thought to phosphorylate the activation function domain 1 of the oestrogen receptor, which is responsible for ligand-independent receptor activation. Everolimus reduces levels of vascular endothelial growth factor (VEGF), which potentiates tumour angiogenic processes. Everolimus is a potent inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood-vessel-associated smooth muscle cells and has been shown to reduce glycolysis in solid tumours *in vitro* and *in vivo*.

Clinical efficacy and safety

Hormone receptor-positive advanced breast cancer

BOLERO-2 (study CRAD001Y2301), a randomised, double-blind, multicentre phase III study of Afinitor + exemestane versus placebo + exemestane, was conducted in postmenopausal women with oestrogen receptor-positive, HER2/neu negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. Randomisation was stratified by documented sensitivity to prior hormonal therapy and by the presence of visceral metastasis. Sensitivity to prior hormonal therapy was defined as either (1) documented clinical benefit (complete response [CR], partial response [PR], stable disease ≥ 24 weeks) from at least one prior hormonal therapy in the advanced setting or (2) at least 24 months of adjuvant hormonal therapy prior to recurrence.

The primary endpoint for the study was progression-free survival (PFS) evaluated by RECIST (Response Evaluation Criteria in Solid Tumors), based on the investigator's assessment (local radiology). Supportive PFS analyses were based on an independent central radiology review.

Secondary endpoints included overall survival (OS), objective response rate, clinical benefit rate, safety, change in quality of life (QoL) and time to ECOG PS (Eastern Cooperative Oncology Group performance status) deterioration.

A total of 724 patients were randomised in a 2:1 ratio to the combination everolimus (10 mg daily) + exemestane (25 mg daily) (n=485) or to the placebo + exemestane arm (25 mg daily) (n=239). At the time of the final OS analysis, the median duration of everolimus treatment was 24.0 weeks (range 1.0-199.1 weeks). The median duration of exemestane treatment was longer in the everolimus + exemestane group at 29.5 weeks (1.0-199.1) compared to 14.1 weeks (1.0-156.0) in the placebo + exemestane group.

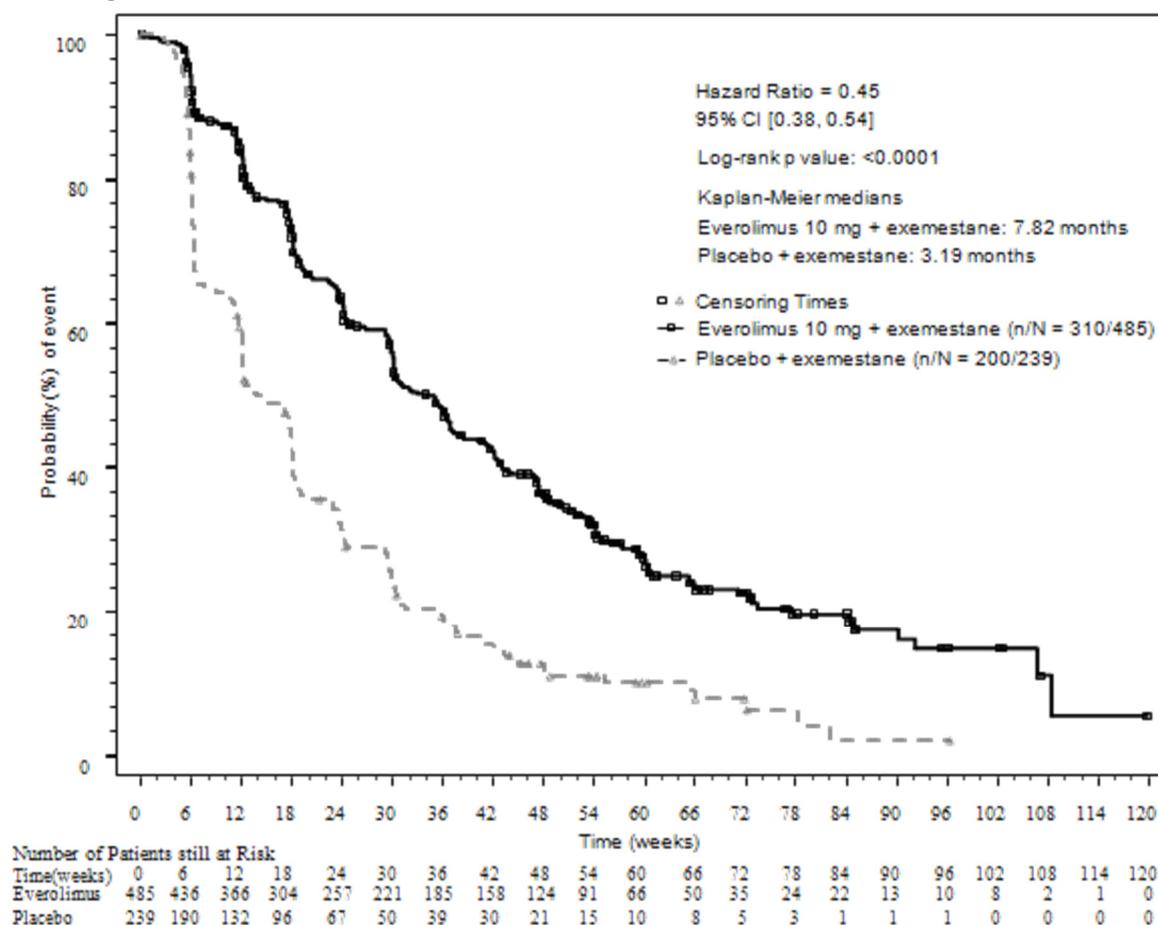
The efficacy results for the primary endpoint were obtained from the final PFS analysis (see Table 4 and Figure 1). Patients in the placebo + exemestane arm did not cross over to everolimus at the time of progression.

Table 4 BOLERO-2 efficacy results

Analysis	Afinitor ^a n=485	Placebo ^a n=239	Hazard ratio	p value
Median progression-free survival (months) (95% CI)				
Investigator radiological review	7.8 (6.9 to 8.5)	3.2 (2.8 to 4.1)	0.45 (0.38 to 0.54)	<0.0001
Independent radiological review	11.0 (9.7 to 15.0)	4.1 (2.9 to 5.6)	0.38 (0.31 to 0.48)	<0.0001
Median overall survival (months) (95% CI)				
Median overall survival	31.0 (28.0 – 34.6)	26.6 (22.6 – 33.1)	0.89 (0.73 – 1.10)	0.1426
Best overall response (%) (95% CI)				
Objective response rate ^b	12.6% (9.8 to 15.9)	1.7% (0.5 to 4.2)	n/a ^d	<0.0001 ^e
Clinical benefit rate ^c	51.3% (46.8 to 55.9)	26.4% (20.9 to 32.4)	n/a ^d	<0.0001 ^e
a Plus exemestane				
b Objective response rate = proportion of patients with complete or partial response				

c Clinical benefit rate = proportion of patients with complete or partial response or stable disease ≥ 24 weeks
d Not applicable
e p value is obtained from the exact Cochran-Mantel-Haenszel test using a stratified version of the Cochran-Armitage permutation test.

Figure 1 BOLERO-2 Kaplan-Meier progression-free survival curves (investigator radiological review)



The estimated PFS treatment effect was supported by planned subgroup analysis of PFS per investigator assessment. For all analysed subgroups (age, sensitivity to prior hormonal therapy, number of organs involved, status of bone-only lesions at baseline and presence of visceral metastasis, and across major demographic and prognostic subgroups) a positive treatment effect was seen with everolimus + exemestane with an estimated hazard ratio versus placebo + exemestane ranging from 0.25 to 0.60.

No differences in the time to $\geq 5\%$ deterioration in the global and functional domain scores of QLQ-C30 were observed in the two arms.

Advanced neuroendocrine tumours of pancreatic origin (pNET)

RADIANT-3 (study CRAD001C2324), a phase III, multicentre, randomised, double-blind study of Afinitor plus best supportive care (BSC) versus placebo plus BSC in patients with advanced pNET, demonstrated a statistically significant clinical benefit of Afinitor over placebo by a 2.4-fold prolongation of median progression-free-survival (PFS) (11.04 months versus 4.6 months), (HR 0.35; 95% CI: 0.27, 0.45; p<0.0001) (see Table 5 and Figure 2).

RADIANT-3 involved patients with well- and moderately-differentiated advanced pNET whose disease had progressed within the prior 12 months. Treatment with somatostatin analogues was allowed as part of BSC.

The primary endpoint for the study was PFS evaluated by RECIST (Response Evaluation Criteria in Solid Tumors). Following documented radiological progression, patients could be unblinded by the investigator. Those randomised to placebo were then able to receive open-label Afinitor.

Secondary endpoints included safety, objective response rate, response duration and overall survival (OS).

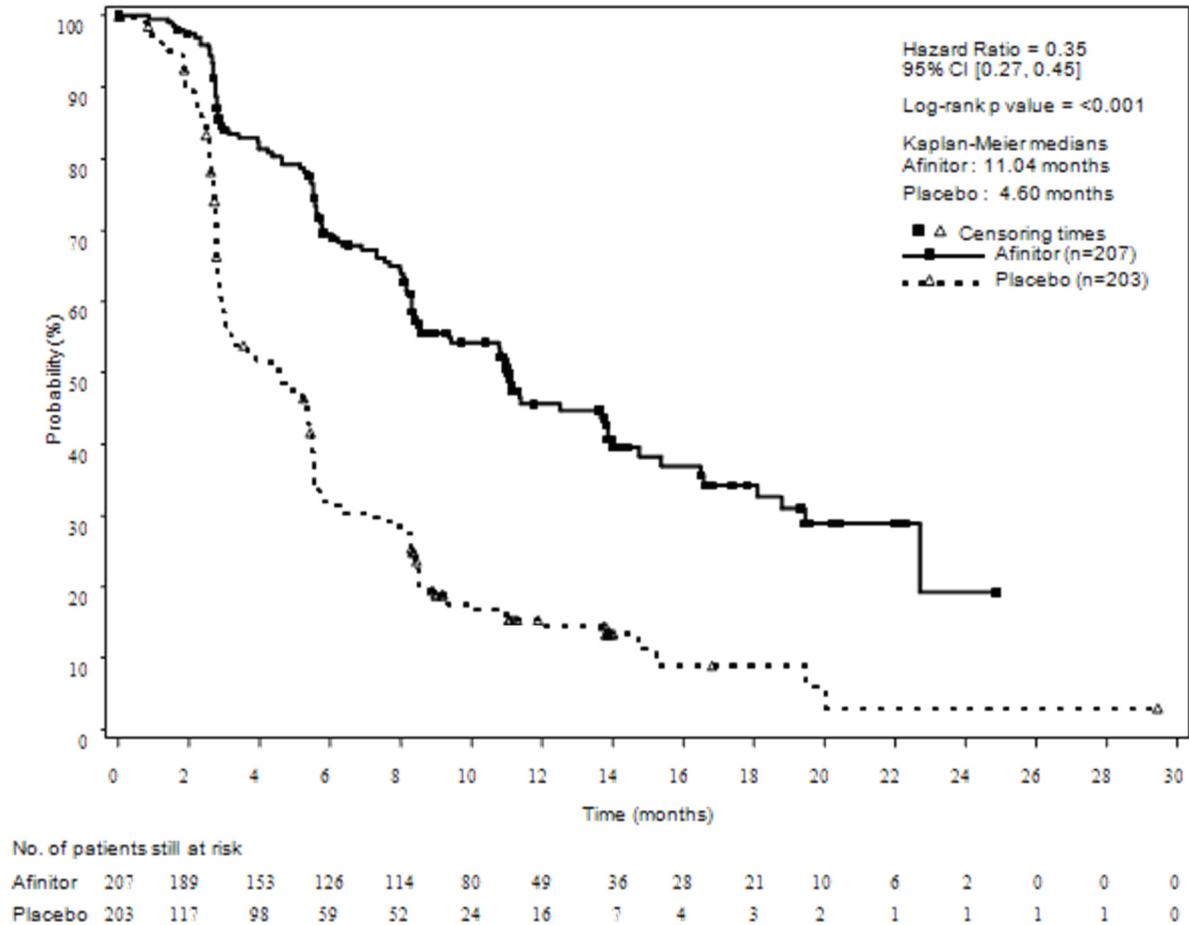
In total, 410 patients were randomised 1:1 to receive either Afinitor 10 mg/day (n=207) or placebo (n=203). Demographics were well balanced (median age 58 years, 55% male, 78.5% Caucasian). Fifty-eight percent of the patients in both arms received prior systemic therapy. The median duration of blinded study treatment was 37.8 weeks (range 1.1-129.9 weeks) for patients receiving everolimus and 16.1 weeks (range 0.4-147.0 weeks) for those receiving placebo.

Following disease progression or after study unblinding, 172 of the 203 patients (84.7%) initially randomised to placebo crossed over to open-label Afinitor. The median duration of open-label treatment was 47.7 weeks among all patients; 67.1 weeks in the 53 patients randomised to everolimus who switched to open-label everolimus and 44.1 weeks in the 172 patients randomised to placebo who switched to open-label everolimus.

Table 5 RADIANT-3 – efficacy results

Population	Afinitor n=207	Placebo n=203	Hazard ratio (95% CI)	p-value
Median progression-free survival (months) (95% CI)				
Investigator radiological review	11.04 (8.41, 13.86)	4.60 (3.06, 5.39)	0.35 (0.27, 0.45)	<0.0001
Independent radiological review	13.67 (11.17, 18.79)	5.68 (5.39, 8.31)	0.38 (0.28, 0.51)	<0.0001
Median overall survival (months) (95% CI)				
Median overall survival	44.02 (35.61, 51.75)	37.68 (29.14, 45.77)	0.94 (0.73, 1.20)	0.300

Figure 2 RADIANT-3 – Kaplan-Meier progression-free survival curves (investigator radiological review)



Advanced neuroendocrine tumours of gastrointestinal or lung origin

RADIANT-4 (study CRAD001T2302), a randomised, double-blind, multicentre, phase III study of Afinitor plus best supportive care (BSC) versus placebo plus BSC was conducted in patients with advanced, well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumours of gastrointestinal or lung origin without a history of and no active symptoms related to carcinoid syndrome.

The primary endpoint for the study was progression-free survival (PFS) evaluated by Response Evaluation Criteria in Solid Tumors (RECIST), based on independent radiology assessment. Supportive PFS analysis was based on local investigator review. Secondary endpoints included overall survival (OS), overall response rate, disease control rate, safety, change in quality of life (FACT-G) and time to World Health Organisation performance status (WHO PS) deterioration.

A total of 302 patients were randomised in a 2:1 ratio to receive either everolimus (10 mg daily) (n=205) or placebo (n=97). Demographics and disease characteristics were generally balanced (median age 63 years [range 22 to 86], 76% Caucasian, history of prior somatostatin analogue [SSA] use). The median duration of blinded treatment was 40.4

weeks for patients receiving Afinitor and 19.6 weeks for those receiving placebo. Patients in the placebo arm did not cross-over to everolimus at the time of progression.

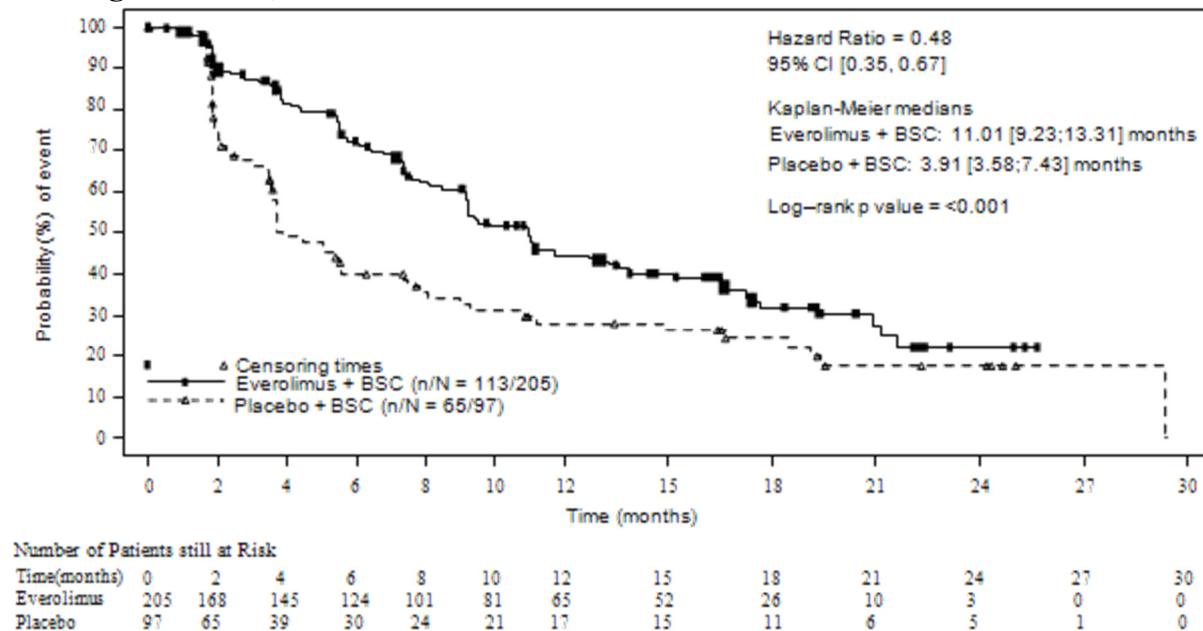
The efficacy results for the primary endpoint were obtained from the final PFS analysis (see Table 6 and Figure 3).

Table 6 RADIANT-4 – Progression-free survival results

Population	Afinitor n=205	Placebo n=97	Hazard ratio (95% CI)	p-value ^a
Median progression-free survival (months) (95% CI)				
Independent radiological review	11.01 (9.2, 13.3)	3.91 (3.6, 7.4)	0.48 (0.35, 0.67)	<0.0001
Investigator radiological review	13.96 (11.2, 17.7)	5.45 (3.7, 7.4)	0.39 (0.28, 0.54)	<0.0001

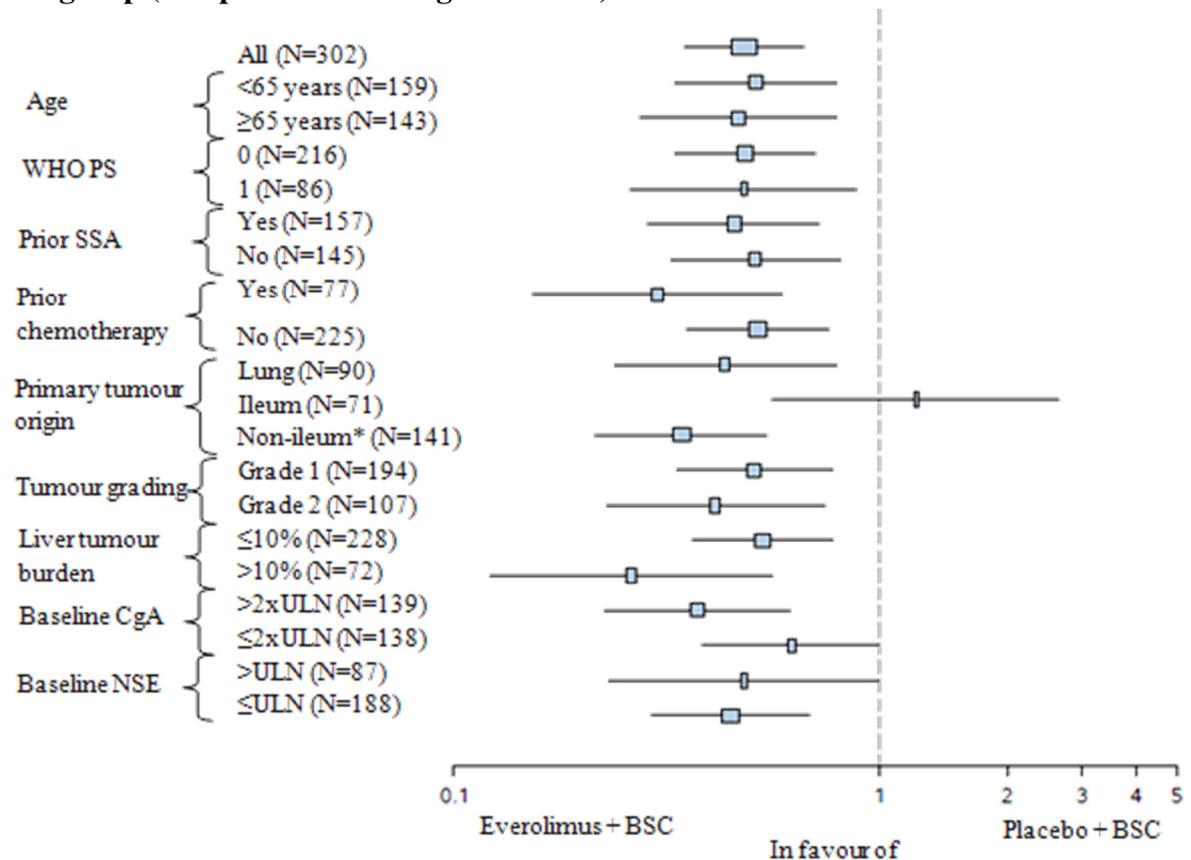
^a One-sided p-value from a stratified log-rank test

Figure 3 RADIANT-4 – Kaplan-Meier progression-free survival curves (independent radiological review)



In supportive analyses, positive treatment effect has been observed in all subgroups with the exception of the subgroup of patients with ileum as primary site of tumour origin (Ileum: HR=1.22 [95% CI: 0.56 to 2.65]; Non-ileum: HR=0.34 [95% CI: 0.22 to 0.54]; Lung: HR=0.43 [95% CI: 0.24 to 0.79]) (see Figure 4).

Figure 4 RADIANT-4 – Progression free survival results by pre-specified patient subgroup (independent radiological review)



*Non-ileum: stomach, colon, rectum, appendix, caecum, duodenum, jejunum, carcinoma of unknown primary origin and other gastrointestinal origin

ULN: Upper limit of normal

CgA: Chromogranin A

NSE: Neuron specific enolase

Hazard ratio (95% CI) from stratified Cox model

The pre-planned OS interim analysis after 101 deaths (out of 191 required for final analysis) and 33 months follow-up favoured the everolimus arm; however, no statistically significant difference in OS was noted (HR= 0.73 [95% CI: 0.48 to 1.11; p=0.071]).

No difference in the time to definitive deterioration of WHO PS (≥ 1 point) and time to definitive deterioration in quality of life (FACT-G total score ≥ 7 points) was observed between the two arms.

Advanced renal cell carcinoma

RECORD-1 (study CRAD001C2240), a phase III, international, multicentre, randomised, double-blind study comparing everolimus 10 mg/day and placebo, both in conjunction with best supportive care, was conducted in patients with metastatic renal cell carcinoma whose disease had progressed on or after treatment with VEGFR-TKI (vascular endothelial

growth factor receptor tyrosine kinase inhibitor) therapy (sunitinib, sorafenib, or both sunitinib and sorafenib). Prior therapy with bevacizumab and interferon- α was also permitted. Patients were stratified according to Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score (favourable- vs. intermediate- vs. poor-risk groups) and prior anticancer therapy (1 vs. 2 prior VEGFR-TKIs).

Progression-free survival, documented using RECIST (Response Evaluation Criteria in Solid Tumours) and assessed via a blinded, independent central review, was the primary endpoint. Secondary endpoints included safety, objective tumour response rate, overall survival, disease-related symptoms, and quality of life. After documented radiological progression, patients could be unblinded by the investigator: those randomised to placebo were then able to receive open-label everolimus 10 mg/day. The Independent Data Monitoring Committee recommended termination of this trial at the time of the second interim analysis as the primary endpoint had been met.

In total, 416 patients were randomised 2:1 to receive Afinitor (n=277) or placebo (n=139). Demographics were well balanced (pooled median age [61 years; range 27-85], 78% male, 88% Caucasian, number of prior VEGFR-TKI therapies [1-74%, 2-26%]). The median duration of blinded study treatment was 141 days (range 19-451 days) for patients receiving everolimus and 60 days (range 21-295 days) for those receiving placebo.

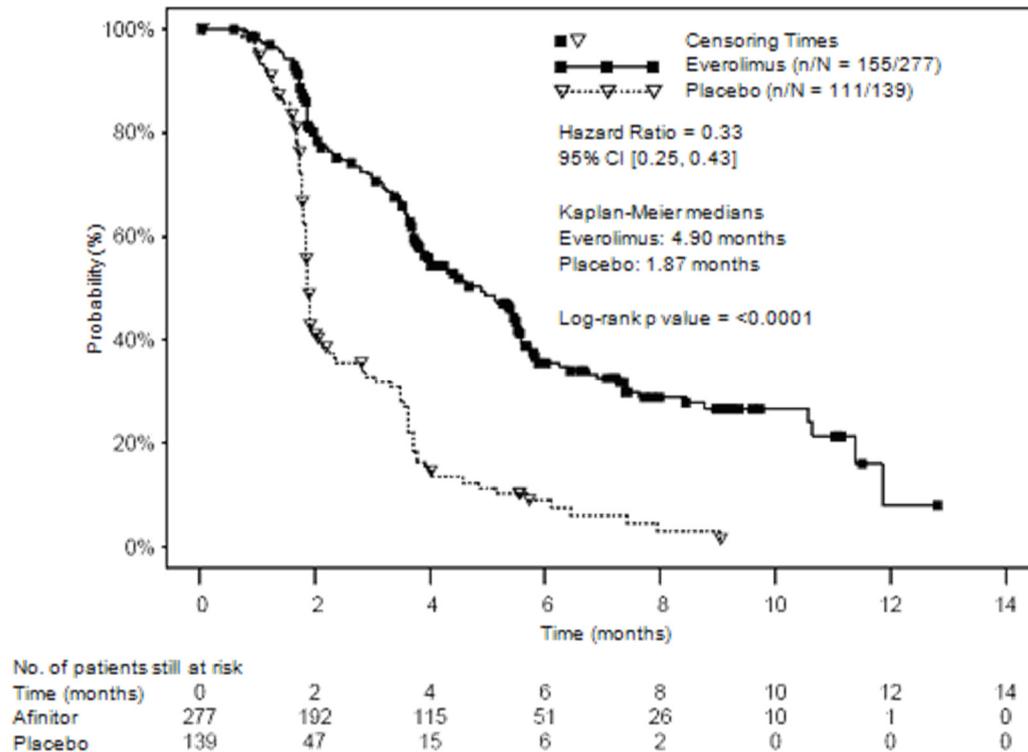
Afinitor was superior to placebo for the primary endpoint of progression-free survival, with a statistically significant 67% reduction in the risk of progression or death (see Table 7 and Figure 5).

Table 7 RECORD-1 – Progression-free survival results

Population	n	Afinitor n=277	Placebo n=139	Hazard ratio (95% CI)	p-value
		Median progression-free survival (months) (95% CI)			
Primary analysis					
All (blinded independent central review)	416	4.9 (4.0-5.5)	1.9 (1.8-1.9)	0.33 (0.25-0.43)	<0.0001 ^a
Supportive/sensitivity analyses					
All (local review by investigator)	416	5.5 (4.6-5.8)	1.9 (1.8-2.2)	0.32 (0.25-0.41)	<0.0001 ^a
<i>MSKCC prognostic score (blinded independent central review)</i>					
Favourable risk	120	5.8 (4.0-7.4)	1.9 (1.9-2.8)	0.31 (0.19-0.50)	<0.0001

Intermediate risk	235	4.5 (3.8-5.5)	1.8 (1.8-1.9)	0.32 (0.22-0.44)	<0.0001
Poor risk	61	3.6 (1.9-4.6)	1.8 (1.8-3.6)	0.44 (0.22-0.85)	0.007
^a Stratified log-rank test					

Figure 5 RECORD-1 – Kaplan-Meier progression-free survival curves (independent central review)



Six-month PFS rates were 36% for Afinitor therapy compared with 9% for placebo. Confirmed objective tumour responses were observed in 5 patients (2%) receiving Afinitor, while none were observed in patients receiving placebo. Therefore, the progression-free survival advantage primarily reflects the population with disease stabilisation (corresponding to 67% of the Afinitor treatment group).

No statistically significant treatment-related difference in overall survival was noted (hazard ratio 0.87; confidence interval: 0.65-1.17; p=0.177). Crossover to open-label Afinitor following disease progression for patients allocated to placebo confounded the detection of any treatment-related difference in overall survival.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Afinitor in all subsets of the paediatric population in neuroendocrine tumours of pancreatic origin, thoracic neuroendocrine tumours and in renal cell carcinoma.

- **Pharmacokinetic properties**

Absorption

In patients with advanced solid tumours, peak everolimus concentrations (C_{\max}) are reached at a median time of 1 hour after daily administration of 5 and 10 mg everolimus under fasting conditions or with a light fat-free snack. C_{\max} is dose-proportional between 5 and 10 mg. Everolimus is a substrate and moderate inhibitor of PgP.

Food effect

In healthy subjects, high fat meals reduced systemic exposure to everolimus 10 mg (as measured by AUC) by 22% and the peak plasma concentration C_{\max} by 54%. Light fat meals reduced AUC by 32% and C_{\max} by 42%. Food, however, had no apparent effect on the post absorption phase concentration-time profile.

Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5,000 ng/ml, is 17% to 73%. Approximately 20% of the everolimus concentration in whole blood is confined to plasma in cancer patients given everolimus 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment. In patients with advanced solid tumours, V_d was 191 l for the apparent central compartment and 517 l for the apparent peripheral compartment.

Biotransformation

Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, everolimus is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus. These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100 times less activity than everolimus itself. Hence, everolimus is considered to contribute the majority of the overall pharmacological activity.

Elimination

Mean oral clearance (CL/F) of everolimus after 10 mg daily dose in patients with advanced solid tumours was 24.5 l/h. The mean elimination half-life of everolimus is approximately 30 hours.

No specific excretion studies have been undertaken in cancer patients; however, data are available from the studies in transplant patients. Following the administration of a single dose of radiolabelled everolimus in conjunction with ciclosporin, 80% of the radioactivity was recovered from the faeces, while 5% was excreted in the urine. The parent substance was not detected in urine or faeces.

Steady-state pharmacokinetics

After administration of everolimus in patients with advanced solid tumours, steady-state $AUC_{0-\tau}$ was dose-proportional over the range of 5 to 10 mg daily dose. Steady-state was achieved within two weeks. C_{max} is dose-proportional between 5 and 10 mg. t_{max} occurs at 1 to 2 hours post-dose. There was a significant correlation between $AUC_{0-\tau}$ and pre-dose trough concentration at steady-state.

Special populations

Hepatic impairment

The safety, tolerability and pharmacokinetics of everolimus were evaluated in two single oral dose studies of Afinitor tablets in 8 and 34 subjects with impaired hepatic function relative to subjects with normal hepatic function.

In the first study, the average AUC of everolimus in 8 subjects with moderate hepatic impairment (Child-Pugh B) was twice that found in 8 subjects with normal hepatic function.

In the second study of 34 subjects with different impaired hepatic function compared to normal subjects, there was a 1.6-fold, 3.3-fold and 3.6-fold increase in exposure (i.e. $AUC_{0-\infty}$) for subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, respectively.

Simulations of multiple dose pharmacokinetics support the dosing recommendations in subjects with hepatic impairment based on their Child-Pugh status.

Based on the results of the two studies, dose adjustment is recommended for patients with hepatic impairment.

Renal impairment

In a population pharmacokinetic analysis of 170 patients with advanced solid tumours, no significant influence of creatinine clearance (25-178 ml/min) was detected on CL/F of everolimus. Post-transplant renal impairment (creatinine clearance range 11-107 ml/min) did not affect the pharmacokinetics of everolimus in transplant patients.

Elderly patients

In a population pharmacokinetic evaluation in cancer patients, no significant influence of age (27-85 years) on oral clearance of everolimus was detected.

Ethnicity

Oral clearance (CL/F) is similar in Japanese and Caucasian cancer patients with similar liver functions. Based on analysis of population pharmacokinetics, CL/F is on average 20% higher in black transplant patients.

• **Preclinical safety data**

The preclinical safety profile of everolimus was assessed in mice, rats, minipigs, monkeys and rabbits. The major target organs were male and female reproductive systems (testicular tubular degeneration, reduced sperm content in epididymides and uterine atrophy) in several species; lungs (increased alveolar macrophages) in rats and mice; pancreas (degranulation and vacuolation of exocrine cells in monkeys and minipigs, respectively, and degeneration of islet cells in monkeys), and eyes (lenticular anterior suture line opacities) in rats only. Minor kidney changes were seen in the rat (exacerbation of age-related lipofuscin in tubular epithelium, increases in hydronephrosis) and mouse (exacerbation of background lesions). There was no indication of kidney toxicity in monkeys or minipigs.

Everolimus appeared to spontaneously exacerbate background diseases (chronic myocarditis in rats, coxsackie virus infection of plasma and heart in monkeys, coccidian infestation of the gastrointestinal tract in minipigs, skin lesions in mice and monkeys). These findings were generally observed at systemic exposure levels within the range of therapeutic exposure or above, with the exception of the findings in rats, which occurred below therapeutic exposure due to a high tissue distribution.

In a male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count, and plasma testosterone levels were diminished at 5 mg/kg which caused a reduction in male fertility. There was evidence of reversibility.

In animal reproductive studies female fertility was not affected. However, oral doses of everolimus in female rats at ≥ 0.1 mg/kg (approximately 4% of the AUC_{0-24h} in patients receiving the 10 mg daily dose) resulted in increases in pre-implantation loss.

Everolimus crossed the placenta and was toxic to the foetus. In rats, everolimus caused embryo/ foetotoxicity at systemic exposure below the therapeutic level. This was manifested as mortality and reduced foetal weight. The incidence of skeletal variations and malformations (e.g. sternal cleft) was increased at 0.3 and 0.9 mg/kg. In rabbits, embryotoxicity was evident in an increase in late resorptions.

Genotoxicity studies covering relevant genotoxicity endpoints showed no evidence of clastogenic or mutagenic activity. Administration of everolimus for up to 2 years did not indicate any oncogenic potential in mice and rats up to the highest doses, corresponding respectively to 3.9 and 0.2 times the estimated clinical exposure.

EXPIRY DATE

Do not use later than the date of expiry.

PACKAGING INFORMATION

Lopamide is available in blister strip of 10 tablets.

STORAGE AND HANDLING INSTRUCTIONS

Store at a temperature not exceeding 30°C, Protected from light and moisture. Not to be administered in children below 12 years.

PRESENTATION

Ersteine 5 and Ersteine 10 available in Strip of 10 tablets.

MARKETED BY



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IN/ERSTEINE 10mg/JUL-17/01/PI