AFINITOR®

(everolimus)

2.5 mg*, 5 mg and 10 mg tablets

Leaflet

* *Disclaimer: Afinitor 2.5 mg tablet is not registered and marketed in Indonesia*

Disetujui oleh BPOM: 15/01/2021

ID REG: 218243728; 218243730

Trade Name(s)

2.5 mg tablets*

Afinitor 2.5 mg tablets

5 mg tablets

Afinitor 5 mg tablets

10 mg tablets

Afinitor 10 mg tablets

Description and Composition

Pharmaceutical form(s)

Tablet

White to slightly yellow, elongated tablets with a bevelled edge and no score.

- **2.5 mg***: The tablets are engraved with “LCL” on one side and “NVR” on the other.
- **5 mg**: The tablets are engraved with “5” on one side and “NVR” on the other.
- **10 mg**: The tablets are engraved with “UHE” on one side and “NVR” on the other.

Active substance

Tablet

- **2.5 mg*:** Each tablet contains 2.5 mg everolimus.
- **5 mg:** Each tablet contains 5 mg everolimus.
- **10 mg:** Each tablet contains 10 mg everolimus

Excipients

Tablet: Butylated hydroxytoluene (E321), magnesium stearate, lactose monohydrate, hypromellose, crospovidone and lactose anhydrous.

Indications

- AFINITOR® is indicated for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.
- **Advanced Neuroendocrine Tumors of Pancreatic Origin (PNET)**
  AFINITOR® is indicated for the treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic

disease. The safety and effectiveness of AFINITOR® in the preatment of patients with carcinoid tumors have not been established.

- **Advanced Neuroendocrine Tumors of Gastrointestinal (GI) or Lung Origin**
  AFINITOR® is indicated for the treatment of unresectable or metastatic, well-differentiated (grade 1 or 2), non-functional neuroendocrine tumors of gastrointestinal or lung origin in adults with progressive disease.
- **Patients with TSC who have Subependymal Giant Cell Astrocytoma (SEGA) that required therapeutic intervention but cannot curatively resected**
  AFINITOR® is indicated for the treatment of patients (aged 3 – 18 years) with SEGA associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not candidates for curative surgical resection. The effectiveness of AFINITOR® is based on an analysis of change in SEGA volume. Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated.
- Post-menopausal women with hormone receptor-positive locally advanced or metastatic breast cancer in combination with aromatase inhibitor, who are refractory to prior endocrine therapy such as letrozole or anastrozole.
- Patients with tuberous sclerosis complex (TSC) who have renal angiomyolipoma not requiring immediate surgery

Afinitor should not be used concomitantly with enzyme-inducing antiepileptic drug.

Dosage regimen and administration

Dosage regimen

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

General target population:

Adults

- **Dosing in hormone receptor positive advanced breast cancer, advanced neuroendocrine tumors of gastrointestinal, lung or pancreatic origin and advanced renal cell carcinoma:**

Treatment with Afinitor should be initiated by a physician experienced in the use of anticancer therapies.

The recommended dose of Afinitor is 10 mg, to be taken once daily.

- **Dosing in TSC with renal angiomyolipoma:**

Treatment with Afinitor should be initiated by a physician experienced in the treatment of patients with TSC.

The recommended dose of Afinitor is 10 mg, to be taken once daily.

- **Dose modifications in hormone receptor positive advanced breast cancer, advanced neuroendocrine tumors of gastrointestinal, lung or pancreatic origin, advance renal carcinoma and TSC with renal angiomyolipoma**

Adverse reactions: Management of severe or intolerable suspected adverse drug reactions (ADRs) may require temporary dose reduction and/or interruption of Afinitor therapy. If dose reduction is required, the suggested dose is approximately 50% lower than the daily dose previously administered (see section Warnings and precautions).

Table 1 summarizes recommendations for dose reduction, interruption or discontinuation of Afinitor in the management of ADRs. 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.

Table 1 Afinitor dose adjustment and management recommendations for adverse drug reactions

Adverse Drug Reaction	Severity[1]	Afinitor Dose Adjustment[2] and Management Recommendations
Non-infectious pneumonitis	Grade 1	No dose adjustment required. Initiate appropriate monitoring.
	Grade 2	Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to < grade 1. Re-initiate Afinitor at a lower dose. Discontinue treatment if failure to recover within 4 wks.
	Grade 3	Discontinue Afinitor, rule out infection, and consider treatment with corticosteroids until symptoms resolve to < grade 1 Consider re-initiating Afinitor at a lower dose.
	Grade 4	Discontinue Afinitor, rule out infection, and consider treatment with corticosteroids.
Stomatitis	Grade 1	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouth wash several times a day.
	Grade 2	Temporary dose interruption until recovery to grade ≤1. Re-initiate Afinitor at same dose. If stomatitis recurs at grade 2, interrupt dose until recovery to grade ≤1. Re-initiate Afinitor at lower dose. Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl aminobenzoate, tetracaine hydrocholoride, methol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[3]
	Grade 3	Temporary dose interruption until recovery to grade ≤1. Re-initiate Afinitor at a lower dose. Manage with topical analgesic mouth treatments (i.e. benzocaine, butyl aminobenzoate, tetracaine hydrocholoride, methol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[3]
	Grade 4	Discontinue Afinitor and treat with appropriate medical therapy.
Other non-hematologic toxicities (excluding metabolic events)	Grade 1	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor. If toxicity becomes intolerable, temporary dose interruption until recovery to grade ≤1. Re-initiate Afinitor at same dose.

Adverse Drug Reaction	Severity[1]	Afinitor Dose Adjustment[2] and Management Recommendations
		If toxicity recurs at grade 2, interrupt Afinitor until recovery to grade ≤1. Re-initiate Afinitor at lower dose.
	Grade 3	Temporary dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Re-initiate Afinitor at a lower dose.
	Grade 4	Discontinue Afinitor and treat with appropriate medical therapy.
Metabolic events (e.g. hyperglycemia, dyslipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.
	Grade 3	Temporary dose interruption. Re-initiate Afinitor at lower dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue Afinitor and treat with appropriate medical therapy.

[1] Severity grade description: 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms.

[2] If dose reduction is required, the suggested dose is approximately 50% lower than the dose previously administered.

[3]Avoid using agents containing hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

Moderate CYP3A4 or PgP inhibitors: Use caution when administered in combination with moderate CYP3A4 inhibitors or PgP inhibitors. If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, reduce the Afinitor dose to approximately 50% lower than the dose previously administered. For dose reductions below the lowest available Afinitor strength, alternate day dosing should be considered. Further dose reduction may be required to manage ADRs (see sections Warnings and precautions and Interactions).

Strong CYP3A4 inducers: Avoid the use of concomitant strong CYP3A4 inducers. If patients require co-administration of a strong CYP3A4 inducer, an Afinitor dose increase from 10 mg daily up to 20 mg daily should be considered (based on pharmacokinetic data), using 5 mg increments. 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 in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the Afinitor dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer (see sections Warnings and precautions and Interactions).

Adults and pediatrics

- **Dosing in tuberous sclerosis complex (TSC) with subependymal giant cell astrocytoma (SEGA):**

Treatment with Afinitor should be initiated by a physician experienced in the treatment of patients with TSC and with access to everolimus therapeutic drug monitoring services. Therapeutic drug monitoring of everolimus blood concentrations is required for patients treated for TSC with SEGA (see “Therapeutic Drug Monitoring” in the text below).

Titration may be required to obtain the optimal therapeutic effect. Doses that are tolerated and effective vary between patients. Concomitant antiepileptic therapy may affect the metabolism of everolimus and may contribute to this variance (see section Interactions).

Dosing is individualized based on Body Surface Area (BSA, in m^2) using the Dubois formula, where weight (W) is in kilograms and height (H) is in centimeters:

$$BSA = (W^{0.425} \times H^{0.725}) \times 0.007184$$

The recommended starting daily dose for Afinitor for the treatment of patients with TSC who have SEGA is 4.5 mg/m^2, rounded to the nearest strength of Afinitor Tablets. Different strengths of Afinitor Tablets can be combined to attain the desired dose.

Everolimus whole blood trough concentrations should be assessed approximately 2 weeks after commencing treatment. Dosing should be titrated to attain trough concentrations of 3 to 15 ng/mL. The dose may be increased to attain a higher trough concentration within the target range to obtain optimal efficacy, subject to tolerability. If concentrations are below 3 ~~5~~ ng/mL, the daily dose may be increased by 2.5 mg, (in patients taking tablets) subject to tolerability (see section Clinical pharmacology).

SEGA volume should be evaluated approximately 3 months after commencing Afinitor therapy, with subsequent dose adjustments taking into consideration changes in SEGA volume, corresponding trough concentration, and tolerability (see section Clinical pharmacology). Afinitor has not been studied in patients with SEGA < 3 years of age or with BSA < 0,58 m^2. The optimal duration of therapy for patients with SEGA is unknown.

Dose modifications in TSC with SEGA

Adverse reactions: Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption of therapy. If dose reduction is required, the suggested dose is approximately 50% lower than the dose previously administered (see sections Dosage regimen and administration, Table 1 and Warnings and precautions). For dose reductions below the lowest dosage strengths, alternate day dosing should be considered.

Moderate CYP3A4 or PgP inhibitors: Use caution when administered in combination with moderate CYP3A4 inhibitors or PgP inhibitors. If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, reduce the Afinitor daily dose by approximately 50%. Further Afinitor dose reduction may be required to manage adverse reactions (see sections Warnings and precautions and Interactions). Everolimus trough concentrations should be assessed approximately 2 weeks after the addition of a moderate CYP3A4 or PgP inhibitor. If the moderate inhibitor is discontinued the Afinitor dose should be returned to the dose used prior to initiation of the moderate CYP3A4 or PgP inhibitor and the everolimus trough concentration should be re-assessed approximately 2 weeks later (see sections Warnings and precautions and Interactions). Avoid the use of strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, atazanafir, nefazodone, saquinavir, telithromycin, ritonavir, nelfinavir, voriconazole).

Strong CYP3A4 inducers: Avoid the use of concomitant strong CYP3A4 inducers. Patients receiving concomitant strong CYP3A4 inducers (e.g., enzyme inducing antiepileptic drug) may require an increased Afinitor dose to attain trough concentrations of 3 to 15 ng/mL. If concentrations are below 3 ng/mL, the daily dose may be increased by 2.5 mg (in patients

taking tablets), checking the trough level and assessing tolerability before increasing the dose. If the strong inducer is discontinued the Afinitor dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer and the everolimus trough concentrations should be assessed approximately 2 weeks later (see sections Warnings and precautions and Interactions).

Therapeutic drug monitoring for patients treated for TSC with SEGA

Routine everolimus whole blood therapeutic drug concentration monitoring is recommended for all patients using a validated assay. Trough concentrations should be assessed approximately 2 weeks after commencing treatment. Dosing should be titrated to attain trough concentrations of 5 to 10 ng/mL.

There is limited safety experience with patients having trough concentrations > 10 ng/mL. If concentrations are between 10 to 15 ng/mL, and the patients has demonstrated adequate tolerability and tumor response, no dose reductions are needed. The dose Afinitor should be reduced if trough concentrations > 15 ng/mL are observed.

If concentrations are < 5 ng/mL, the daily dose may be increased by 2.5 mg every 2 weeks, subject to tolerability. Daily dose may be reduced by 2.5 mg every 2 weeks to attain a target of 5 to 10 ng/mL. If dose reduction is required for patients receiving 2.5 mg daily, alternate day dosing should be used.

Trough concentrations should be assessed approximately 2 weeks after any change in dose, or after an initiation or change in co-administration of CYP3A4 and/or PgP inducers or inhibitors (Dosage regimen and Administration, Warnings and Precautions, Interactions), or after any change in hepatic status (Child-Pugh) (see sections Dosage regimen and administration and Clinical pharmacology). Dosing should be titrated with the objective of attaining everolimus trough concentrations of 3 to 15 ng/mL, subject to tolerability (see section Clinical pharmacology). The dose may be increased to attain a higher trough concentration within the target range to obtain optimal efficacy, subject to tolerability.

Dosing in special populations:

Pediatric population

- Afinitor is not recommended for use in paediatric cancer patients.
- Afinitor is not recommended for use in paediatric patients with TSC who have renal angiomyolipoma in the absence of SEGA.
- Dosing recommendations for paediatric patients with TSC who have SEGA are consistent with those for the corresponding adult population with the exception of those patients with hepatic impairment. Afinitor is not recommended for patients <18 years of age with TSC who have SEGA and hepatic impairment.

Elderly patients (≥ 65 years)

No dosage adjustment is required (see section Clinical pharmacology).

Patients with renal impairment

No dosage adjustment is required (see section Clinical pharmacology).

Patients with hepatic impairment

Hormone receptor positive advanced breast cancer, advanced neuroendocrine tumors of gastrointestinal, lung or pancreatic origin, advanced renal cell carcinoma and TSC with renal angiomyolipoma:

- Mild hepatic impairment (Child-Pugh A) – the recommended dose is 7.5 mg daily.
- Moderate hepatic impairment (Child-Pugh B) – the recommended dose is 2.5 mg daily.
- Severe hepatic impairment (Child-Pugh class C) – not recommended. If the desired benefit outweighs the risk, a dose of 2.5 mg daily must not be exceeded.

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

TSC with SEGA

Patients ≥18 years of age

- Mild hepatic impairment (Child-Pugh A) – 75% of the dose calculated based on BSA (rounded to the nearest strength)
- Moderate hepatic impairment (Child-Pugh B) – 25% of the dose calculated based on BSA (rounded to the nearest strength)
- Severe hepatic impairment (Child-Pugh C) – not recommended

Everolimus whole blood trough concentrations should be assessed approximately 2 weeks after commencing treatment or after any change in hepatic status (Child-Pugh). Dosing should be titrated to attain trough concentrations of 3 to 15 ng/mL. The dose may be increased to attain a higher trough concentration within the target range to obtain optimal efficacy, subject to tolerability. If concentrations are below 3 ng/mL, the daily dose may be increased by 2.5 mg (in patients taking tablets), subject to tolerability (see section Clinical Pharmacology).

Patients <18 years of age

Afinitor is not recommended for patients <18 years of age with TSC who have SEGA and hepatic impairment.

Method of administration

Afinitor should be administered orally once daily at the same time every day, either consistently with or consistently without food (see section Clinical pharmacology).

Tablets

Afinitor tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed. For patients unable to swallow tablets, Afinitor tablet(s) should be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring, immediately prior to drinking. The glass should be rinsed with the same volume of water and

the rinse completely swallowed to ensure the entire dose is administered (see section Clinical pharmacology).

Contraindications

Afinitor is contraindicated in patients with:

- hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients (see section Warnings and Precautions).
- hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain, or angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus and other rapamycin derivatives.

Warnings and precautions

Non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking Afinitor (see section Adverse drug reactions). Some of these have been 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 pneumonia (PJP) should be ruled out in the differential diagnosis of non-infectious pneumonitis (see sub-section Infections).

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 alteration.

If symptoms are moderate (grade 2), consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Afinitor may be reintroduced at a daily dose approximately 50% lower than the dose previously administered.

For cases where symptoms of non-infectious pneumonitis are severe (grade 3 or 4), Afinitor therapy should be discontinued and the use of corticosteroids may be indicated until clinical symptoms resolve. For cases of grade 3 non-infectious pneumonitis, Afinitor may be re-initiated at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances (see section Dosage regimen and administration section, Table 1).

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

The development of pneumonitis has also been reported at a reduced dose (see section Dosage regimen and administration, Table 1).

Infections

Afinitor has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens (see section Adverse drug reactions). Localised and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis, candidiasis or pneumocystis jirovecii pneumonia (PJP) 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 including septic shock, respiratory or hepatic failure) and occasionally have had a fatal outcome in adult and pediatric patients (see section Adverse drug reactions).

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, discontinue Afinitor and treat with appropriate antifungal therapy (see section Dosage regimen and administration, Table 1).

Cases of pneumocystis jirovecii pneumonia (PJP), some with fatal outcome, have been reported in patients who received everolimus. PJP may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP 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 (see section Contraindications).

Angioedema with concomitant use of angiotensin-converting enzyme (ACE) inhibitors

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

Stomatitis

Stomatitis, including mouth ulceration and oral mucositis, is the most commonly reported adverse drug reaction in patients treated with Afinitor (see section Adverse drug reactions). Stomatitis mostly occurs within the first 8 weeks of treatment. If stomatitis occurs, topical treatments are recommended, but alcohol-, hydrogen peroxide-, iodine-, or thyme-containing products should be avoided as they may exacerbate the condition (see section Dosage regimen

and administration, Table-1). Antifungal agents should not be used unless fungal infection has been diagnosed (see section Interactions).

In a single arm study in 92 postmenopausal breast cancer patients, a topical alcohol-free corticosteroid oral solution was administered as a mouthwash during the initial 8 weeks of starting treatment with Afinitor plus exemestane. In this study, a clinically meaningful reduction in the incidence and severity of stomatitis was observed (see section Adverse drug reactions).

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 of patients should be monitored particularly where patients have additional risk factors that may further impair renal function. (see section Laboratory tests and monitoring and Adverse drug reactions).

Laboratory tests and monitoring

Renal function

Elevations of serum creatinine, usually mild, and proteinuria have been reported in patients taking Afinitor (see section Adverse drug reactions). 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 in patients taking Afinitor (see section Adverse drug reactions). 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 drugs that may induce hyperglycemia. Optimal glycaemic should be achieved before starting a patient on Afinitor.

Blood lipids

Dyslipidemia (including hypercholesterolemia and hypertriglyceridemia) has been reported in patients taking Afinitor. 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.

Hematological parameters

Decreased haemoglobin, lymphocytes, platelets and neutrophils have been reported in patients treated with Afinitor (see section Adverse drug reactions). Monitoring of complete blood count is recommended prior to the start of Afinitor therapy and periodically thereafter.

Interactions

Co-administration with strong CYP3A4 or P-glycoprotein (PgP) inhibitors should be avoided (see section Interactions).

Use caution when administered in combination with moderate CYP3A4/PgP inhibitors. If Afinitor must be co-administered with a moderate CYP3A4/PgP inhibitor, the patient should be carefully monitored for undesirable effects and Afinitor the dose reduced if necessary (see section Dosage regimen and administration and section Interactions).

Co-administration with strong CYP3A4/PgP inducers should be avoided (see section Interactions). If Afinitor must be co-administered with a strong CYP3A4/PgP inducer, the patient should be carefully monitored for clinical response. Consider a dose increase of Afinitor when co-administered with strong CYP3A4/PgP inducers if alternative treatment is not possible (see Section Dosage regimen and Administration and section Interactions).

Exercise caution 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, the patient should be monitored for undesirable effects described in the product information of the orally administered CYP3A4 substrate (see section Interactions).

Hepatic impairment

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

The safety and pharmacokinetics of Afinitor were evaluated in a study in eight patients with moderate hepatic impairment (Child-Pugh class B) and eight subjects with normal hepatic function. Exposure was increased in patients with moderate hepatic impairment, therefore a dose reduction is recommended.

Afinitor is not recommended in patients ≥18 years of age with severe hepatic impairment (Child-Pugh C) unless the potential benefit outweighs the risk (see sections Dosage regimen and administration and clinical pharmacology).

Afinitor is not recommended for use in patients < 18 years of age with with TSC who have SEGA with concomitant hepatic impairment (Child-Pugh A, B or C) (see sections Dosage regimen and administration and clinical pharmacology).

Vaccinations

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with Afinitor (see section Interactions). Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

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.

Use in Pregnancy

Pregnancy Category D.

There are no adequate and well-controlled studies of Afinitor in pregnant women. However, based on mechanism of action, Afinitor may cause fetal harm when administered to a pregnant woman. Everolimus caused embryo-fetal toxicities in animals at maternal exposures that were lower than human exposures at the recommended dose of 10 mg daily. If this drug is used during pregnancy or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to use an effective method of contraception while using Afinitor and for up to 8 weeks after ending treatment.

Adverse drug reactions

Oncology - Summary of the safety profile

Adverse drug reaction (ADR, suspected to be related to treatment by the investigator) information is based on pooled safety data in patients receiving Afinitor (N=2470) in clinical studies including randomized, double-blind, placebo- or active comparator-controlled phase-III and phase-II studies related to the approved indications in oncology.

The most common ADRs (incidence ≥ 1/10 and suspected to be related to treatment by the investigator) 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 common grade 3/4 ADRs (incidence ≥ 1/100 to <1/10 and suspected to be related to treatment by the investigator) were stomatitis, anaemia, hyperglycaemia, fatigue, infections, pneumonitis, diarrhoea, asthenia, thrombocytopenia, neutropenia, dyspnoea, lymphopenia, proteinuria, haemorrhage, hypophosphataemia, rash, hypertension, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, pneumonia and diabetes mellitus.

Tabulated summary of adverse drug reactions from clinical trials in oncology

Table-2 presents the frequency category of ADRs reported in the pooled safety analysis.

ADRs are listed according to MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, ADRs are presented in order of decreasing frequency. In addition, the corresponding frequency category using the following convention (CIOMS III) very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table-2 Adverse drug reactions from oncology trials

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
Psychiatric disorders	
Common	Insomnia
Nervous system disorders	
Very common	Dysgeusia, headache
Uncommon	Ageusia
Cardiac disorders	
Uncommon	Congestive cardiac failure
Vascular disorders	
Common	Haemorrhage[b], hypertension,
Uncommon	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, oral pain, dyspepsia, dysphagia
Skin and subcutaneous tissue disorders	
Very common	Rash, pruritus
Common	Dry skin, nail disorder, erythema, acne, hand-foot syndrome[e]
Rare	Angioedema
Musculoskeletal and connective tissue disorders	
Common	Arthralgia
Renal and urinary disorders	
Common	Proteinuria, renal failure
Uncommon	Increased daytime urination, acute renal failure
Reproductive system and breast disorders	

Common	Menstruation irregular[f]
Uncommon	Amenorrhoea[f]
General disorders and administration site conditions	
Very common	Fatigue, asthenia, oedema peripheral
Common	Pyrexia, mucosal inflammation
Uncommon	Non-cardiac chest pain, impaired wound healing
Investigations	
Very common	Weight decreased
Common	Aspartate aminotransferase increased, alanine aminotransferase increased, blood creatinine increased

[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, and hepatitis B) and rare: viral myocarditis.

[b] Includes different bleeding events from different sites not listed individually

[c] Includes common: pneumonitis, interstitial lung disease, lung infiltration; and rare: alveolitis, pulmonary alveolar haemorrhage, and pulmonary toxicity

[d] Includes very common: stomatitis; common: aphthous stomatitis, mouth and tongue ulceration; uncommon: glossitis, glossodynia

[e] reported as palmar-plantar erythrodysaesthesia syndrome

[f] frequency is based upon number of women age 10 to 55 yrs of age in the safety pool

Clinically relevant laboratory abnormalities

In the pooled double-blind phase III safety database the following new or worsening clinically relevant laboratory abnormalities were reported with an incidence of ≥1/10 (very common, listed in decreasing frequency):

- Haematology: haemoglobin decreased, lymphocytes decreased, white blood cells decreased, platelets count decreased, and neutrophils decreased (or collectively as pancytopenia).
- Clinical chemistry: glucose (fasting) increased, cholesterol, triglycerides increased, AST increased, phosphate decreased, ALT increased, creatinine increased, potassium decreased and albumin decreased.

Most of the observed abnormalities were mild (Grade 1) or moderate (Grade 2). Grade 3/4 haematology and chemistry abnormalities include

- Haematology: lymphocytes decreased, haemoglobin decreased (very common); neutrophils decreased, platelet count decreased, white blood cells decreased (all common).
- Clinical chemistry: glucose (fasting) increased (very common); phosphate decreased, potassium decreased, AST increased, ALT increased, creatinine increased cholesterol (total) increased, triglycerides increased, albumin decreased (all common).

Tuberous sclerosis complex (TSC) - Summary of the safety profile

Adverse drug reaction (ADR) information is based on pooled data from patients with TSC receiving Afinitor (N=612, including 409 patients <18 years of age) in three randomized, double-blind, placebo-controlled, phase III studies including blinded and open label treatment

periods, and one non-randomized, open-label, single-arm phase II study which serve as the basis for the listed indications (see Table-3 and section Indications).

Table-3 Afinitor TSC studies in the pooled safety data

Study name Indication	CRAD001C2485[a] TSC-SEGA	EXIST-1 (M2301) TSC-SEGA	EXIST-2 (M2302) TSC-Renal angiomyolipoma	EXIST-3 (M2304) TSC-Seizures*
Total number of patients receiving everolimus	28	111[b]	112	361[c]
Median duration of exposure, months (range)	67.8 (4.7 to 83.2)	47.1(1.9 to 58.3)	46.9 (0.5 to 63.9)	20.8 (0.5 to 37.9)
Exposure in Patient-Years	146	391	391	603

[a] *Open label single arm trial, no comparator or control arm*

[b] *Total number of patients receiving everolimus during the double blind and open label extension phases including patients from the placebo arm who crossed over to everolimus treatment*

[c] *Total number of patients receiving everolimus during the core and extension phases, including patients from placebo arm who crossed over to everolimus treatment*

**Note: TSC-Seizures is not yet registered in Indonesia*

The most frequent ADRs (incidence ≥1/10) from the pooled safety database are (in decreasing order): stomatitis, nasopharyngitis, pyrexia, diarrhoea, upper respiratory tract infections, vomiting, cough, headache, rash, amenorrhea, acne, menstruation irregular, pneumonia, sinusitis, urinary tract infection, pharyngitis, decreased appetite, fatigue, and hypercholesterolemia.

The most frequent grade 3/4 adverse reactions (incidence ≥1/100 to <1/10) were pneumonia, stomatitis, amenorrhea, neutropenia, pyrexia, menstruation irregular, cellulitis and hypophosphataemia.

Tabulated summary of adverse drug reactions from clinical trials in TSC

Table-4 shows the incidence of ADRs based on pooled data in patients receiving everolimus in the TSC studies (including both the double-blind and open-label study and extension periods) covering a median duration of exposure of 18.25 months (with up to 47.1 months in the TSC-SEGA and TSC-Renal angiomyolipoma studies). ADRs are listed according to MedDRA system organ class. Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, ADRs are presented in order of decreasing frequency.

Table - 4 Adverse drug reactions from clinical trials in TSC

Infections and infestations	
Very common	Nasopharyngitis, upper respiratory tract infection, pneumonia, sinusitis, urinary tract infection, pharyngitis
Common	Otitis media, cellulitis, pharyngitis streptococcal, gastroenteritis viral, gingivitis
Uncommon	Herpes zoster, sepsis, bronchitis viral
Blood and lymphatic system disorders	
Common	Anaemia, neutropenia, leukopenia, thrombocytopenia, lymphopenia
Immune system disorders	
Uncommon	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Decreased appetite, hypercholesterolaemia
Common	Hypertriglyceridaemia, hyperlipidaemia, hypophosphataemia, hyperglycaemia
Psychiatric disorders	
Common	Insomnia, aggression, irritability
Nervous system disorders	
Very common	Headache
Uncommon	Dysgeusia
Vascular disorders	
Common	Hypertension, lymphoedema
Respiratory, thoracic and mediastinal disorders	
Very common	Cough
Common	Epistaxis, pneumonitis
Gastrointestinal disorders	
Very common	Stomatitis[a], diarrhoea, vomiting
Common	Constipation, nausea, abdominal pain, flatulence, oral pain, gastritis
Skin and subcutaneous tissue disorders	
Very Common	Rash[b], acne
Common	Dry skin, dermatitis acneiform
Uncommon	Angioedema
Renal and urinary disorders	
Common	Proteinuria
Reproductive system and breast disorders	
Very Common	Amenorrhoea[c], menstruation irregular[c]
Common	Menorrhagia, ovarian cyst, vaginal haemorrhage
Uncommon	Menstruation delayed[c]
General disorders and administration site conditions	
Common	Pyrexia, fatigue

Investigations	
Common	Blood lactate dehydrogenase increased, blood luteinizing hormone increased Blood follicle stimulating hormone increased
Uncommon	

[a] Includes very common: stomatitis, mouth ulceration, aphthous ulcer; common: tongue ulceration, lip ulceration; uncommon: gingival pain, glossitis.

[b] Includes very common: rash, common: rash erythematous; uncommon: rash generalized, erythema, rash maculo-papular, rash macular.

[c] frequency is based upon number of women 10 to 55 yrs of age while on treatment in the safety pool

Clinically relevant laboratory abnormalities

In the pooled TSC safety database the following new or worsening clinically relevant laboratory abnormalities reported with an incidence of ≥1/10 (very common, listed in decreasing frequency):

- Haematology: partial thromboplastin time increased, neutrophils decreased, hemoglobin decreased, white blood cells decreased, platelet count decreased, and lymphocytes decreased.
- Clinical chemistry: cholesterol increased, triglycerides increased, AST increased, ALT increased, phosphate decreased, alkaline phosphatase increased, and glucose (fasting) increased.

Most of the laboratory abnormalities were mild (grade 1) or moderate (grade 2). Grade 3/4 hematology and chemistry abnormalities included:

- Haematology: neutrophils decreased, partial thromboplastin time increased, hemoglobin decreased (common); lymphocytes decreased, platelet count decreased, and white blood cells decreased (uncommon).
- Clinical chemistry: phosphate decreased, triglycerides increased, alkaline phosphatase increased, AST increased, ALT increased, cholesterol increased (common) ; and glucose (fasting) increased (uncommon).

Description of selected adverse drug reactions

In clinical trials, everolimus has been associated with serious cases of hepatitis B reactivation, including fatal outcome. Reactivation of infections is an expected event during periods of immunosuppression. Pulmonary embolism has been reported in clinical trials.

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

In clinical trials and post-marketing spontaneous reports, everolimus has been associated with cases of amenorrhea (including secondary amenorrhea).

In clinical trials and post-marketing spontaneous reports, everolimus has been associated with pneumocystis jirovecii pneumonia (PJP), some with fatal outcome (see section Warnings and precautions).

In clinical trials and post-marketing spontaneous reports, angioedema has been reported with and without concomitant use of ACE inhibitors (see section Warnings and precautions).

In a post-marketing single arm study in postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (N=92), topical treatment with dexamethasone 0.5 mg/5 mL alcohol-free oral solution (10 mL swished in the mouth for 2 minutes and then spat out, to be repeated 4 times daily for 8 weeks) was administered as a mouthwash to patients at the time of initiating treatment with Afinitor (10 mg/day) plus exemestane (25 mg/day) to reduce the incidence and severity of stomatitis. No food or drink was to be consumed for at least 1 hour after swishing and spitting the dexamethasone oral solution. The incidence of grade ≥2 stomatitis at 8 weeks was 2.4% (n=2/85 evaluable patients) which was lower than historically reported at 27.4% (n=132/482) in the phase III study in this patient population (BOLERO-2). The incidence of grade 1 stomatitis was 18.8% (n=16/85) and no grade 3 or 4 stomatitis were reported. The overall safety profile in this study was consistent with that established for everolimus in the oncology and TSC settings, with the exception of oral candidiasis which was reported in 2.2% (n=2/92) of patients in this study compared to 0.2% (n=1/482) of patients in BOLERO-2.

Special populations

Geriatrics patients (65 years of age or older)

In the pooled oncology safety database, 37% of the Afinitor-treated patients were ≥65 years of age.

The number of oncology patients with an ADR leading to discontinuation of Afinitor was higher in patients ≥65 years of age (20% vs. 13%). The most common ADRs (≥1/100) leading to discontinuation were pneumonitis, stomatitis, fatigue, and dyspnea.

Interactions

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump P-glycoprotein (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.

Agents that may increase everolimus blood concentrations:

Everolimus blood concentrations may be increased by substances that inhibit CYP3A4 activity and thus decrease everolimus metabolism.

Everolimus blood concentrations may be increased by inhibitors of PgP that may decrease the efflux of everolimus from intestinal cells.

Concurrent treatment with strong CYP3A4/PgP inhibitors (including but not limited to ketoconazole, itraconazole, ritonavir, clarithromycin and telithromycin) should be avoided.

There was a significant increase in exposure to everolimus (C_{max} and AUC increased by 3.9- and 15.0-fold, respectively) in healthy subjects when everolimus was co-administered with ketoconazole (a strong CYP3A4 inhibitor and PgP inhibitor).

Concomitant treatment with moderate inhibitors of CYP3A4 including but not limited to erythromycin, verapamil, ciclosporin, fluconazole, diltiazem, amprenavir, fosamprenavir, or aprepitant) and PgP inhibitors requires caution. Reduce the Afinitor dose if co-administered with moderate CYP3A4/PgP inhibitors (see section Dosage regimen and administration and section Warnings and precautions).

There was an increase in exposure to everolimus in healthy subjects when everolimus was co-administered with:

- erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor; C_{max} and AUC increased by 2.0- and 4.4-fold, respectively).
- verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor; C_{max} and AUC increased by 2.3-and 3.5-fold, respectively).
- ciclosporin (a CYP3A4 substrate and a PgP inhibitor; C_{max} and AUC increased by 1.8- and 2.7-fold, respectively).

Grapefruit, grapefruit juice, star fruit, Seville oranges, and other foods that are known to affect cytochrom P450 and PgP activity should be avoided during treatment.

No difference in everolimus C_{min} was apparent when administered in the presence or absence of substrates of CYP3A4 and/or PgP following treatment with the 10-mg or 5-mg daily dose.

Coadministration of weak inhibitors of CYP3A4 with or without PgP inhibitors had no apparent impact on everolimus C_{min} following treatment with the 10-mg or 5-mg daily dose regimen.

Agents that may decrease everolimus blood concentrations:

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

Concurrent treatment with strong CYP3A4/PgP inducers should be avoided. If Afinitor must be co-administered with a strong CYP3A4/PgP inducer (e.g. rifampicin and rifabutin), it may be necessary to adjust the dose (see section Dosage regimen and administration and section Warnings and precautions).

Pre-treatment of healthy subjects with multiple doses of rifampicin (a strong CYP3A4 and PgP inducer) 600 mg daily for 8 days followed by a single dose of everolimus, increased everolimus oral-dose clearance nearly 3-fold and decreased C_{max} by 58% and AUC by 63%.

Other strong inducers of CYP3A4 and/or PgP that may increase the metabolism of everolimus and decrease everolimus blood levels include St. John's wort (*Hypericum perforatum)*, anticonvulsants (e.g. carbamazepine, phenobarbital, phenytoin,) and anti HIV agents (e.g. efavirenz, nevirapine).

Agents whose plasma concentration may be altered by everolimus:

Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between Afinitor and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate) and population pharmacokinetic analyses also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of Afinitor.

In vitro, everolimus competitively inhibited the metabolism of the CYP3A4 substrate ciclosporin and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan. The mean steady-state of everolimus C_{max} with an oral dose of 10 mg daily or 70 mg weekly is more than 12- to 36-fold below the Ki-values of the *in vitro* inhibition. An effect of everolimus on the metabolism of CYP3A4 and CYP2D6 substrates is therefore unlikely.

A study in healthy subjects demonstrated that co-administration of an oral dose of midazolam (CYP3A4 substrate) with everolimus resulted in a 25% increase in midazolam C_{max} and a 30% increase in midazolam $AUC_{(0\text{-}inf)}$, whereas the metabolic $AUC_{(0\text{-}inf)}$ ratio (1-hydroxy-midazolam/midazolam) and the terminal $t_{1/2}$ of midazolam were not affected. This suggests that increased exposure to midazolam is due to effects of everolimus in the gastrointestinal system when both drugs are taken at the same time. Therefore, everolimus may affect the bioavailability of orally co-administered drugs which are CYP3A4 substrates. Everolimus is unlikely to affect the exposure of other CYP3A4 substrate drugs which are administered by non-oral routes such as intravenous, subcutaneous, and transdermal administrations (see section Warnings and precautions).

Everolimus increased pre-dose concentrations of the antiepileptic drugs (AEDs) carbamazepine, clobazam, and the clobazam metabolite N-desmethylclobazam by approximately 10%. The increase in the pre-dose concentrations of these AEDs may not be clinically significant and dose adjustments for AEDs with a narrow therapeutic index, e.g carbamazepine, may be considered. Everolimus had no impact on pre-dose concentrations of AEDs that are substrates of CYP3A4 (clonazepam, diazepam, felbamate and zonisamide). Everolimus had no impact on the pre-dose concentration of other AEDs, including valproic acid, topiramate, oxcarbazepine, phenobarbital, phenytoin and primidone.

Co-administration of everolimus and depot octreotide increased octreotide C_{min} with a geometric mean ratio (everolimus/placebo) of 1.47 (90% CI: 1.32 to 1.64) which was unlikely to have clinically significant effects on the efficacy response to everolimus in patients with advanced neuroendocrine tumors.

Co-administration of everolimus and exemestane increased exemestane C_{min} and C_{2h} by 45% and 71%, respectively. However, the corresponding estradiol 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.

Vaccinations

Immunosuppressants may affect the response to vaccination and vaccination during treatment with Afinitor may therefore be less effective. The use of live vaccines should be avoided during treatment with Afinitor (see section Warnings and precautions). Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

Pregnancy, lactation, females and males of reproductive potential

1. Pregnancy

Risk Summary

There are no adequate data from the use of Afinitor in pregnant women. The potential risk for humans is unknown. Studies in animals have shown reproductive toxicity effects including embryotoxicity and foetotoxicity. Afinitor should not be given to pregnant women unless the potential benefit outweighs the potential risk to the fetus.

Animal Data

Oral doses of everolimus in female rats at ≥0.1 mg/kg (approximately 4% the $AUC_{0\text{-}24h}$ in patients receiving the 10 mg daily dose) resulted in increased incidence of pre-implantation loss. Everolimus crossed the placenta and was toxic to the conceptus. In rats, everolimus caused embryo/feto-toxicity at systemic exposure below the therapeutic level. This was manifested as mortality and reduced fetal 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 via an increase in late resorptions that occurred at an oral dose of 0.8 mg/kg (9.6 mg/m^2), approximately 1.6 times either the 10 mg daily dose in adults or the median dose administered to SEGA patients, and 1.3 times the median dose for patients with TSC, on a body surface area basis. In rats, there was no evidence of adverse effects by treating males with everolimus on embryo-fetal parameters.

Human data

There have been reports of exposure to everolimus during pregnancy, some due to exposure via the mother and some via the father (pregnancy in a female partner of a male patient while under treatment with everolimus). There were no reports of congenital abnormalities. In some cases the pregnancies progressed uneventfully with delivery of healthy, normal babies.

2. Lactation

Risk Summary

It is not known whether everolimus is excreted in human breast milk. There are no reported cases of exposure to everolimus during breast-feeding in humans. However, in animal studies everolimus and/or its metabolites readily passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum.

Women taking Afinitor should therefore not breast-feed during treatment and for 2 weeks after the last dose.

3. Females and males of reproductive potential

Contraception

Females of reproductive potential should be advised that animal studies have been performed showing Afinitor to be harmful to the developing fetus. Sexually-active females of

reproductive potential should use highly effective contraception (one that results in an annual pregnancy rate <1% when used correctly) while receiving Afinitor, and for up to 8 weeks after ending treatment. Male patients taking Afinitor should not be prohibited from attempting to father children (see section Non-Clinical safety data).

Infertility

Females and Males

Animal data

In animal reproductive studies, female fertility was not affected. However, pre-implantation losses were observed. In male 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 is within the range of therapeutic exposure (52 ng.hr/mL and 414 ng.hr/mL respectively compared to 560 ng.hr/mL human exposure at 10 mg/day) and which caused a reduction in male fertility. There was evidence of reversibility.

Human data

Both male and female fertility may be compromised by treatment with everolimus (see section Non-clinical safety data).

Menstrual irregularities, secondary amenorrhea and associated luteinizing hormone (LH)/follicle stimulating hormone (FSH) imbalance have been observed in female patients receiving everolimus. Blood levels of FSH and LH increased, blood levels of testosterone decreased, and azoospermia have been observed in male patients receiving everolimus.

Overdosage

In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity was observed in either mice or rats given single oral doses of 2,000 mg/kg (limit test).

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.

Clinical pharmacology

Pharmacotherapeutic group, ATC

Protein kinase inhibitors, ATC code: L01XE10.

Mechanism of action (MOA)

Everolimus is a signal transduction inhibitor targeting mTOR (mammalian target of rapamycin), or more specifically, mTORC1 (mammalian 'target of rapamycin' complex 1). mTOR is a key serine-threonine kinase playing a central role in the regulation of cell growth, proliferation and survival. The regulation of mTORC1 signalling is complex, being modulated

by mitogens, growth factors, energy and nutrient availability. mTORC1 is an essential regulator of global protein synthesis downstream on the PI3K/AKT pathway, which is dysregulated in the majority of human cancers as well as genetic diseases such as TSC.

Activation of the mTOR pathway is a key adaptive change driving endocrine resistance in breast cancer. Various signal transduction pathways are activated to escape the effect of endocrine therapy. One pathway is the PI3K/Akt/mTOR pathway, which is constitutively activated in aromatase inhibitor (AI)-resistant and long-term estrogen-deprived breast cancer cells. In breast cancer cells, resistance to AIs due to Akt activation can be reversed by co-administration with everolimus.

Two primary regulators of mTORC1 signaling are the oncogene suppressors tuberin-sclerosis complexes 1 & 2 (TSC1, TSC2). Loss or inactivation of either TSC1 or TSC2 leads to elevated rheb-GTP levels, a ras family GTPase, which interacts with the mTORC1 complex to cause its activation. mTORC1 activation leads to a downstream kinase signaling cascade, including activation of the S6K1. A substrate of mTOR complex 1 (mTORC1), S6K1, phosphorylates the activation function domain 1 of the estrogen receptor, which is responsible for ligand-independent receptor activation. In tuberous sclerosis syndrome, a genetic disorder, inactivating mutations in either the TSC1 or the TSC2 gene lead to hamartoma formation throughout the body.

Pharmacodynamics (PD)

Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor, specifically targeting the mTOR-raptor signal transduction complex (mTORC1). mTOR is a key serine-threonine kinase in the PI3K /AKT signalling cascade, a pathway known to be dysregulated in the majority of human cancers. Everolimus exerts its activity through high affinity interaction with the intracellular receptor protein FKBP12. The FKBP12/everolimus complex binds to mTORC1, inhibiting its signalling capacity. mTORC1 signalling is effected through modulation of the phosphorylation of downstream effectors, the best characterised of which are the translational regulators S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP1). Disruption of S6K1 and 4E-BP1 function, as a consequence of mTORC1 inhibition, interferes with the translation of mRNAs encoding pivotal proteins involved in cell cycle regulation, glycolysis and adaptation to low oxygen conditions (hypoxia). This inhibits tumour growth and expression of hypoxia-inducible factors (e.g. HIF-1 transcription factors); the latter resulting in reduced expression of factors involved in the potentiation of tumour angiogenic processes (e.g. the vascular endothelial growth factor VEGF). Everolimus is a potent inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood vessel-associated smooth muscle cells Consistent with the central regulatory role of mTORC1, everolimus has been shown to reduce tumour cell proliferation, glycolysis and angiogenesis in solid tumours *in vivo*, and thus provides two independent mechanisms for inhibiting tumour growth: direct antitumour cell activity and inhibition of the tumour stromal compartment.

In a mouse neuronal model of TSC in which TSC1 is ablated in most neurons during cortical development, everolimus improved median survival from 33 days to more than 100 days, and behavior, phenotype, and weight gain all also markedly improved. There was brain penetration, with accumulation over time with repetitive treatment, and effective reduction of

levels of phospho-S6, a downstream marker of mTORC1. Neurofilament abnormalities, myelination, and cell enlargement were all improved by the treatment, although dysplastic neuronal features persisted, and there were only modest changes in dendritic spine density and length. Mice treated with everolimus for 23 days only (postnatal days 7–30) displayed a persistent improvement in phenotype, with median survival of 78 days. In summary, everolimus is a highly active in this neuronal model of TSC, with benefit apparently attributable to effects on mTORC1 and Akt signaling and, consequently, cell size and myelination.

Pharmacokinetics (PK)

Absorption

In patients with advanced solid tumours, peak everolimus concentrations are reached 1 to 2 hours after administration of an oral dose of 5 to 70 mg everolimus under fasting conditions or with a light fat-free snack. C_{max} is dose-proportional between 5 and 10 mg in the daily and weekly regimens. At doses of 20 mg/week and higher, the increase in C_{max} is less than dose-proportional, however AUC shows dose-proportionality over the 5 to 70 mg dose range.

Food effect:

In healthy subjects, high fat meals reduced systemic exposure to 10 mg Afinitor Tablets (as measured by AUC) by 22% and the peak plasma concentration C_{max} by 54%. Low-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%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given Afinitor 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.

Following intravenous administration in a rat model, everolimus was shown to cross the blood-brain barrier in a non-linear dose-dependent manner, suggesting saturation of an efflux pump at the blood-brain barrier. Brain penetration of everolimus has also been demonstrated in rats receiving oral doses of everolimus.

Biotransformation/metabolism

Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, it 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, the parent substance is considered to contribute the majority of the overall pharmacological activity of everolimus.

In vitro, everolimus competitively inhibited the metabolism of CYP3A4 and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan. The mean steadystate Cmax following

an oral dose of 10 mg daily is more than 12-fold below the Ki-values of the *in vitro* inhibition. Therefore, an effect of everolimus on the metabolism of CYP3A4 and CYP2D6 substrates is unlikely.

Elimination

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

Steady-state pharmacokinetics

After daily or weekly administration of Afinitor Tablets in patients with advanced solid tumours, steady-state $AUC_{0-\tau}$ was dose-proportional over the range of 5 to 10 mg in the daily dosing regimen and 5 to 70 mg on the weekly regimen. Steady-state was achieved within two weeks with the daily dosing regimen. C_{max} is dose-proportional between 5 and 10 mg on the daily and weekly regimens. At doses of 20 mg/week and higher, the increase in C_{max} is less than dose-proportional. 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 on the daily regimen. The mean elimination half-life of everolimus is approximately 30 hours.

Special populations

Hepatic impairment

The safety, tolerability and pharmacokinetics of Afinitor were evaluated in a single oral dose study of everolimus in 34 subjects with impaired hepatic function relative to subjects with normal hepatic function. Compared to normal subjects, there was a 1.6-fold, 3.3-fold, and 3.6-fold increase in exposure (i.e. $AUC_{(0-inf)}$) 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 hepatic impaired subjects based on their Child Pugh status. Dose adjustment is recommended for patients with hepatic impairment (see sections Warnings and Precautions and Dosage regimen and administration).

Renal impairment

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

Pediatric patients (below 18 years)

- There is no indication for use of Afinitor in the paediatric cancer population (see section Dosage regimen and administration) or in paediatric patients with TSC who have renal angiomyolipoma in the absence of SEGA.

- In patients with TSC who have SEGA, everolimus C_{min} was approximately dose-proportional within the dose range from 1.35 mg/m^2 to 14.4 mg/m^2.
- In patients with TSC who have SEGA, the geometric mean C_{min} values normalized to mg/m^2 dose in patients aged < 10 years and 10-18 years were statistically lower than those observed in adults (> 18 years of age), suggesting that everolimus clearance was higher in younger patients

Geriatric patients (65 years of age or older)

In a population pharmacokinetic evaluation in cancer patients, no significant influence of age (27 to 85 years) on oral clearance (CL/F: range 4.8 to 54.5 litres/hour) of everolimus was detected.

Race/ Ethnicity

Oral clearance (CL/F) is similar in Japanese and Caucasian cancer patients with similar liver functions.

Based on analysis of population pharmacokinetics, oral clearance (CL/F) is on average 20% higher in black transplant patients.

Exposure-response relationships

There was a moderate correlation between the decrease in the phosphorylation of 4E-BP1 (P4E-BP1) in tumour tissue and the average everolimus C_{min} at steady state in blood after daily administration of 5 or 10 mg everolimus. Further data suggest that the inhibition of phosphorylation of the S6 kinase is very sensitive to the mTOR inhibition by everolimus. Inhibition of phosphorylation of elF-4G was complete at all C_{min} values after the 10 mg daily dose.

A trend suggestive of longer progression-free survival with higher time-normalized everolimus C_{min} (defined as (area under the C_{min}-time curve from study start to the time of the event)/(time from study start to the event)) was evident in patients with advanced pancreatic neuroendocrine tumors (pNET, risk ratio 0.73; 95% CI: 0.50 to 1.08) and in patients with advanced carcinoid tumor (risk ratio 0.66; 95% CI: 0.40 to 1.08). Everolimus C_{min} impacted the probability of tumor size reduction ($p<0.001$) with the odds ratios of 1.62 and 1.46, respectively, for a change in exposure from 5 ng/mL to 10 ng/mL in patients with advanced pNET and in patients with advanced carcinoid tumor.

In patients with TSC who have SEGA, a model based analysis indicated that a 2-fold C_{min} increase led to a 13% (95% CI: -18.2%, -7.5%) tumor size reduction from baseline, which was statistically significant at a 5% level.

Clinical studies

Hormone receptor-positive advanced breast cancer

BOLERO-2 (Study CRAD001Y2301) a randomized, double-blind, multicentre phase III study of Afinitor + exemestane versus placebo + exemestane was conducted in

postmenopausal women with estrogen receptor-positive, HER 2-neu/non-amplified advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. Patients were randomized in a 2:1 ratio to receive either everolimus (10 mg daily) or matching placebo in addition to open-label exemestane (25 mg daily). Randomization was stratified by documented sensitivity to prior hormonal therapy (yes vs. no) and by the presence of visceral metastasis (yes vs. no). Sensitivity to prior hormonal therapy was defined as either (1) documented clinical benefit (complete response [CR], partial response [PR], stable disease ≥24 weeks) to 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 trial was progression-free survival (PFS) evaluated by Response Evaluation Criteria in Solid Tumors (RECIST), based on the investigators (local radiology) assessment. Supportive PFS analyses were based on an independent central radiology review.

Secondary endpoints included overall survival (OS), Overall Response Rate (ORR), Clinical Benefit Rate (CBR), Safety, change in Quality of Life (QoL) and time to ECOG PS deterioration. Additional endpoints included changes in bone turnover markers at 6 and 12 weeks.

A total of 724 patients were randomised in 2:1 ratio to the combination everolimus (10 mg daily) + exemestane (25 mg daily) (n = 485) or placebo + exemestane arm (25 mg daily) (n = 239). The two treatment groups were generally balanced with respect to the baseline demographics of disease characteristics and history of prior anti-neoplastic usages. The median age of patients was 61 years (range 28 to 93) and 75% were Caucasian.

The efficacy results were obtained from an interim analysis after 359 local PFS events and 217 central PFS events were observed. Patients in the placebo+exemestane arm did not cross-over to everolimus at the time of progression.

The study demonstrated a statistically significant clinical benefit of everolimus + exemestane over placebo + exemestane by a 2.4-fold prolongation in median PFS (median: 6.93 months versus 2.83 months), resulting in a 57% risk reduction of progression or death (PFS HR 0.43; 95%CI: 0.35, 0.54; one-sided log-rank test p-value <0.0001 per local investigator assessment (see Table 5 and Figure 1).

The analysis of PFS based on independent central radiological assessment was supportive and showed a 2.6-fold prolongation in median progression-free-survival (10.58 months versus 4.14 months), resulting in a 64% risk reduction of progression or death (PFS HR 0.36; 95%CI: 0.27, 0.47; one-sided log-rank test p-value<0.0001 (see Table 5 and Figure 2).

Objective response as per investigator assessment based on RECIST was observed in 9.5% of patients (95% CI: 7.0, 12.4) in the everolimus + exemestane arm vs. 0.4% (95% CI: 0.0-2.3) in the placebo + exemestane arm (p<0.0001 for comparison between arms). Clinical benefit rate for everolimus + exemestane was 33.4% vs. 18.0% in the control arm; p<0.0001(see Table 5).

Table 5 BOLERO-2 – efficacy results

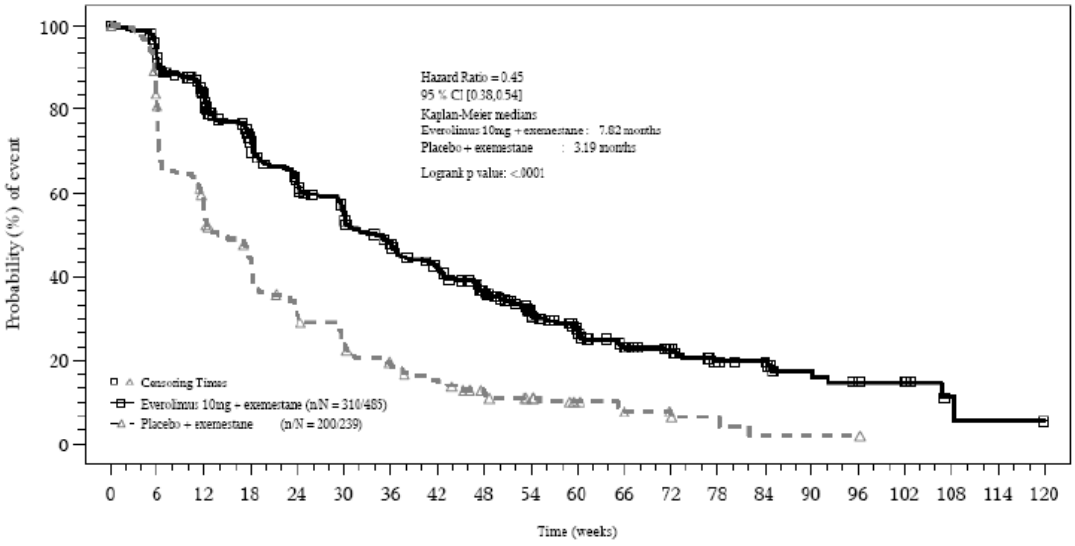
Analysis	Afinitor[a] N = 485	Placebo[a] N = 239	Hazard ratio	P-value
Median progression-free survival (months, 95% CI)				
Investigator radiological review	7.82 (6.93 to 8.48)	3.19 (2.76 to 4.14)	0.45 (0.38 to 0.54)	<0.0001
Independent radiological review	11.01 (9.66 to 15.01)	4.14 (2.89 to 5.55)	0.38 (0.31 to 0.48)	<0.0001
Best overall response (%, 95% CI)				
Objective response rate (ORR)[b]	12.6% (9.8 to 15.9)	1.7% (0.5 to 4.2)	n/a[d]	<0.0001[e]
Clinical benefit rate (CBR) [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 CR or PR*
[c] *Clinical benefit rate = proportion of patients with CR or PR or SD ≥ 24 weeks*
[d] *not applicable*
[e] *p-value is obtained from the exact CMH test using a stratified version of the Cochran-Armitage permutation test*

At the time of the final overall survival (OS) analysis, the median duration of OS was 31 months versus 26.6 months for the everolimus + exemestane arm versus the placebo + exemestane arm, respectively [HR= 0.89 (95% CI: 0.73 to 1.10; p=0.1426)] (see Figure-3).

Twelve-month PFS rates were 33% of patients receiving everolimus + exemestane compared with 11% in the placebo + exemestane arm.

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



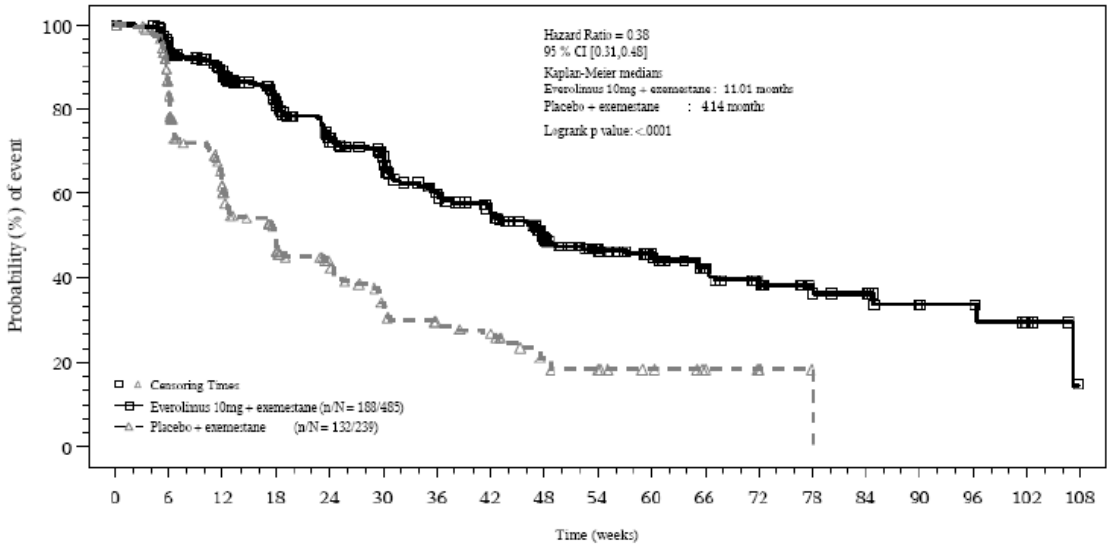
Number of Patients still at Risk

Time(weeks)	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	102	108	114	120
Everolimus	485	436	366	304	257	221	185	158	124	91	66	50	35	24	22	13	10	8	2	1	0
Placebo	239	190	132	96	67	50	30	30	21	15	10	8	5	3	1	1	1	0	0	0	0

- One-sided P-value is obtained from the log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis from IXRS.

Nine-month PFS rates were 40% of patients receiving everolimus + exemestane compared with 15% in the placebo + exemestane arm at a median follow-up of 7.6 months.

Figure 2 **BOLERO-2 - Kaplan-Meier progression-free survival curves (independent radiological review)**

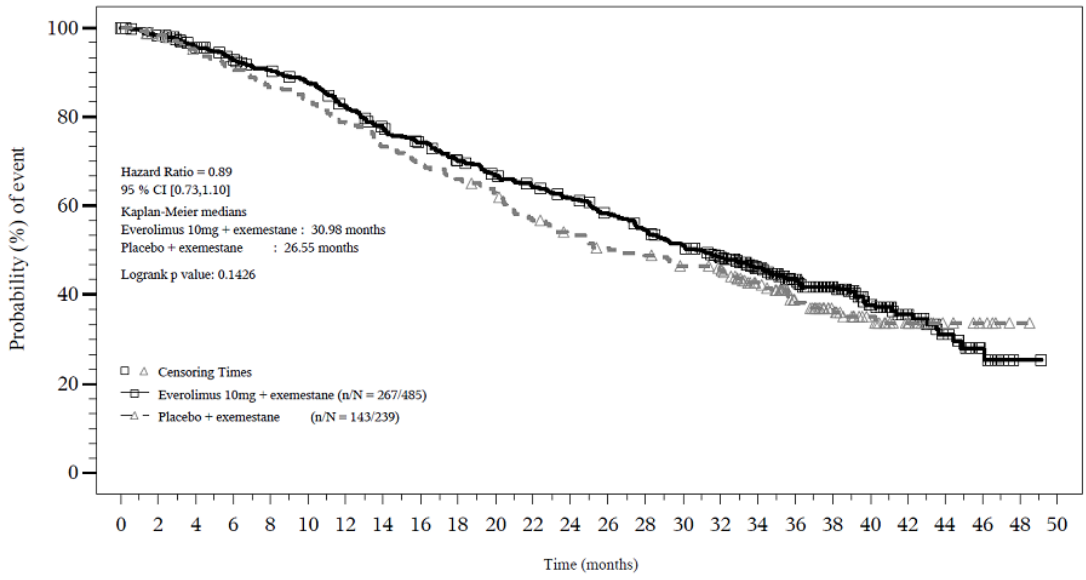


Number of Patients still at Risk

Time(weeks)	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	102	108
Everolimus	485	427	359	292	239	211	166	140	108	77	62	48	32	21	18	11	10	5	0
Placebo	239	179	114	76	56	39	31	27	16	13	9	6	4	1	0	0	0	0	0

- One-sided P-value is obtained from the log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis from IXRS.

Figure 3 BOLERO-2 – Kaplan-Meier plot of overall survival (Full Analysis Set)



Number of Patients still at Risk

Time(months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50
Everolimus	485	471	448	429	414	399	373	347	330	311	292	279	266	248	232	216	196	154	118	91	58	39	23	11	1	0
Placebo	239	232	220	211	201	194	182	170	162	153	145	130	120	113	109	102	98	77	56	41	28	18	8	5	1	0

One-sided P-value is obtained from the log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis from IXRS

The estimated PFS treatment effect was supported by planned subgroup analysis of PFS per investigator assessment. For all analyzed subgroups, a positive treatment effect was seen with everolimus + exemestane with an estimated hazard ratio vs. placebo + exemestane ranging from 0.25 to 0.60 (see Table 6). Subgroup analyses demonstrated a homogeneous and consistent treatment effect irrespective of sensitivity to prior hormonal therapy and presence of visceral metastasis, and across major demographic and prognostic subgroups.

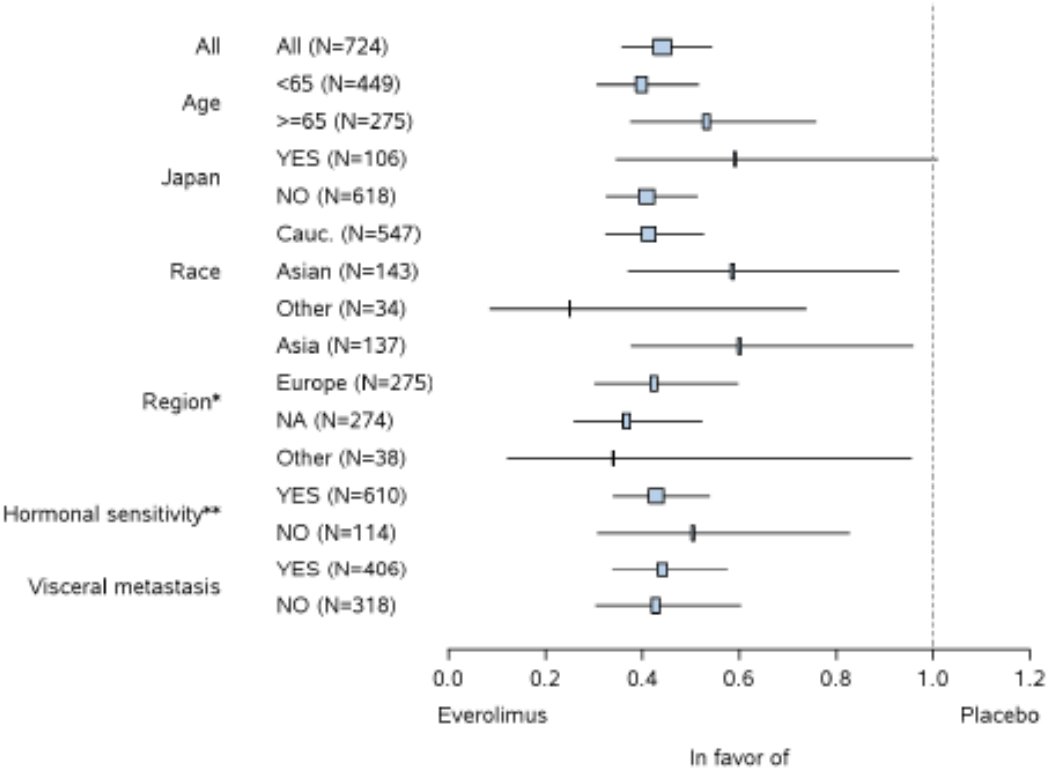
Table-6 Analysis of PFS as per investigator by subgroup - Full Analysis Set

	n	Everolimus + exemestane	Placebo + exemestane	HR[1]	95% CI
		Median PFS (months)			
Sensitivity to prior hormonal therapy					
No	114	6.70	2.83	0.50	0.31, 0.83
Yes	610	6.93	2.92	0.43	0.34, 0.54
Presence of visceral metastasis					
No	318	8.48	4.24	0.43	0.30, 0.60
Yes	406	6.18	2.69	0.44	0.34, 0.58
Age group					
< 65 years	449	6.97	2.83	0.40	0.31, 0.52
≥ 65 years	275	6.44	4.01	0.53	0.37, 0.76

	n	Everolimus + exemestane	Placebo + exemestane	HR[1]	95% CI
		Median PFS (months)			
Region					
Asia	137	6.97	4.14	0.60	0.38, 0.96
Europe	275	6.70	2.76	0.42	0.30, 0.60
North America	274	8.84	3.94	0.37	0.26, 0.52
Other	38	4.21	1.45	0.34	0.12, 0.96
Japanese					
Japanese	106	8.41	4.14	0.59	0.35, 1.01
Non-Japanese	618	6.83	2.79	0.41	0.32, 0.51
Prior chemotherapy					
No	232	6.83	3.45	0.53	0.37, 0.76
Yes	492	6.93	2.79	0.40	0.31, 0.52
Bone only lesions at baseline					
No	569	6.70	2.76	0.44	0.35, 0.56
Yes	155	9.89	4.37	0.43	0.25, 0.76
Baseline ECOG performance status					
0	435	6.97	4.01	0.47	0.36, 0.62
1 or 2	274	6.77	2.76	0.37	0.26, 0.52
PgR status					
Negative	184	6.93	2.76	0.45	0.30, 0.68
Positive	523	6.93	2.96	0.43	0.34, 0.55
Race					
Asian	143	6.93	4.14	0.59	0.37, 0.93
Caucasian	547	6.93	2.83	0.41	0.32, 0.53
Other	34	7.03	1.41	0.25	0.09, 0.74
Prior use of hormonal therapy other than NSAI					
No	327	6.83	4.01	0.51	0.37, 0.70
Yes	397	6.97	2.76	0.38	0.29, 0.51
Number of organs involved					
1	224	8.48	4.21	0.43	0.28, 0.66
2	233	5.59	2.79	0.48	0.33, 0.68
≥ 3	264	6.70	2.60	0.44	0.31, 0.61
Number of prior therapies					
1	118	6.97	4.17	0.52	0.31, 0.88
2	217	6.70	2.92	0.55	0.38, 0.81
≥ 3	389	7.16	2.79	0.36	0.27, 0.48

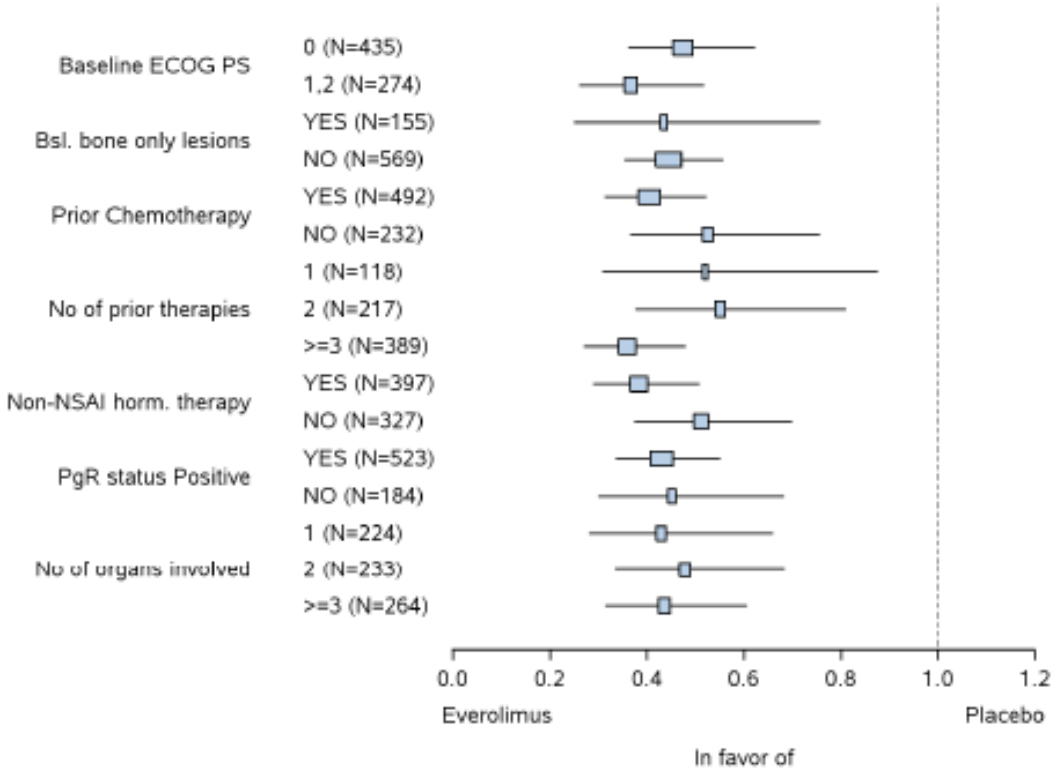
[1] *Hazard ratio obtained using unstratified Cox model*

Figure 4 Forest plot of PFS as per investigator by subgroup (1)



Hazard ratio was obtained using unstratified Cox proportional hazard model.
* NA: North America
** sensitivity to prior hormonal therapy

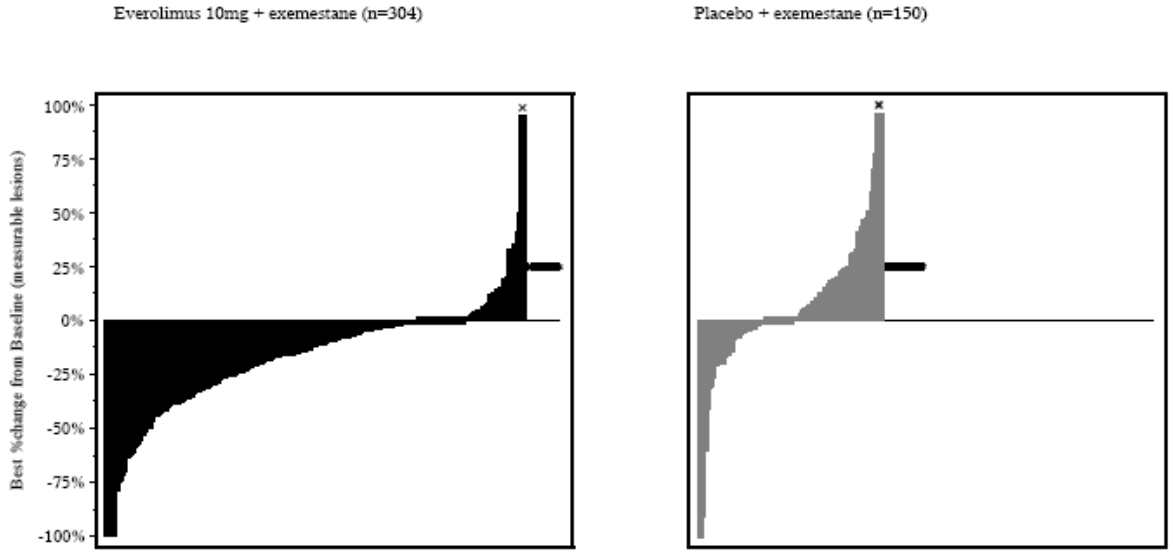
Figure 5 Forest plot of PFS as per investigator by subgroup (2)



Hazard ratio was obtained using unstratified Cox proportional hazard model.
* NA: North America
** sensitivity to prior hormonal therapy

Tumor reduction was also evident from the corresponding waterfall plot. Results indicate that 68.1% of patients in the everolimus + exemestane arm experienced tumor shrinkage versus 28.0% for placebo + exemestane (Figure 6).

Figure 6 **Tumor shrinkage: best percentage change from baseline in sum of longest diameters as per investigator**



	Everolimus	Placebo
Decrease in best percentage change from baseline	68.09% (207)	28.00% (42)
Zero change in best percentage change from baseline	10.86% (33)	14.00% (21)
Increase in best percentage change from baseline	12.83% (39)	38.67% (58)
* % change in target lesion available but contradicted by Overall lesion response = PD	8.22% (25)	19.33% (29)

Clinically or statistically significant differences were not observed between the two treatment arms in terms of time to deterioration of ECOG PS (≥1 point) and median times to deterioration (≥5%) of QLQ-C30 domain scores.

Effects on bone

There are no long-term data on the effect of everolimus on bone. Comparative data from BOLERO-2 showed marked improvement in serum bone-turnover markers during the first 12 weeks of therapy, suggesting a favorable effect on bone turnover.

Advanced neuroendocrine tumors of pancreatic origin

RADIANT-3 (Study CRAD001C2324), a randomized, double-blind, multicentre phase III study of Afinitor plus best supportive care (BSC) versus placebo plus BSC in patients with advanced pancreatic neuroendocrine tumors (pNET), demonstrated a statistically significant clinical benefit of Afinitor over placebo by a 2.4-fold prolongation in median progression-free-survival PFS (11.04 months versus 4.6 months), resulting in a 65% risk reduction in PFS (HR 0.35; 95%CI: 0.27, 0.45; p<0.0001) (see Table 7 and Figure 7).

RADIANT-3 enrolled patients with advanced pNET whose disease had progressed within the prior 12 months. Patients were stratified by prior cytotoxic chemotherapy (yes/no) and by WHO performance status (0 *vs*. 1 and 2). Treatment with somatostatin analogs was allowed as part of BSC.

The primary endpoint for the trial was PFS evaluated by RECIST (Response Evaluation Criteria in Solid Tumors, version 1.0) as per investigator radiology review. After documented radiological progression, patients could be unblinded by the investigator: those randomised to placebo were then able to receive open-label Afinitor.

Secondary endpoints include safety, objective response rate ORR (complete response (CR) or partial response (PR)), response duration, and overall survival OS.

In total, 410 patients were randomised 1:1 to receive either Afinitor 10mg/day (n=207) or placebo (n=203). Demographics were well balanced (median age 58 years, 55% male, 78.5% Caucasian). Median duration of blinded study treatment was 37.8 weeks for patients receiving Afinitor and 16.1 weeks for those receiving placebo.

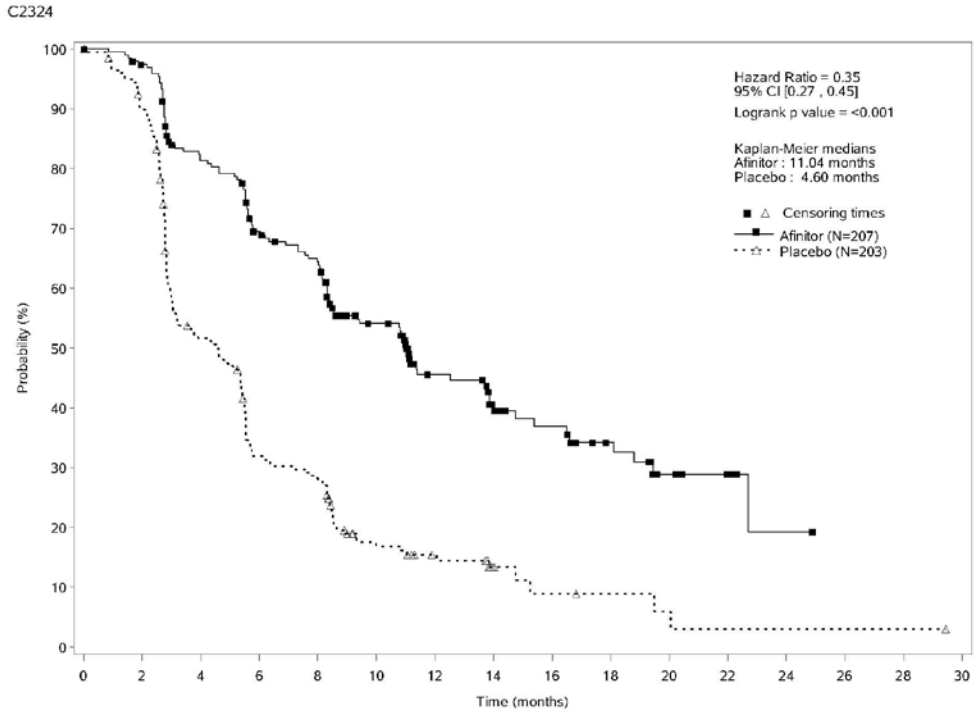
Table 7 RADIANT-3 – Progression Free Survival results

Analysis	**N**	**Afinitor N=207**	**Placebo N=203**	**Hazard Ratio (95%CI)**	**p-value**
	410	**Median progression-free survival (months) (95% CI)**			
Investigator radiological review		11.04 (8.41 to 13.86)	4.60 (3.06 to 5.39)	0.35 (0.27 to 0.45)	<0.0001
Independent radiological review [a]		11.40 (10.84 to 14.75)	5.39 (4.34 to 5.55)	0.34 (0.26 to 0.44)	<0.0001

[a] *Includes adjudication for discrepant assessments between investigator radiological review and central radiological review*

[b] *One-sided p-value from a stratified log-rank test*

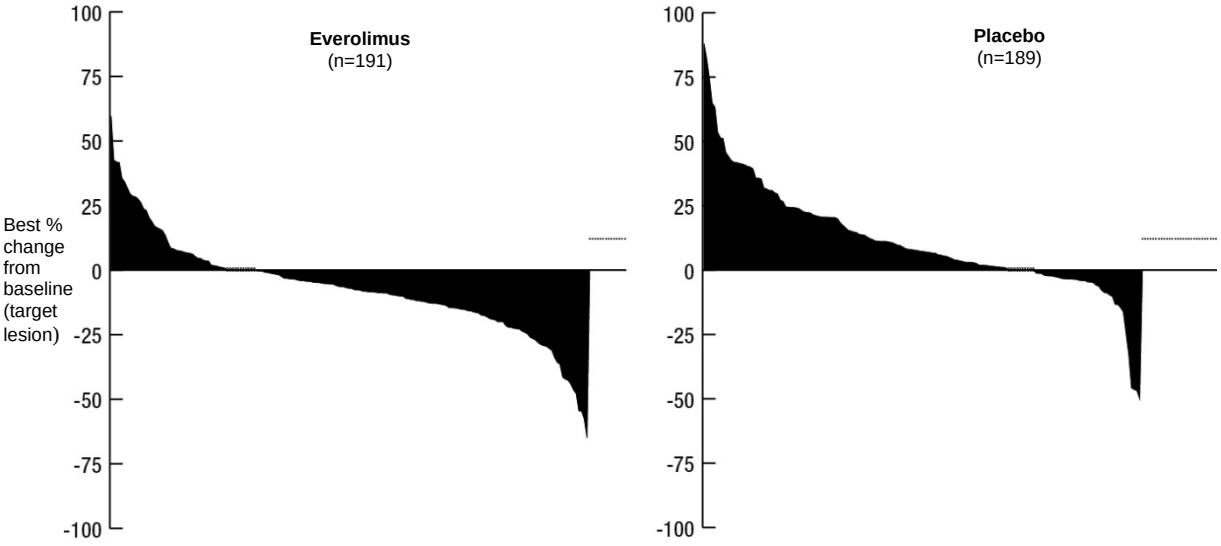
Figure 7 RADIANT-3 – Kaplan-Meier progression-free survival curves (investigator radiological review)



Eighteen-months PFS rates were 34.2% for Afinitor therapy compared to 8.9% for placebo.

The objective response rate per adjudicated central assessment was 2.3% for the everolimus plus depot octreotide (Sandostatin LAR®) arm vs. 1.9% for the placebo plus depot octreotide (Sandostatin LAR®) arm. Tumor reduction was also evident from the corresponding waterfall plot. Results indicate that 75.0% of patients in the everolimus plus depot octreotide (Sandostatin LAR®) arm experienced tumor shrinkage versus 44.8% in the placebo plus depot octreotide (Sandostatin LAR®) arm (Figure 8).

Figure 8 **Tumor shrinkage: best percentage change from baseline in sum of longest diameters as per investigator assessment**

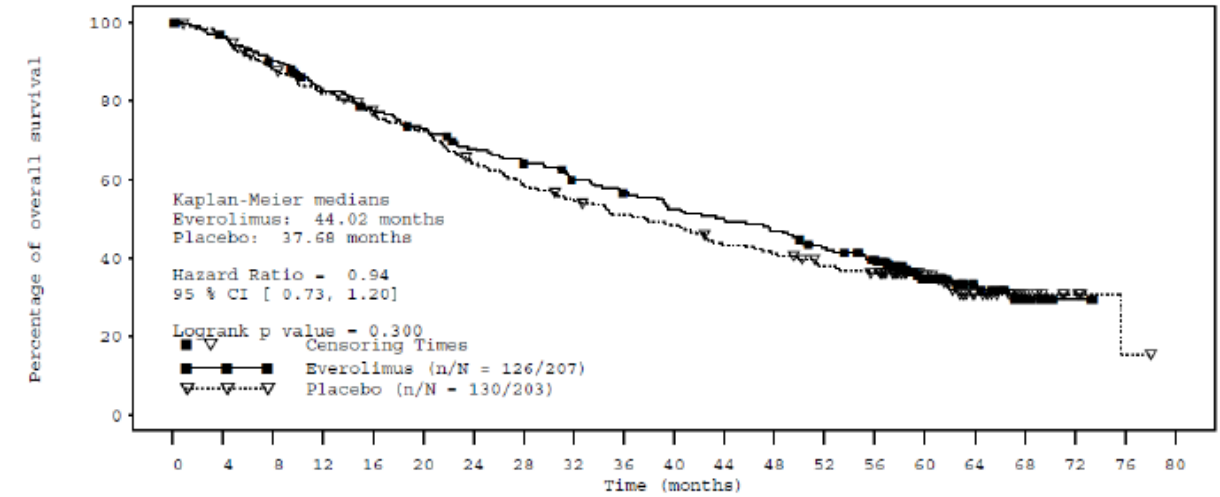


	Everolimus n (%)	Placebo n (%)
Decrease in best percentage change from baseline	123 (64.4%)	39 (20.6%)
Zero change in best percentage change from baseline	11 (5.8%)	10 (5.3%)
Increase in best percentage change from baseline	43 (22.5%)	112 (59.3%)
% change in target lesion available but contradicted by overall lesion response = PD*	14 (7.3%)	28 (14.8%)

**Patients for whom the best % change in target lesions was either unavailable or was contradicted by overall lesion response of "unknown" were excluded from this analysis. Percentages use remaining number of evaluable patients (n) as denominator.*

At the time of the final overall survival (OS) analysis, the median duration of OS was 44 months for the everolimus arm versus 37.7 months for the placebo arm, respectively [HR=0.94 (95% CI 0.73 to 1.20)] ; p=0.300 (Figure 9). Following disease progression, crossover to open-label Afinitor occurred in 172 of 203 patients (84.7%) randomized to placebo and may have confounded the detection of any treatment-related difference in overall survival.

Figure 9 RADIANT-3 – Kaplan-Meier plot of overall survival (Full Analysis Set)



No. of patients still at risk

Time (months)	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80
Everolimus	207	194	181	163	152	142	130	122	112	105	97	93	87	77	67	39	22	10	2	0	0
Placebo	203	195	175	162	150	140	123	113	104	96	91	81	77	68	64	45	25	10	6	1	0

RADIANT-4 (Study CRAD001T2302), a randomised, double-blind, multicenter phase III study of Afinitor plus best supportive care (BSC) versus placebo plus best supportive care was conducted in patients with advanced non-functional neuroendocrine tumors (NET) of gastrointestinal or lung origin without a history of and no active symptoms related to carcinoid syndrome. Randomization was stratified by prior somatostatin analog (SSA) use, tumor origin and WHO performance status.

The primary endpoint for the study was progression-free survival (PFS) evaluated by Response Evaluation Criteria in Solid Tumors (modified RECIST version 1.0), based on independent radiological assessment. Supportive PFS analysis was based on local investigator review.

Secondary endpoints included overall survival (OS), Overall Response Rate (ORR), Disease Control Rate (DCR = proportion of patients with a best overall response of complete response, partial response or stable disease), Safety, change in Quality of Life (QoL) via FACT-G and time to 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). The two treatment groups were generally balanced with respect to the baseline demographics, disease characteristics and history of prior somatostatin analog (SSA) use. The median age of patients was 63 years (range 22 to 86) and 76% were Caucasian. 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 were obtained from the final analysis of PFS after 178 PFS events were observed per independent radiological review.

The study demonstrated a statistically significant clinical benefit of everolimus over placebo by a 2.8-fold prolongation in median PFS (11.01 months versus 3.91 months), resulting in a

52% risk reduction of progression or death (HR 0.48; 95% CI: 0.35, 0.67; one-sided stratified log-rank test p-value <0.0001) per independent assessment (see Table 8 and Figure 10).

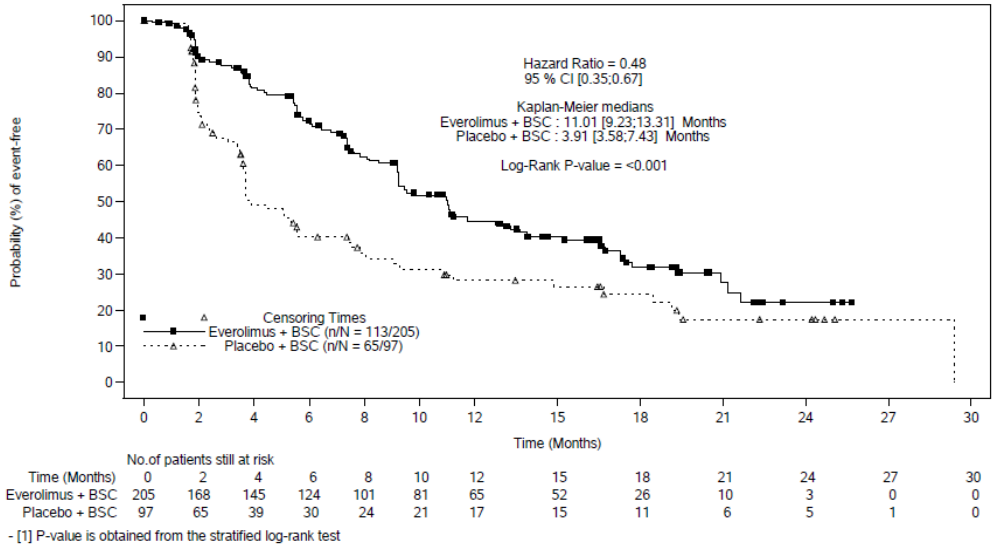
The analysis of PFS based on local investigator assessment was supportive and showed a 2.5-fold prolongation in median progression-free-survival (13.96 months versus 5.45 months), resulting in a 61% risk reduction of progression or death (HR 0.39; 95% CI: 0.28, 0.54; one-sided stratified log-rank test p-value<0.0001) (see Table 8 and Figure 11).

Table 8 RADIANT-4 – Progression Free Survival results

Analysis	N	Afinitor N=205	Placebo N=97	Hazard Ratio (95%CI)	p-value[a]
	302	Median progression-free survival (months) (95% CI)			
Independent radiological review		11.01 (9.2 to 13.3)	3.91 (3.6 to 7.4)	0.48 (0.35 to 0.67)	<0.0001
Investigator radiological review		13.96 (11.2 to 17.7)	5.45 (3.7 to 7.4)	0.39 (0.28 to 0.54)	<0.0001

[a]*One-sided p-value from a stratified log-rank test*

Figure 10 RADIANT-4 – Kaplan-Meier progression-free survival curves (independent radiological review)

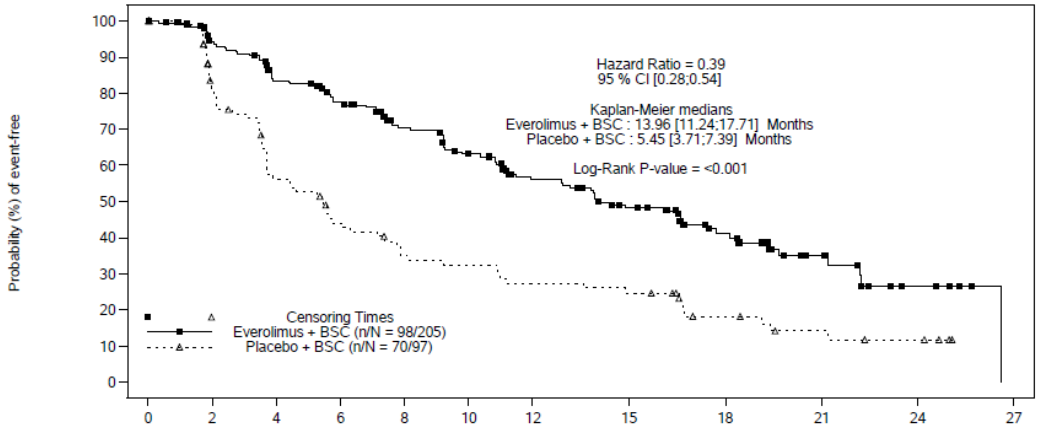


No.of patients still at risk

Time (Months)	0	2	4	6	8	10	12	15	18	21	24	27	30
Everolimus + BSC	205	168	145	124	101	81	65	52	26	10	3	0	0
Placebo + BSC	97	65	39	30	24	21	17	15	11	6	5	1	0

- [1] P-value is obtained from the stratified log-rank test

Figure 11 RADIANT-4 – Kaplan-Meier progression-free survival curves (investigator radiological review)



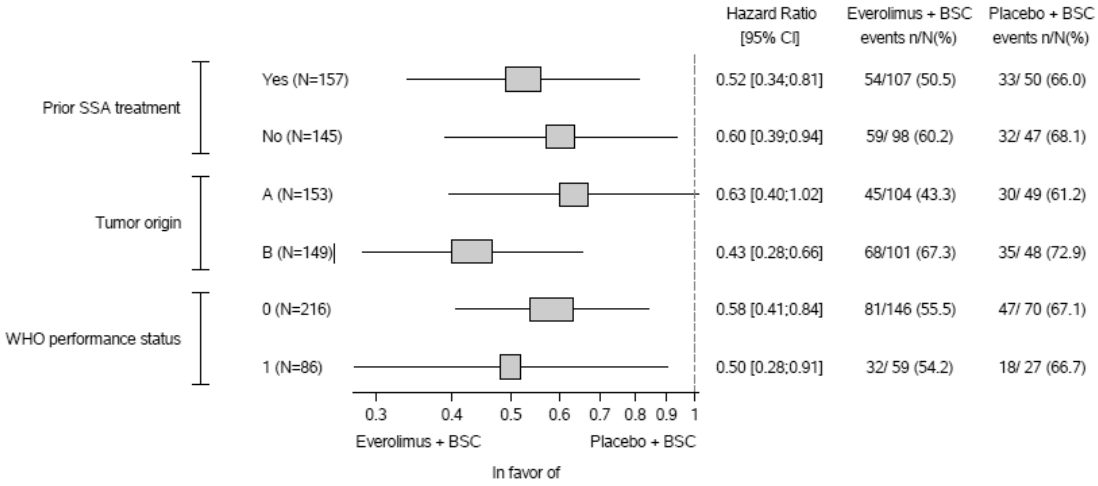
No.of patients still at risk

Time (Months)	0	2	4	6	8	10	12	15	18	21	24	27
Everolimus + BSC	205	171	148	132	108	93	75	59	33	15	5	0
Placebo + BSC	97	70	47	35	27	25	21	19	10	6	4	0

- [1] P-value is obtained from the stratified log-rank test.
- Hazard ratio is obtained from stratified Cox model.

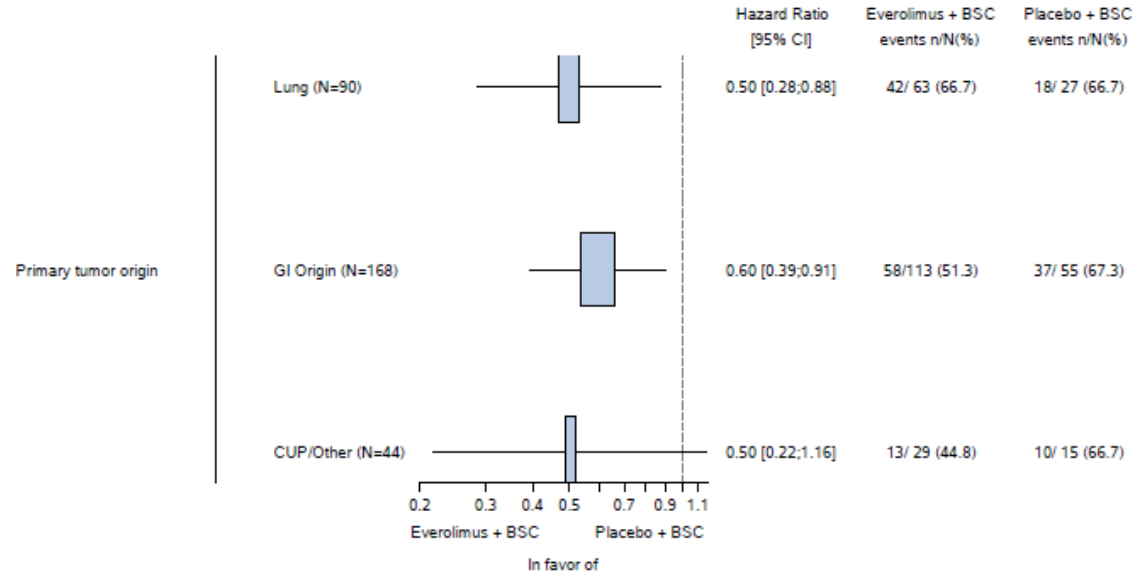
The overall PFS benefit favored Afinitor across predefined demographic and prognostic stratification subgroups (See Figure 12). A post-hoc subgroup analysis of PFS for sites of tumor origin by gastrointestinal, lung and carcinoma of unknown primary/other origin, showed a positive PFS benefit (See Figure 13).

Figure 12 Forest plot of hazard ratio for PFS based on independent radiological review by subgroup based on stratification factors (Full Analysis Set)



- Hazard ratio is obtained from unstratified Cox model
- The somatostatin analogs (SSA) pretreated stratum is defined as patients who had continuously received SSA for >=12 weeks any time prior to study inclusion.
- The tumor origin stratum is A for appendix, caecum, jejunum, ileum, duodenum and carcinoma of unknown primary (CUP).
- The tumor origin stratum is B for lung, stomach, rectum, and colon except caecum.
- Stratification factors are as per IRT.

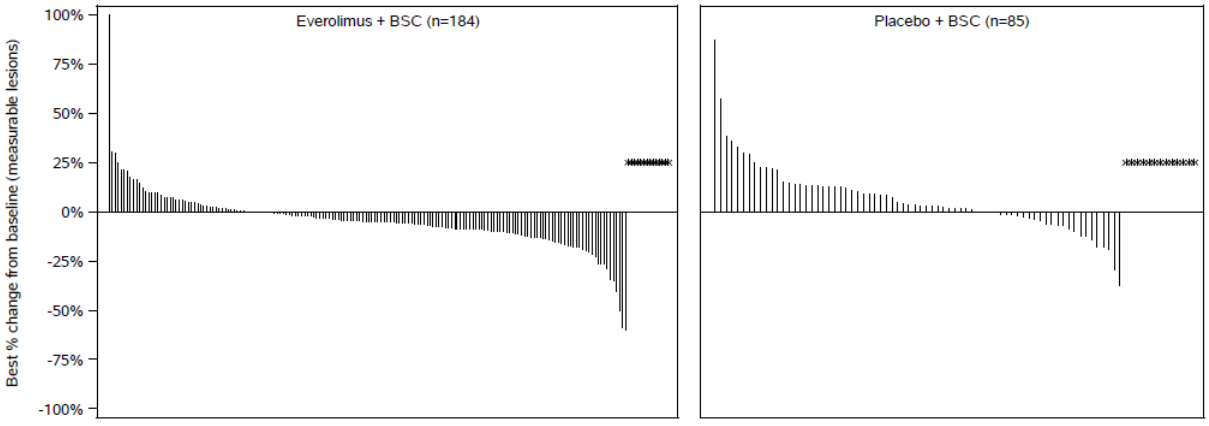
Figure 13 **Forest plot of hazard ratio for PFS based on independent radiological review by subgroup analysis for sites of tumor origin by GI, lung, and CUP/other origin (Full Analysis Set)**



- Hazard ratio is obtained from unstratified Cox model
- Stomach, Colon, Rectum, Appendix, Caecum, Ileum, Duodenum and Jejunum are grouped as GI origin.

The overall response rate as per independent assessment was 2% in the everolimus arm vs. 1% in the placebo arm. Disease control rate (CR or PR or SD) for everolimus was 82.4% vs. 64.9% in the placebo arm. Tumor reduction was also evident from the corresponding waterfall plot. Results indicate that 63.6% of patients in the everolimus arm experienced tumor shrinkage versus 25.9% for placebo (see Figure 14).

Figure 14 **Tumor shrinkage: best percentage change from baseline in sum of longest diameters as per independent radiological assessment**

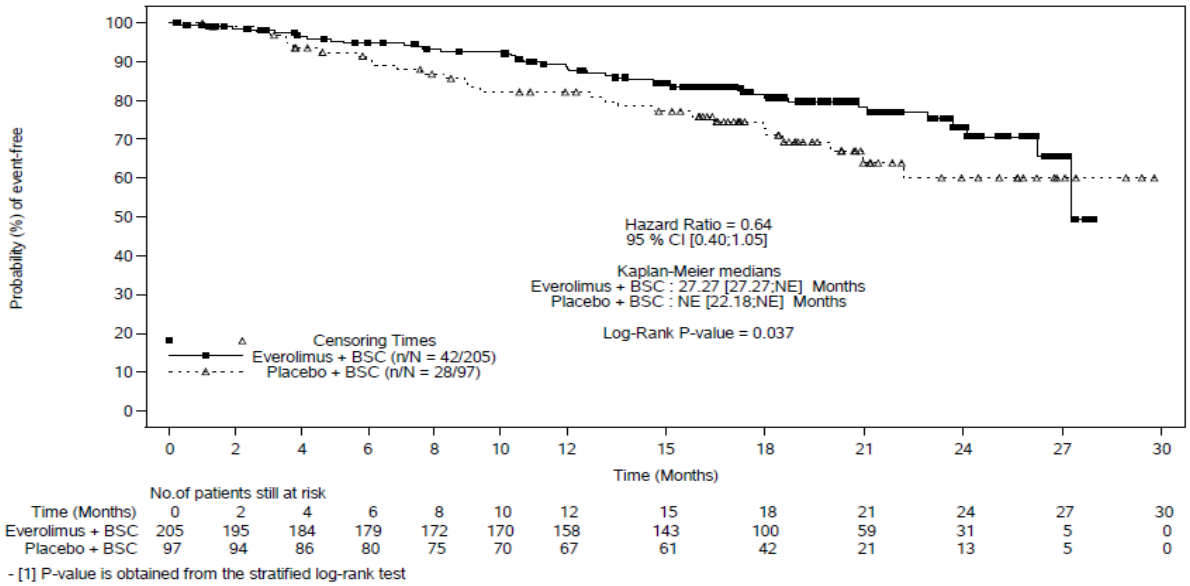


	Everolimus + BSC	Placebo + BSC
Decrease in best percentage change from baseline	63.6%	25.9%
Increase/zero change in best percentage change from baseline	28.8%	58.8%
* % change in target lesion contradicted by overall lesion response = PD	7.6%	15.3%

Patients for whom the best % change in target lesions was not available and patients for whom the best % change in target lesions was contradicted by overall lesion response = UNK were excluded from the analysis, percentages above use n as denominator.

The overall survival (OS) analysis is not yet mature. At the first interim analysis, 42 (20.5%) deaths were observed in the Afinitor arm vs. 28 (28.9%) deaths in the placebo arm; however the results of this analysis did not meet the pre-specified stopping boundary for statistical significance [HR= 0.64 (95% CI: 0.40 to 1.05; p=0.037)] (see Figure 15).

Figure 15 RADIANT-4 - Kaplan-Meier plot of overall survival (Full Analysis Set)



No.of patients still at risk

Time (Months)	0	2	4	6	8	10	12	15	18	21	24	27	30
Everolimus + BSC	205	195	184	179	172	170	158	143	100	59	31	5	0
Placebo + BSC	97	94	86	80	75	70	67	61	42	21	13	5	0

- [1] P-value is obtained from the stratified log-rank test

Clinically or statistically significant differences were not observed between the two treatment arms in terms of time to deterioration of WHO PS (≥1 point) and time to deterioration of FACT-G total score (≥7 points).

RADIANT-2 (Study CRAD001C2325), a randomized, double-blind, multicentre phase III study of Afinitor plus depot octreotide (Sandostatin LAR®) versus placebo plus depot octreotide in patients with advanced neuroendocrine tumors (carcinoid tumor) primarily of gastrointestinal or lung origin showed evidence of clinical benefit of Afinitor over placebo by a 5.1-month prolongation in median PFS (16.43 months versus 11.33 months; HR 0.77; 95%CI: 0.59 to 1.00; p=0.026), resulting in a 23% risk reduction in primary PFS (see Table 8 and Figure 10). Although statistical significance was not reached for the primary analysis (boundary for statistical significance was p=0.0246), analyses which adjusted for informative censoring and imbalances in the two treatment arms showed a treatment effect in favor of everolimus.

RADIANT-2 enrolled patients with advanced neuroendocrine tumors (carcinoid tumor) primarily of gastrointestinal or lung origin whose disease had progressed within the prior 12 months and had a history of secretory symptoms. 80.1% of the patients in the Afinitor group received somatostatin analog therapy prior to study entry compared to 77.9% in the placebo group.

The primary endpoint is PFS evaluated by RECIST as per independent radiological review. After documented radiological progression, patients could be unblinded by the investigator: those randomised to placebo were then able to receive open-label Afinitor.

Secondary endpoints include safety, best overall response, response duration, and overall survival.

In total, 429 patients were randomised 1:1 to receive either Afinitor 10mg/day (n=216) or placebo (n=213), in addition to depot octreotide (Sandostatin LAR®, administered intramuscularly) 30 mg every 28 days. Median duration of blinded study treatment was 37.0 weeks for patients receiving Afinitor and 36.6 weeks for those receiving placebo. Notable imbalances were evident for several important baseline prognostic factors, mainly in favor of the placebo group.

Table 9 RADIANT-2 – Progression Free Survival results

Analysis	**N**	**Afinitor[a] N=216**	**Placebo[b] N=213**	**Hazard Ratio (95%CI)**	**p-value[c]**
	429	**Median progression-free survival (months) (95% CI)**			
Independent radiological review[b]		16.43 (13.67 to 21.19)	11.33 (8.44 to 14.59)	0.77 (0.59 to 1.00)	0.026
Investigator radiological review		11.99 (10.61 to 16.13)	8.61 (8.08 to 11.14)	0.78 (0.62 to 0.98)	0.018

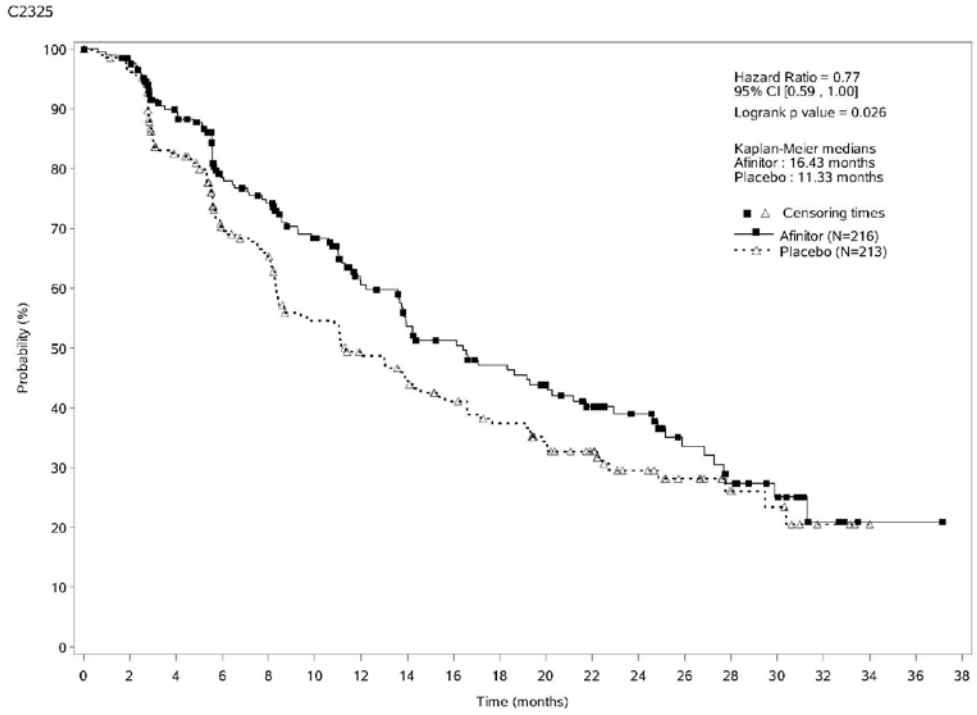
[a] *Plus depot octreotide (Sandostatin LAR®)*

[b] *Includes adjudication for discrepant assessments between investigator radiological review and central radiological review*

[c] *One-sided p-value from stratified log-rank tes*t

Additional analyses for independent radiological review which adjusted for informative censoring and imbalances in the two treatment arms showed a treatment effect in favor of everolimus. Results of an additional adjusted multivariate analysis which corrected for imbalances between treatment arms yielded a HR of 0.73 (95% CI 0.56 to 0.97). A Cox model with Inverse Probability of Censoring Weights (IPCW) was used to address and correct for informative censoring and imbalances in baseline characteristics between the two study arms. The estimated HR (95% CI) from the IPCW weighted analysis was 0.60 (0.44 to 0.84), with one-sided p-value=0.0014 in favor of Afinitor.

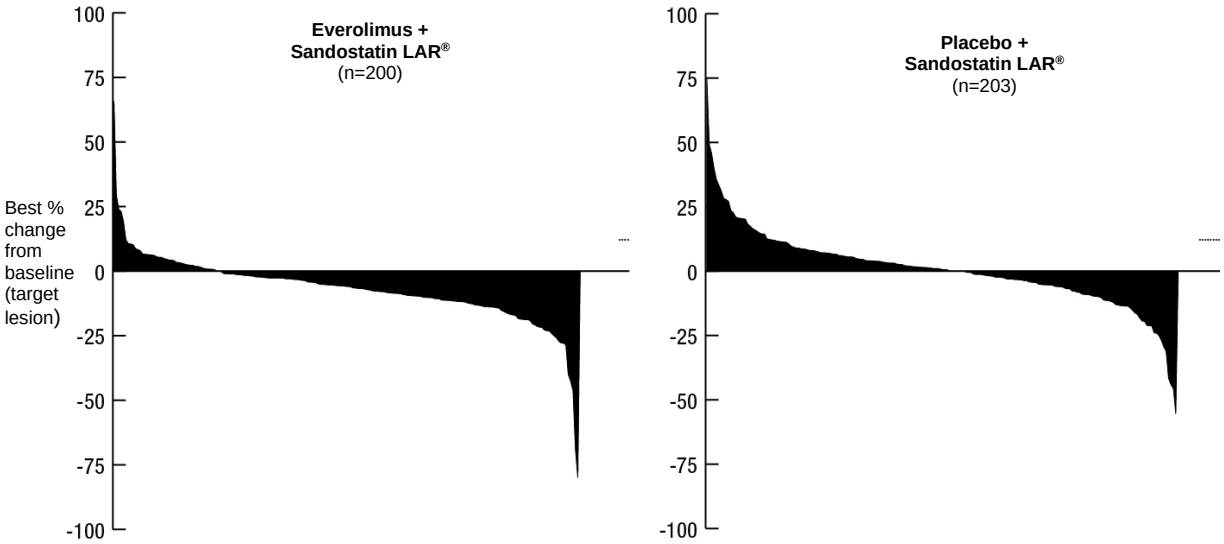
Figure 16 RADIANT-2 – Kaplan-Meier progression-free survival curves (independent radiological review)



Eighteen-months PFS rates were 47.2% for everolimus therapy plus depot octreotide (Sandostatin LAR®) compared with 37.4% for placebo plus depot octreotide (Sandostatin LAR®).

The objective response rate per adjudicated central assessment was 2.3% for the everolimus plus depot octreotide (Sandostatin LAR®) arm vs. 1.9% for the placebo plus depot octreotide (Sandostatin LAR®) arm. Tumor reduction was also evident from the corresponding waterfall plot. Results indicate that 75.0% of patients in the everolimus plus depot octreotide (Sandostatin LAR®) arm experienced tumor shrinkage versus 44.8% in the placebo plus depot octreotide (Sandostatin LAR®) arm (Figure 17).

Figure 17 Tumor shrinkage: best percentage change from baseline in sum of longest diameters as per independent radiology review



	Everolimus + Sandostatin LAR® n (%)	Placebo + Sandostatin LAR® n (%)
Decrease in best percentage change from baseline	150 (75.0%)	91 (44.8%)
Increase in best percentage change from baseline	43 (21.5%)	94 (46.3%)
Zero change in best percentage change from baseline	3 (1.5%)	10 (4.9%)
% change in target lesion available but contradicted by overall lesion response = PD*	4 (2.0%)	8 (3.9%)

*Patients for whom the best % change in target lesions was either unavailable or was contradicted by overall lesion response of “unknown” were excluded from the analysis. Percentages use remaining number of evaluable patients (n) as denominator.

The final analysis of overall survival did not show a statistically significant difference in OS (HR =1.16; (95% CI: 0.91 to 1.49)). There were 133 (61.6%) deaths in the everolimus plus depot octreotide arm and 120 (56.3%) in the placebo plus depot octreotide arm. Crossover of >58% of patients from placebo to open-label Afinitor following disease progression, imbalance between treatment arms in subsequent use of octreotide and imbalance of key prognostic factors at baseline likely confounded the detection of any treatment-related difference in OS. When adjusted for important prognostic factors, the OS hazard ratio inclined towards unity (HR 1.06; 95% CI: 0.82, 1.36).

Advanced renal cell carcinoma

RECORD-1 (CRAD001C2240), a phase III, international, multicentre, randomised, double-blind study comparing Afinitor 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 despite prior 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-alpha 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 Afinitor 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 to 85], 77% male, 88% Caucasian, 74% one prior VEGFR-TKI therapy). Median duration of blinded study treatment was 141 days for patients receiving Afinitor and 60 days for those receiving placebo.

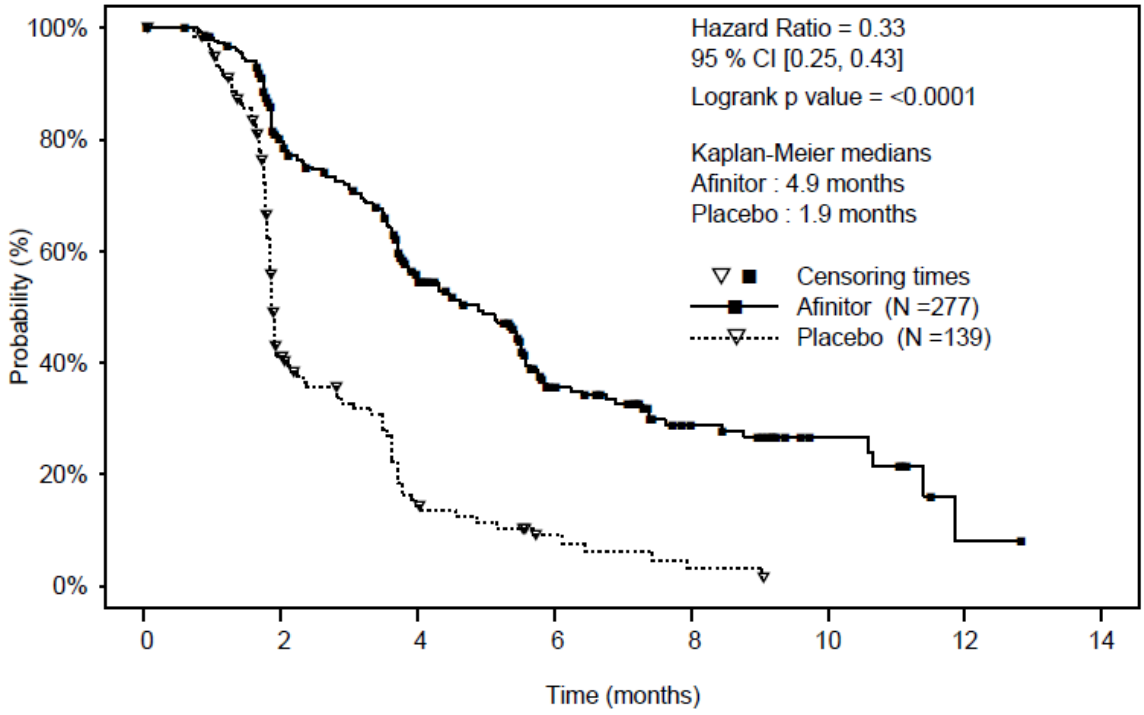
Results from a planned interim analysis showed that Afinitor was superior to placebo for the primary endpoint of progression-free survival, with a statistically significant 67% reduction in the risk of progression or death (see Table 10 and Figure 18).

Table 10 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 to 5.5)	1.9 (1.8 to 1.9)	0.33 (0.25 to 0.43)	<0.001 [a]
Supportive/sensitivity analyses					
All (local review by investigator)	416	5.5 (4.6 to 5.8)	1.9 (1.8 to 2.2)	0.32 (0.25 to 0.41)	<0.001 [a]
MSKCC prognostic score					
Favourable risk	120	5.8 (4.0 to 7.4)	1.9 (1.9 to 2.8)	0.31 (0.19 to 0.50)	<0.001 [b]
Intermediate risk	235	4.5 (3.8 to 5.5)	1.8 (1.8 to 1.9)	0.32 (0.22 to 0.44)	<0.001 [b]
Poor risk	61	3.6 (1.9 to 4.6)	1.8 (1.8 to 3.6)	0.44 (0.22 to 0.85)	0.007 [b]
Prior VEGFR-TKI therapy					
Sunitinib only	184	3.9 (3.6 to 5.6)	1.8 (1.8 to 1.9)	0.34 (0.23 to 0.51)	<0.001 [b]
Sorafenib only	124	5.9 (4.9 to 11.4)	2.8 (1.9 to 3.6)	0.25 (0.16 to 0.42)	<0.001 [b]
Sunitinib and sorafenib	108	4.0 (3.6 to 5.4)	1.8 (1.8 to 2.0)	0.32 (0.19 to 0.54)	<0.001 [b]

[a] *Log-rank test stratified by prognostic score*
[b] *Unstratified one-sided log-rank test*

Figure 18 RECORD-1 – Kaplan-Meier progression-free survival curves



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. The progression-free survival advantage therefore primarily reflects the population with disease stabilisation (corresponding to 67% of the Afinitor treatment group).

Final overall survival results yielded a trend in favor of Afinitor; the difference between treatment arms was not statistically significant (HR 0.90; 95% CI: 0.71 to 1.14; p=0.183). Crossover to open-label Afinitor following disease progression occurred in 111 of 139 patients (79.9%) allocated to placebo and may have confounded the detection of any treatment-related difference in overall survival. A strong trend is evident supporting better quality of life among patients receiving Afinitor as measured by disease-related symptoms (HR 0.75; 95% CI: 0.53 to 1.06; p=0.053).

Tuberous sclerosis complex (TSC) with renal angiomyolipoma

EXIST-2 (Study CRAD001M2302), a randomized, double-blind, multicentre phase III study of Afinitor versus placebo was conducted in patients with TSC who have angiomyolipoma (n=113) or sporadic LAM who have angiomyolipoma (n=5). Patients were randomised in a 2:1 ratio to receive either Afinitor or matching placebo. Presence of at least one angiomyolipoma ≥ 3 cm in longest diameter using CT/MRI (based on local radiology assessment) was required for entry.

The primary efficacy endpoint was angiomyolipoma response rate based on independent central radiology review. The analysis was stratified by use of enzyme-inducing antiepileptic drugs (EIAEDs) at randomisation (yes/no).

Key secondary endpoints included time to angiomyolipoma progression and skin lesion response rate.

A total of 118 patients were randomised, 79 to Afinitor 10 mg daily and 39 to placebo. The two treatment arms were generally well balanced with respect to demographic and baseline disease characteristics and history of prior anti-angiomyolipoma therapies. Median age was 31 years (range: 18 to 61; 46.6% were <30 years at enrolment), 33.9% were male, and 89.0% were Caucasian. Of the enrolled patients, 83.1% had angiomyolipomas ≥ 4 cm (with 28.8% with angiomyolipomas ≥ 8 cm), 78.0% had bilateral angiomyolipomas, and 39.0% had undergone prior renal embolization/nephrectomy; 96.6% had skin lesions at baseline and 44.1% had target SEGAs (at least one SEGA ≥ 1 cm in longest diameter).

Results showed that Afinitor was superior to placebo for the primary endpoint of best overall angiomyolipoma response ($p<0.0001$); the difference observed was both clinically relevant and statistically significant. Best overall response rate were 41.8% (95% CI: 30.8, 53.4) for the Afinitor arm compared with 0% (95% CI: 0.0, 9.0) for the placebo arm (Table 11).

Patients initially treated with placebo were allowed to cross over to everolimus at the time of angiomyolipoma progression and upon recognition that treatment with everolimus was superior to treatment with placebo. At the time of the final analysis (4 years following the last patient randomization), the median duration of exposure to everolimus was 204.1 weeks (range 2 to 278). The angiomyolipoma best overall response rate had increased to 58.0% (95% CI: 48.3, 67.3), with a rate of stable disease of 30.4%.

Among patients treated with everolimus during the study, no cases of angiomyolipoma-related nephrectomy and only one case of renal embolization were reported.

Table 11 EXIST-2 - Angiomyolipoma response

	Primary Analysis[3]			**Final analysis[4]**
	Afinitor N=79	**Placebo N=39**	**p-value**	**Afinitor N=112**
Angiomyolipoma response rate[1,2] - %	**41.8**	**0**	**<0.0001**	**58.0**
95% CI	(30.8, 53.4)	(0.0, 9.0)		(48.3, 67.3)
Best overall angiomyolipoma response - %				
Response	41.8	0		58.0
Stable disease	40.5	79.5		30.4
Progression	1.3	5.1		0.9
Not evaluable	16.5	15.4		10.7

[1] *Per independent central radiology review*

[2] *Angiomyolipoma responses were confirmed with a repeat scan. Response was defined as: ≥ 50% reduction in the sum of angiomyolipoma volume relative to baseline, plus absence of new angiomyolipoma ≥ 1.0 cm in longest diameter, plus no increases in renal volume > 20% from nadir, plus absence of Grade ≥ 2 angiomyolipoma-related bleeding.*

[3] *Primary analysis for double blind period*

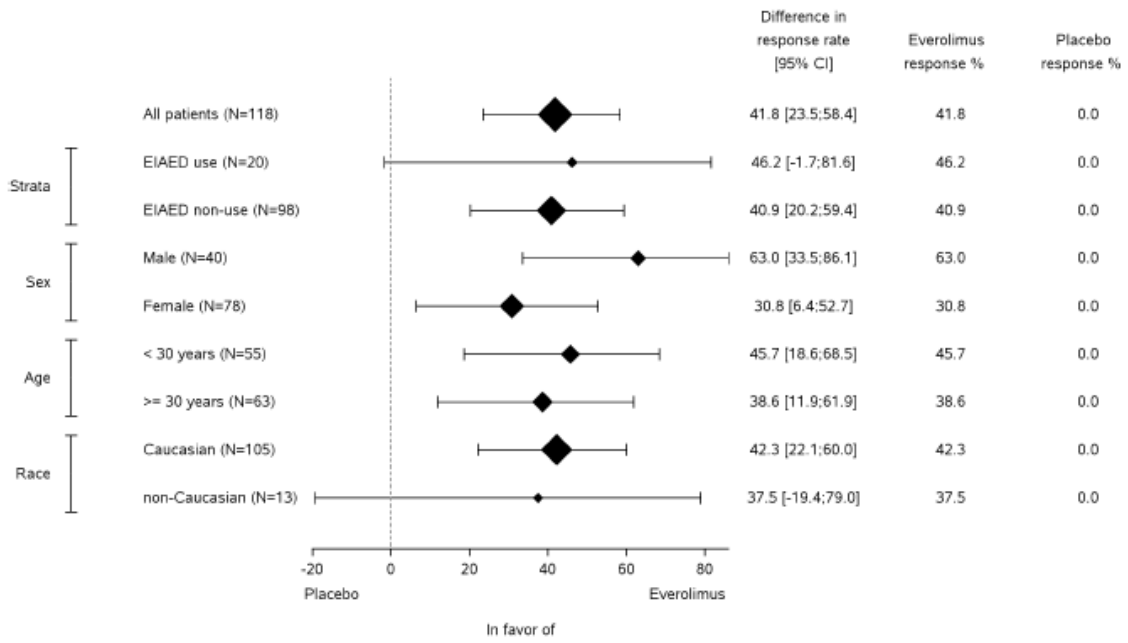
[4] *Final analysis includes patients who crossed over from the placebo group; median duration of exposure to everolimus of 204.1 weeks*

Consistent treatment effects were observed across all subgroups evaluated (i.e., EIAED use vs. EIAED non-use, sex, age, and race) at the primary efficacy analysis (Table 12, Figure 19).

Table 12 EXIST-2 - Angiomyolipoma response by subgroup at primary analysis

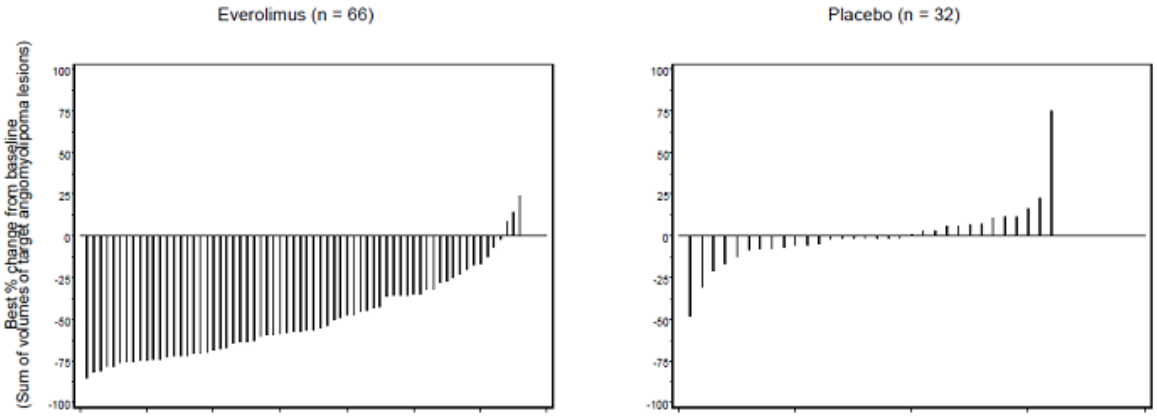
Subgroup	Afinitor		Placebo		Difference in response rates (95% CI)
	N	Responders %	N	Responders %	
All patients	**79**	**41.8**	**39**	**0**	**41.8 (23.5, 58.4)**
Modified strata					
EIAED use	13	46.2	7	0	46.2 (-1.7, 81.6)
No EIAED use	66	40.9	32	0	40.9 (20.2, 59.4)
Sex					
Male	27	63.0	13	0	63.0 (33.5, 86.1)
Female	52	30.8	26	0	30.8 (6.4, 52.7)
Age					
<30 years	35	45.7	20	0	45.7 (18.7, 68.5)
≥30 years	44	38.6	19	0	38.6 (11.9, 61.9)
Race					
Caucasian	71	42.3	34	0	42.3 (22.1, 60.0)
Non-Caucasian	8	37.5	5	0	37.5 (-19.4, 79.0)

Figure 19 EXIST-2 – Forest plot of angiomyolipoma response by subgroup at primary analysis



The waterfall plots provide a graphical representation of the reduction in angiomyolipoma volume (Figure 20) at primary analysis; 95.5% of patients in the Afinitor arm experienced angiomyolipoma shrinkage versus 59.4% in the placebo arm.

Figure 20 EXIST-2 - Angiomyolipoma shrinkage: best percentage change from baseline at primary analysis [1,2]



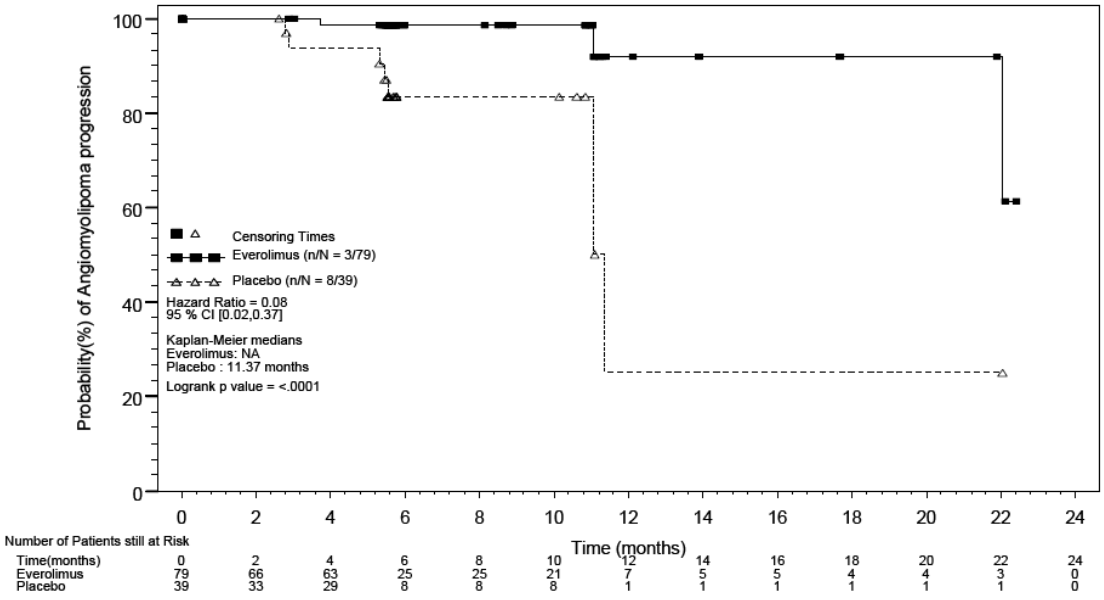
[1] Per independent central radiology review

[2] Patients for whom the best % change in sum of volumes of target angiomyolipoma lesions was not available and patients with overall angiomyolipoma response = Not evaluable were excluded from the graph.

In the final analysis, reduction in angiomyolipoma volume improved with longer term treatment with Afinitor. At weeks 12, 96 and 192, ≥30% reductions in volume were observed in 75.0% (78/104), 80.6% (79/98) and 85.2% (52/61) of the treated patients, respectively. Similarly, at the same timepoints, ≥50% reductions in volume were observed in 44.2% (46/104), 63.3% (62/98) and 68.9% (42/61) of the treated patients, respectively.

Afinitor was associated with a clinically relevant and statistically significant prolongation in time to angiomyolipoma progression (HR 0.08; 95% CI: 0.02, 0.37; p<0.0001) (Figure 21) at the primary analysis. Median time to angiomyolipoma progression was 11.4 months in the placebo arm and was not reached in the Afinitor arm. Progressions were observed in 3.8% (3/79) of patients in the Afinitor arm compared with 20.5% (8/39) in the placebo arm. Estimated progression-free rates at 6 months were 98.4% for the Afinitor arm and 83.4% for the placebo arm. At the final analysis, median time to angiomyolipoma progression was not reached. Angiomyolipoma progressions were observed in 14.3% of the patients (16/112). The estimated angiomyolipoma progression-free rates at 24 months and 48 months were 91.6% (95% CI: 84.0%, 95.7%) and 83.1% (95% CI: 73.4%, 89.5%) respectively (see Figure 22).

Figure 21 EXIST-2 Kaplan-Meier plot of time to angiomyolipoma progression at primary analysis [1,2]

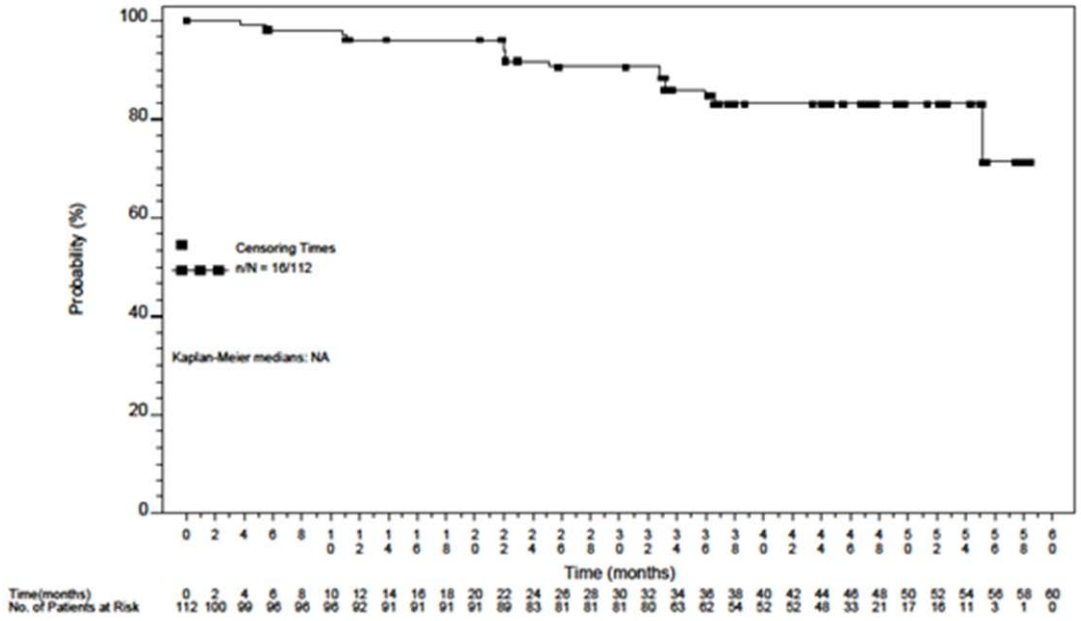


[1] p-value is obtained from the one-sided stratified log-rank test.
[2] Hazard ratio <1 implies reduced risk of angiomyolipoma progression in the Everolimus group.

[1] Per independent central radiology review

[2] Angiomyolipoma progression was defined as: ≥ 25% increase in the sum of angiomyolipoma volume relative to baseline, or appearance of new angiomyolipoma ≥ 1.0 cm in longest diameter, or an increase in renal volume > 20% from nadir, or grade ≥ 2 angiomyolipoma-related bleeding.

Figure 22 EXIST-2 Kaplan-Meier plot of time to AML progression[1,2] at final analysis



[1] Per independent central radiology review
[2] Angiomyolipoma progression was defined as: ≥ 25% increase in the sum of angiomyolipoma volume relative to baseline with a value greater than baseline, or appearance of new angiomyolipoma ≥ 1.0 cm in longest diameter, or an increase in renal volume > 20% from nadir with a value greater than baseline, or Grade ≥ 2 angiomyolipoma-related bleeding

At the primary analysis, Afinitor demonstrated clinically meaningful and statistically significant improvements in skin lesion response (p=0.0002), with response rates of 26.0% (20/77) (95% CI: 16.6, 37.2) for the Afinitor arm and 0% (0/37) (95% CI: 0.0, 9.5) for the placebo arm (see Table 13).

Table 13 EXIST-2 - Best overall skin lesion response

	Primary analysis[5]			Final analysis[6]
	Afinitor N=77	**Placebo N=37**	**p-value[1]**	**Afinitor N=107**
Skin lesion response rate [1,2,3,4] - %	**26.0**	**0**	**0.0002**	**68.2**
95% CI	(16.6, 37.2)	(0.0, 9.5)		(58.5, 76.9)
Best overall skin lesion response – %				
Complete clinical response	0	0		0.9
Partial response	26.0	0		67.3
Stable disease	71.4	97.3		27.1
Progressive disease	0	0		0
Not evaluable	2.6	2.7		4.7

[1] *Complete clinical response or partial response*

[2] *Per investigator*

[3] *Skin lesion response was determined for the 114 patients with ≥ 1 skin lesion at baseline.*

[4] *Skin lesion response was defined as ≥ 50% improvement in appearance of skin lesions by Physician's Global Assessment of Clinical Condition.*

[5] *Primary analysis for double blind period*

[6] *Final analysis includes patients who crossed over from the placebo group; median duration of exposure to everolimus of 204.1 weeks*

In an exploratory analysis of patients with TSC with angiomyolipoma who also had SEGA, the SEGA response rate (proportion of patients with ≥50% reduction from baseline in target lesion volumes in the absence of progression) was 10.3% (4/39) in the everolimus arm at the primary analysis (versus no responses reported in the 13 patients randomized to placebo with a SEGA lesion at baseline) and increased to 48.0% (24/50) at the final analysis.

In EXIST-2, 12 of 16 evaluable patients evaluated for angiomyolipoma volume for up to 1 year after discontinuation of everolimus, experienced an increase in tumor volume compared to their most recent tumor volume assessment performed before treatment discontinuation; though the angiomyolipoma volume did not exceed that measured at baseline. Two of 16 evaluable patients developed protocol-defined angiomyolipoma progression by virtue of angiomyolipoma-related bleeding (n=1) and increase in kidney volume (n=1). These findings suggest that persistence of clinically significant angiomyolipoma volume reduction requires ongoing treatment in most patients.

TSC with SEGA

Phase III trial in patients with TSC who have SEGA

EXIST-1 (Study CRAD001M2301), a randomized, double-blind, multicenter phase III study of Afinitor versus placebo was conducted in patients with TSC who have SEGA, irrespective of age. Patients were randomised in a 2:1 ratio to receive either Afinitor or matching placebo. Presence of at least one SEGA lesion ≥ 1.0 cm in longest diameter using MRI (based on local radiology assessment) was required for entry. In addition, serial radiological evidence of SEGA growth, presence of a new SEGA lesion ≥ 1 cm in longest diameter, or new or worsening hydrocephalus was required for entry.

The primary efficacy endpoint was SEGA response rate based on independent central radiology review. The analysis was stratified by use of enzyme-inducing antiepileptic drugs (EIAEDs) at randomisation (yes/no).

Key secondary endpoints in hierarchal order of testing included the absolute change in frequency of total seizure events per 24-hour EEG from baseline to Week 24, time to SEGA progression, and skin lesion response rate. Angiomyolipoma response rate was evaluated as an exploratory analysis.

A total of 117 patients were randomised, 78 to Afinitor and 39 to placebo. The two treatment arms were generally well balanced with respect to demographic and baseline disease characteristics and history of prior anti-SEGA therapies. Median age was 9.5 years (range: 0.8 to 26.6; 69.2% were 3 to < 18 years at enrolment; 17.1% were < 3 years at enrolment), 57.3% were male, and 93.2% were Caucasian. Of the enrolled patients, 79.5% had bilateral SEGAs,

42.7% had ≥ 2 target SEGA lesions, 25.6% had inferior growth, 9.4% had evidence of deep parenchymal invasion, 6.8% had radiographic evidence of hydrocephalus, and 6.8% had undergone prior SEGA-related surgery; 94.0% had skin lesions at baseline and 37.6% had target renal angiomyolipoma lesions (at least one angiomyolipoma ≥ 1 cm in longest diameter). The median duration of blinded study treatment was 9.6 months (range: 5.5 to 18.1) for patients receiving Afinitor and 8.3 months (range: 3.2 to 18.3) for those receiving placebo.

Results showed that Afinitor was superior to placebo for the primary endpoint of best overall SEGA response ($p<0.0001$). Response rates were 34.6% (95% CI: 24.2, 46.2) for the Afinitor arm compared with 0% (95% CI: 0.0, 9.0) for the placebo arm. In addition, all 8 patients on the Afinitor arm who had radiographic evidence of hydrocephalus at baseline had a decrease in ventricular volume.

Patients initially treated with placebo were allowed to cross over to everolimus at the time of SEGA progression and upon recognition that treatment with everolimus was superior to treatment with placebo. All patients receiving at least one dose of everolimus were followed until drug discontinuation or study completion. At the time of final analysis, the median duration of exposure to everolimus among all such patients was 204.9 weeks (range 8.1 to 253.7). The best overall SEGA response rate had increased to 57.7% (95% CI: 47.9, 67.0) at the final analysis.

No patient required surgical intervention for SEGA during the entire course of the study.

Table 14 EXIST-1 – SEGA response

	Primary Analysis[3]			Final analysis[4]
	Afinitor N=79	**Placebo N=39**	**p-value**	**Afinitor N=112**
Angiomyolipoma response rate[1,2] - %	**41.8**	**0**	**<0.0001**	**58.0** (48.3, 67.3)
95% CI	(30.8, 53.4)	(0.0, 9.0)		
Best overall angiomyolipoma response - %				
Response	41.8	0		58.0
Stable disease	40.5	79.5		30.4
Progression	1.3	5.1		0.9
Not evaluable	16.5	15.4		10.7

[1] *Per independent central radiology review*

[2] *Angiomyolipoma responses were confirmed with a repeat scan. Response was defined as: ≥ 50% reduction in the sum of angiomyolipoma volume relative to baseline, plus absence of new angiomyolipoma ≥ 1.0 cm in longest diameter, plus no increases in renal volume > 20% from nadir, plus absence of Grade ≥ 2 angiomyolipoma-related bleeding.*

[3] *Primary analysis for double blind period*

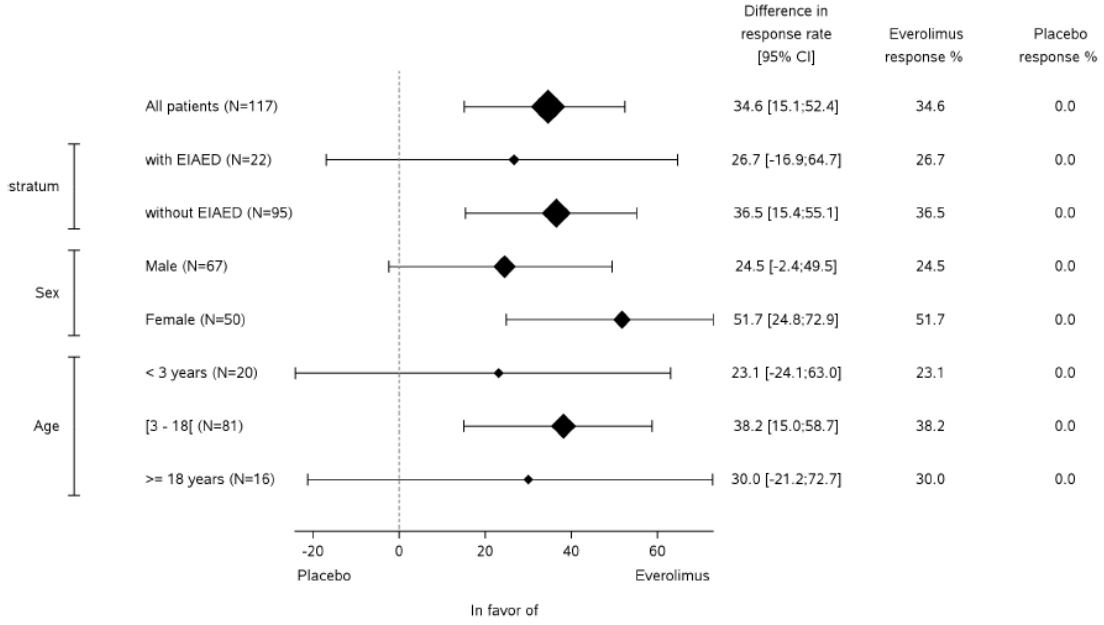
[4] *Final analysis includes patients who crossed over from the placebo group; median duration of exposure to everolimus of 204.1 weeks*

Consistent treatment effects were observed across all subgroups evaluated (i.e., EIAED use vs. EIAED non-use, sex, and age) at the primary analysis (Table 15, Figure 23)

Table 15 EXIST-1 - SEGA response by subgroup at the primary analysis

Subgroup	Afinitor		Placebo		Difference in response rates (95% CI)
	N	Responders %	N	Responders %	
All patients	78	34.6	39	0	34.6 (15.1, 52.4)
Modified strata					
EIAED use	15	26.7	7	0	26.7 (-16.9, 64.7)
No EIAED use	63	36.5	32	0	36.5 (15.4, 55.1)
Sex					
Male	49	24.5	18	0	24.5 (-2.4, 49.5)
Female	29	51.7	21	0	51.7 (24.8, 72.9)
Age					
<3 years	13	23.1	7	0	23.1 (-24.1, 63.0)
3-<18 years	55	38.2	26	0	38.2 (15.0, 58.7)
≥18 years	10	30.0	6	0	30.0 (-21.2, 72.7)

Figure 23 EXIST-1 - Forest plot of SEGA response by subgroup at the primary analysis



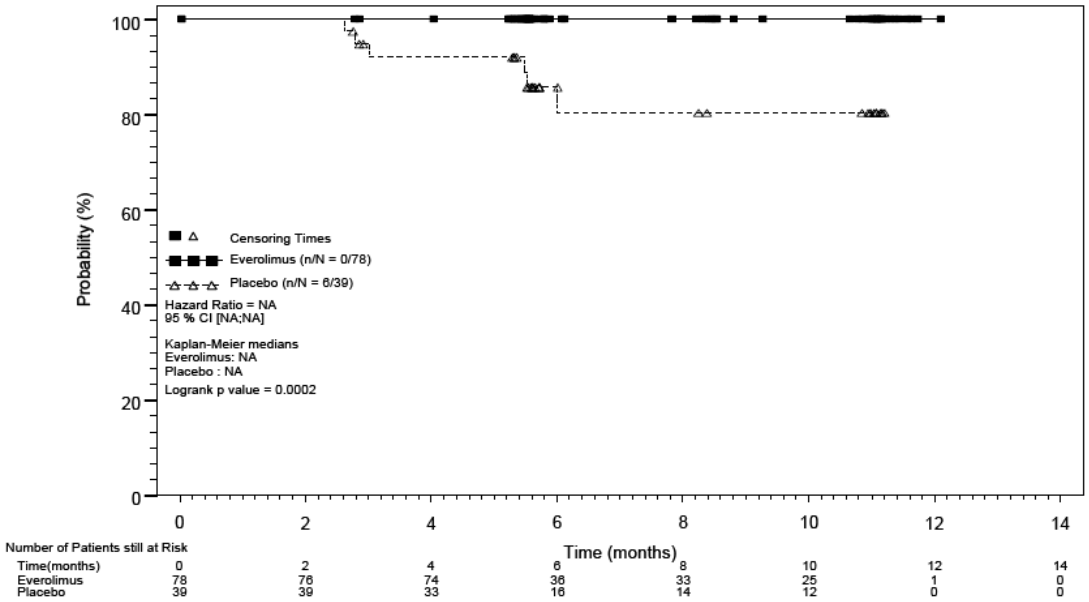
During the double-blind period, reduction of SEGA volume was evident within the initial 12 weeks of treatment with Afinitor: 29.7% (22/74) of patients had ≥50% reductions in volume and 73.0% (54/74) of patients had ≥30% reductions in volume. Sustained reductions were evident at Week 24, 41.9% (31/74) of patients had ≥50% reductions and 78.4% (58/74) of patients had ≥30% reductions in SEGA volume.

In the everolimus treated population (N=111) of the study, including patients who crossed over from the placebo group, tumor response, starting as early as after 12 weeks on everolimus, was sustained at later time points. The proportion of patients achieving at least 50% reductions in SEGA volume was 45.9% (45/98) and 62.1% (41/66) at Weeks 96 and 192 after start of everolimus treatment. Similarly, the proportion of patients achieving at least 30% reductions in SEGA volume was 71.4% (70/98) and 77.3% (51/66) at Weeks 96 and 192 after start of everolimus treatment.

Analysis of the first key secondary endpoint, change in seizure frequency, was inconclusive.

Median time to SEGA progression based on central radiology review was not reached in either treatment arm. Progressions were only observed in the placebo arm (15.4%; unadjusted p=0.0002) (Figure 18. Estimated progression-free rates at 6 months were 100% for the Afinitor arm and 85.7% for the placebo arm. The long-term follow up of patients randomized to everolimus and patients randomized to placebo who thereafter crossed over to everolimus demonstrated durable responses (see Figure 25).

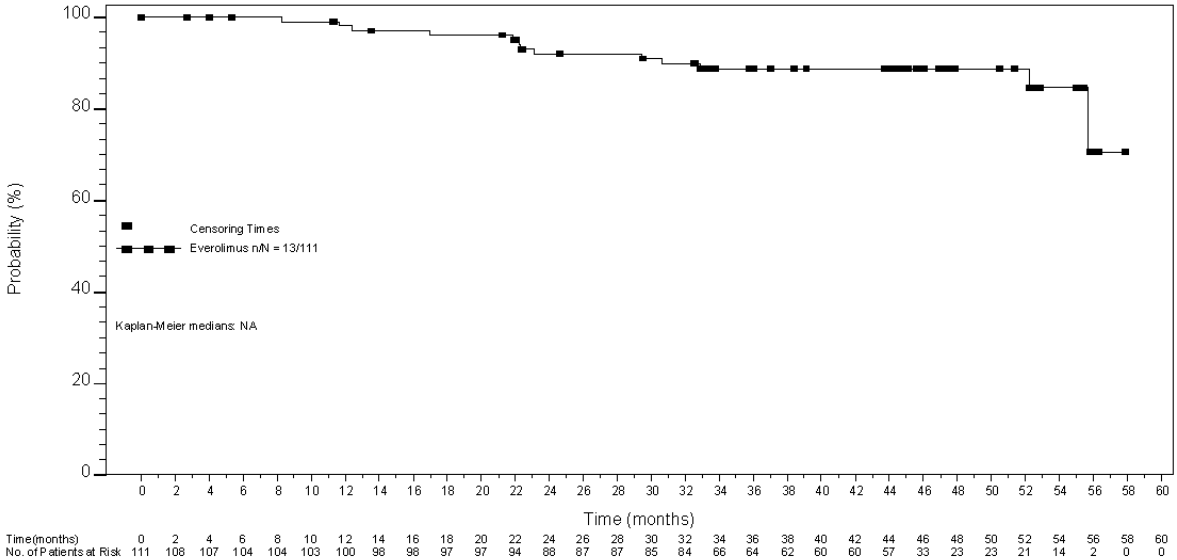
Figure 24 EXIST-1 - Kaplan-Meier plot of time to SEGA progression[1,2] at primary analysis



[1] Per independent central radiology review

[2] SEGA progression was defined as: ≥ 25% increase in the sum of SEGA volume relative to baseline, or unequivocal worsening of non-target SEGA lesions, or appearance of new SEGA ≥ 1.0 cm in longest diameter, or new or worsening hydrocephalus

Figure 25 EXIST-1 Kaplan-Meier plot of time to SEGA progression[1,2] at final analysis



[1] Per independent central radiology review

[2] SEGA progression was defined as: ≥ 25% increase in the sum of SEGA volume relative to baseline, or unequivocal worsening of non-target SEGA lesions, or appearance of new SEGA ≥ 1.0 cm in longest diameter, or new or worsening hydrocephalus

Additional clinical benefits of Afinitor were observed such as reductions in severity of skin lesions and size of renal angiomyolipoma.

At the time of the primary analysis, Afinitor demonstrated clinically meaningful improvements in skin lesion response (unadjusted p=0.0004), with response rates of 41.7% (95% CI: 30.2, 53.9) for the Afinitor arm and 10.5% (95% CI: 2.9, 24.8) for the placebo arm At the final analysis, the skin lesion response rate increased to 58.1% (95% CI: 48.1, 67.7) (see Table 16).

Table 16 EXIST-1 - best overall skin lesion response

	Primary analysis[5]			Final analysis[6]
	Afinitor N=72	**Placebo N=38**	**p-value**	**Afinitor N=105**
Skin lesion response rate[1,2,3,4] - %	41.7	10.5	0.0004	58.1
95% CI	(30.2, 53.9)	(2.9, 24.8)		(48.1, 67.7)
Best overall skin lesion response - %				
Complete clinical response	0	0		8.6
Partial response	41.7	10.5		49.5
Stable disease	58.3	86.8		40.0
Progression	0	0		0
Not evaluable	0	2.6		1.9

[1] *Complete clinical response or partial response*

[2] *Per investigator*

[3] *Skin lesion response was determined for patients with ≥ 1 skin lesion at baseline.*

[4] *Skin lesion response was defined as ≥ 50% improvement in appearance of skin lesions by Physician's Global Assessment of Clinical Condition.*

[5] *Primary analysis for double blind period*

[6] *Final analysis includes patients who crossed over from the placebo group; median duration of exposure to everolimus of 204.9 weeks*

At the time of the primary analysis, angiomyolipoma responses were only observed in the everolimus arm (n/N:16/30; 53.3%; 95% CI: 34.3, 71.7). At the time of final analysis, among the 41 TSC-SEGA patients with an angiomyolipoma lesion(s) present at start of treatment with everolimus, 30 patients (73.2%; 95% CI: 57.1, 85.8) achieved, as their best overall response, at least a 50% reduction in sum of angiomyolipoma volumes. Among the 37 patients with evaluable angiomyolipoma tumor assessments, 35 patients (94.6%) experienced a reduction in the sum of target angiomyolipoma volumes relative to baseline as their best percentage change. Over the entire duration of the study, no new angiomyolipoma lesions were observed, nor were instances of grade 2 or worse bleeding episodes reported.

Phase II trial in patients with TSC who have SEGA

A prospective, open-label, phase II study was conducted to evaluate the safety and efficacy of Afinitor in patients with SEGA. Serial radiological evidence of SEGA growth was required for entry.

Change in SEGA volume during the core 6-month treatment phase, as assessed via an independent central radiology review, was the primary efficacy endpoint. After the core treatment phase, patients could enter into the extension treatment phase where SEGA volume was assessed every 6 months.

In total, 28 patients received treatment with Afinitor; median age was 11 years (range 3 to 34), 61% male, 86% Caucasian. Thirteen patients (46%) had a secondary smaller SEGA including 12 patients with SEGA in the contralateral ventricle. Median duration of exposure was 67.8 months (range: 4.7 – 83.2 months).

Afinitor was associated with a clinically relevant and statistically significant reduction in primary SEGA volume at 6 months relative to baseline (median reduction of 0.80 cm^3; 95% CI: 0.4, 1.2; n=28; p<0.001). Tumour shrinkage was most rapid during the initial 3 months of treatment with evidence of a sustained response at subsequent timepoints (see Table 16). No patient developed new lesions, worsening hydrocephalus, increased intracranial pressure, and none required surgical resection or other therapy for SEGA.

Table 17 C2485 - Response of primary SEGA lesion to Afinitor therapy

SEGA volume (cm3)	Independent central review								
	Baseline N=28	**Month 3 N=26**	**Month 6 N=27**	**Month 12 N=26**	**Month 24 N=24**	**Month 36 N=23**	**Month 48 N=24**	**Month 60 N=23**	**Month 72 N=8**
Primary tumor volume									
Mean (standard deviation)	2.45 (2.813)	1.47 (1.646)	1.33 (1.497)	1.26 (1.526)	1.19 (1.042)	1.26 (1.298)	1.16 (0.961)	1.24 (0.959)	1.24 (1.004)
Median	1.74	0.84	0.93	0.84	0.94	1.12	1.02	1.17	0.81
Range	0.49 - 14.23	0.25 - 8.32	0.31 - 7.98	0.29 - 8.18	0.20 - 4.63	0.22 - 6.52	0.18 - 4.19	0.21 – 4.39	0.35 – 2.94
Reduction from baseline									
Mean (standard deviation)		1.08 (1.338)	1.19 (1.433)	1.07 (1.276)	1.25 (1.994)	1.41 (1.814)	1.43 (2.267)	1.44 (2.230)	1.80 (1.816)
Median		0.63	0.83	0.85	0.71	0.71	0.83	0.50	1.32
Range		-0.12 - 5.91	0.06 - 6.25	0.02 - 6.05	-0.55 - 9.60	0.15 - 7.71	0.00 - 10.96	-0.74 - 9.84	0.09 – 4.51
Percentage reduction from baseline, n (%)									
≥ 50%		10 (38.5)	9 (33.3)	9 (34.6)	12 (50.0)	10 (43.5)	14 (58.3)	12 (52.2)	4 (50.0)
≥ 30%		17 (65.4)	21 (77.8)	20 (76.9)	19 (79.2)	18 (78.3)	19 (79.2)	14 (60.9)	6 (75.0)
> 0%		25 (96.2)	27 (100.0)	26 (100.0)	23 (95.8)	23 (100.0)	23 (95.8)	21 (91.3)	8 (100.0)
No change		0	0	0	0	0	1 (4.2)	0	0
%Increase		1 (3.8)	0	0	1 (4.2)	0	0	2 (8.7)	0

The primary analysis was supported by the:

- Change in primary SEGA volume as per local investigator assessment ($p<0.001$), with 75% and 39% of patients experiencing reductions of ≥ 30% and ≥ 50%, respectively
- Change in total SEGA volume as per independent central review ($p<0.001$) or local investigator assessment ($p<0.001$)

One patient met the prespecified criteria for treatment success (> 75% reduction in SEGA volume) and was temporarily taken off trial therapy; however, SEGA re-growth was evident within 3 months and treatment was restarted.

Long-term follow-up to a median duration of 34.2 months (range: 4.7 to 47.1) demonstrated sustained efficacy with a median reduction in primary SEGA volume per independent central review of 0.50 cm^3 at Month 60 (range: -0.74 to 9.84 cm^3; n=23).

Non-clinical safety data

The pre-clinical 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; 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 juvenile rat toxicity studies at doses as low as 0.15 mg/kg/day, systemic toxicity included decreased body weight gain and food consumption, and delayed attainment of some developmental landmarks at all doses, with full or partial recovery after cessation of dosing[1]. With the possible exception of the rat-specific lens finding (where young animals appeared to be more susceptible[2], it appears that there is no significant difference in the sensitivity of juvenile animals to the adverse effects of everolimus as compared to adult animals at doses of 0.5 to 5 mg/kg per day. No relevant toxicity was evident in juvenile monkeys at doses up to 0.5 mg/kg/day for 4-weeks[3].

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 from a 10 mg daily dose.

Pharmaceutical information

Incompatibilities

Not applicable.

Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from light and moisture.
Keep out of the reach and sight of children.

Shelf life

The expiry date is indicated on the packaging.

Instructions for use and handling

No special requirements.

Package

Box, 3 blisters @ 10 tablets

Reg. No.:

DKI1067507810A1 (5 mg tablet)
DKI1067507810B1 (10 mg tablet)

HARUS DENGAN RESEP DOKTER
To be dispensed only on the prescription of a physician.

Manufactured by Novartis Pharma Stein AG, Stein, Switzerland for Novartis Pharma AG, Basel, Switzerland. Imported by PT Novartis Indonesia, Jakarta, Indonesia.

Leafet based on the latest CDS version released date: 27-Mar-2017

* *Disclaimer: Afinitor 2.5 mg tablet is not registered and marketed in Indonesia*

Disetujui oleh BPOM: 15/01/2021 ID REG: 218243728; 218243730

AFINITOR® (everolimus)

Tablet: 2.5 mg*, 5 mg dan 10 mg

Patient Information Leaflet

** Disclaimer: For Afinitor 2.5 mg tablet is not registered and marketed in Indonesia*

Disetujui oleh BPOM: 15/01/2021 ID REG: 218243728; 218243730

Mohon dibaca leaflet ini dengan hati-hati sebelum menggunakan obat

Simpan leaflet ini. Anda mungkin akan membutuhkannya untuk dibaca kembali.

Jika ada memiliki pertanyaan terkait dengan obat ini, mohon tanyakan kepada dokter, apoteker atau tenaga profesional kesehatan Anda.

Obat ini diresepkan untuk Anda. Mohon jangan menggunakan obat ini untuk mengobati penyakit lain; jangan memberikan obat ini kepada orang lain. Ini dapat membahayakan mereka, bahkan jika yang penyakitnya sama dengan penyakit Anda.

Jika terjadi efek samping yang berat, atau Anda mengetahui adanya efek samping yang tidak disebutkan dalam leaflet ini, mohon informasikan kepada dokter, apoteker atau tenaga profesional kesehatan Anda.

Daftar isi

1 Apakah AFINITOR® dan apa kegunaannya

Apakah AFINITOR®

AFINITOR adalah obat antitumor yang dapat menghambat pertumbuhan sel-sel tertentu. AFINITOR mengandung zat aktif yang disebut everolimus. AFINITOR dapat digunakan untuk mengobati beberapa jenis kanker dan sejumlah massa tak-ganas yang berhubungan dengan gangguan genetik yang disebut sebagai *tuberous sclerosis* atau *tuberous sclerosis complex (TSC)*.

Apakah kegunaan AFINITOR

Dokter Anda dapat meresepkan tablet AFINITOR untuk pengobatan:

- Karsinoma sel ginjal tahap lanjut setelah mengalami kegagalan pengobatan dengan menggunakan sunitinib atau sorafenib.

- Tumor neuroendokrin stadium lanjut pada pankreas *(neuroendocrine tumors of pancreatic origin, PNET)*

  Afinitor diindikasikan untuk pengobatan pasien dengan tumor neuroendokrin progresif pada pankreas *(PNET)* stadium lanjut atau metastatik yang tidak dapat dioperasi. Keamanan dan efektivitas AFINITOR pada pengobatan pasien dengan tumor karsinoid belum diketahui.

- Tumor neuroendokrin stadium lanjut pada saluran pencernaan atau paru-paru *(Neuroendocrine Tumors of Gastrointestinal (GI) or Lung Origin)*
  AFINITOR® diindikasikan untuk pengobatan tumor neuroendokrin yang tidak dapat dioperasi atau metastatik, terdiferensiasi dengan baik (grade 1 atau 2), penyakit progresif dari non-fungsional saluran pencernaan atau paru-paru pada orang dewasa.

- *Tuberus Sclerosis Complex (TSC)* dengan *subependymal giant cell astrocytoma* (SEGA, tumor otak yang spesifik) yang memerlukan intervensi terapeutik namun tidak bisa disembuhkan dengan reseksi.

  AFINITOR diindikasikan untuk pengobatan pasien (usia 3 – 18 tahun) dengan SEGA yang diasosiasikan dengan TSC yang memerlukan intervensi terapi tetapi bukan merupakan kandidat untuk tindakan operasi. Efektifitas AFINITOR didasarkan pada análisis perubahan volumen SEGA. Keuntungan klinis seperti perbaikan dalam gejala terkait penyakit atau peningkatan pada kelangsungan hidup secara keseluruhan belum diketahui.

- Wanita paska menopause yang mengalami kanker payudara hormon reseptor-positif tahap lanjut, yang mana pengobatan dikombinasikan dengan inhibitor aromatase setelah sebelumnya menjalani terapi endokrin seperti letrozole atau anastrozole.

- TSC dengan angiomyolipoma pada ginjal (tumor ginjal) yang tidak memerlukan tindakan operasi segera.

Afinitor tidak boleh digunakan bersamaan dengan *enzyme inducing antiepileptic drug.*

Bagaimana cara kerja AFINITOR

Zat aktif yang terkandung dalam obat AFINITOR adalah everolimus.

Pengobatan pada wanita paska menopause yang mengalami kanker payudara hormon reseptor-positif tahap lanjut

Perkembangan dari jenis kanker payudara ini distimulasi oleh estrogen yang merupakan hormone seks wanita. Inhibitor aromatase mengurangi jumlah estrogen sehingga dapat memperlambat perkembangan kanker payudara. Menggunakan AFINITOR bersamaan dengan suatu inhibitor aromatase dapat mencegah resistensi sel kanker payudara terhadap terapi hormonal, sehingga dapat mengurangi perkembangan kanker payudara dan memperlambat terjadinya kekambuhan kanker payudara.

Pengobatan tumor neuroendokrin tahap lanjut pada pankreas

Tumor neuroendokrin merupakan tumor yang jarang yang dapat ditemukan pada bagian tubuh yang berbeda-beda. AFINITOR dapat mengkontrol perkembangan tumor yang berada pada lambung dan usus, paru-paru atau pankreas.

Pengobatan karsinoma sel ginjal tahap lanjut

AFINITOR dapat menghentikan pembentukan sel kanker baru dan menghentikan suplai darah ke sel kanker. Hal ini dapat memperlambat perkembangan dan penyebaran kanker ginjal.

Pengobatan TSC dengan angiomyolipoma pada ginjal

AFINITOR dapat mengurangi ukuran angiomyolipoma pada ginjal yang disebabkan oleh gangguan genetik yang disebut TSC, sehingga dapat menurunkan resiko komplikasi pendarahan yang disebabkan oleh tumor dan membantu melindungi fungsi ginjal.

Pengobatan TSC dengan SEGA

AFINITOR dapat mengurangi ukuran tumor otak (SEGAs) yang disebabkan oleh gangguan genetik yang disebut TSC, sehingga dapat menurunkan resiko yang ditimbulkan karena perkembangan tumor tersebut, seperti hidrosefalus (akumulasi secara eksesif dari cairan didalam otak).

Pengawasan selama pengobatan dengan AFINITOR

Pemeriksaan darah akan dilakukan secara regular selama pengobatan. Hal ini dilakukan untuk memonitor jumlah sel darah (sel darah putih, sel darah merah dan trombosit) pada tubuh Anda untuk melihat apakah AFINITOR memberikan efek yang tidak diinginkan terhadap sel darah tersebut. Pemeriksaan darah juga dilakukan untuk memonitor fungsi ginjal (kadar kreatinin, nitrogen urea darah atau protein urin), fungsi hati (kadar transaminase) dan gula darah serta kadar lemak, karena hal ini juga merupakan efek yang dapat ditimbulkan oleh AFINITOR.

Jika Anda diberikan obat AFINITOR untuk pengobatan TSC dengan SEGA, pemeriksaan darah secara reguler penting dilakukan untuk mengukur kadar AFINITOR dalam darah sehingga dapat membantu dokter Anda dalam menentukan dosis AFINITOR yang akan Anda gunakan.

Jika Anda memiliki pertanyaan mengapa AFINITOR diresepkan untuk Anda, mohon tanyakan pada dokter Anda.

2 Apa yang harus diketahui sebelum dan selama menggunakan AFINITOR

Mohon agar mengikuti instruksi dari dokter dengan hati-hati karena instruksi tersebut dapat berbeda dari informasi umum yang terdapat dalam brosur ini.

AFINITOR hanya akan diresepkan oleh dokter Anda jika Anda pernah menggunakan terapi antikanker sebelumnya atau untuk pengobatan TSC.

AFINITOR dapat meningkatkan risiko untuk masalah penyembuhan luka. Oleh karena itu, Anda harus memberitahukan dokter Anda jika Anda ingin menjalani operasi, jika Anda menjalani operasi baru-baru ini, atau jika Anda masih memiliki luka yang belum sembuh pasca operasi.

Jangan menggunakan AFINITOR

- **Jika Anda alergi** (hipersensitif) terhadap everolimus, obat yang sejenis dengan everolimus seperti sirolimus (rapamisin), temsirolimus, atau zat tambahan lain dari AFINITOR yang tertulis pada bagian akhir brosur ini.

Jika hal ini terjadi pada Anda, **mohon beritahukan kepada dokter Anda untuk tidak memberikan AFINITOR.**

Jika Anda kemungkinan alergi, mohon untuk meminta saran kepada dokter Anda.

Perhatian dalam menggunakan AFINITOR

Jika hal-hal dibawah terjadi pada Anda, **mohon beritahukan kepada dokter Anda sebelum menggunakan AFINITOR**:

- Jika Anda memiliki masalah dengan hati atau sebelumnya pernah mengalami penyakit yang dapat berpengaruh terhadap hati Anda. Modifikasi dosis AFINITOR yang Anda gunakan mungkin diperlukan.
- Jika Anda memiliki penyakit diabetes (kadar gula yang tinggi dalam darah).
- Jika Anda mengalami infeksi. Penting untuk mengobati infeksi Anda terlebih dahulu sebelum memulai pengobatan dengan AFINITOR.
- Jika sebelumnya Anda pernah memiliki penyakit hepatitis B, karena hepatitis B tersebut dapat tereaktivasi selama pengobatan menggunakan AFINITOR (lihat bagian “Kemungkinan efek samping”).
- Jika Anda sedang menggunakan obat-obatan lain (lihat bagian “Penggunaan obat lain”).
- Jika Anda sedang hamil, atau kemungkinan hamil atau kemungkinan dapat mengalami kehamilan selama pengobatan dengan AFINITOR (lihat bagian “Kehamilan”).
- Jika Anda sedang menyusui (lihat bagian “Menyusui”).
- Jika Anda dijadwalkan untuk menjalani vaksinasi.

Apa yang harus Anda ketahui selama pengobatan dengan AFINITOR

- **Gangguan paru atau pernafasan:** Pasien dapat mengalami gangguan paru atau pernafasan, seperti pneumonitis, emboli paru atau sindrom distress pernafasan akut. **Mohon segera beritahukan kepada dokter Anda** jika Anda mengalami gejala gangguan atau perburukan paru/pernafasan seperti batuk, nyeri dada atau nafas pendek, karena gangguan paru atau pernafasan dapat membahayakan Anda. Dokter Anda mungkin dapat menginterupsi atau menghentikan pengobatan dengan AFINITOR, dan memberikan tambahan obat lain untuk mengatasi efek samping ini. Dokter Anda dapat memulai kembali pengobatan menggunakan AFINITOR dengan dosis yang lebih rendah.
- **Infeksi**: AFINITOR dapat menyebabkan Anda lebih mudah mengalami infeksi (seperti pneumonia, infeksi saluran kemih, infeksi jamur, atau infeksi virus seperti reaktivasi hepatitis B). Beberapa infeksi dapat menjadi berat sehingga dapat membahayakan Anda. Beberapa infeksi dapat menjadi berat sehingga dapat membahayakan pada orang dewasa dan anak-anak. **Mohon segera beritahukan kepada dokter Anda** jika Anda mengalami gejala infeksi. Dokter Anda

mungkin dapat menginterupsi atau menghentikan pengobatan dengan AFINITOR, dan memberikan tambahan obat lain untuk mengatasi efek samping ini.

- **Lesi pada mulut:** Pasien dapat mengalami lesi dan luka pada mulut. **Mohon beritahukan kepada dokter Anda** jika Anda mengalami sakit atau rasa tidak nyaman pada mulut atau memiliki luka terbuka pada mulut. Dokter Anda mungkin dapat menginterupsi atau menghentikan pengobatan dengan AFINITOR. Anda mungkin memerlukan pengobatan dengan larutan pembersih mulut *(mouthwash)*, gel, atau produk lainnya. Akan tetapi, beberapa gel atau pembersih mulut dapat memperburuk lesi Anda, oleh karena itu mohon untuk tidak mencoba apapun sebelum berkonsultasi dengan dokter Anda terlebih dahulu. Dokter Anda dapat memulai kembali pengobatan menggunakan AFINITOR dengan dosis yang sama atau yang lebih rendah.
- **Reaksi alergi:** Jika selama pengobatan dengan AFINITOR anda mengalami gejala seperti pembengkakan pada lidah atau saluran pernafasan dan/atau kesulitan bernafas, ini kemungkinan merupakan gejala alergi serius. Dalam hal ini, mohon segera hubungi dokter Anda.
- **Gangguan ginjal:** Kegagalan ginjal dapat terjadi pada pasien yang menggunakan AFINITOR. Kegagalan ginjal tersebut dapat menjadi serius dan membahayakan Anda. Dokter Anda akan memonitor fungsi ginjal Anda selama pengobatan dengan AFINITOR.
- **Vaksinasi:** Jika Anda kemungkinan akan menjalani vaksinasi selama pengobatan dengan AFINITOR, mohon agar meminta saran kepada dokter Anda terlebih dahulu. Untuk pasien anak-anak dengan TSC, mohon untuk melengkapi rangkaian vaksinasi yang direkomendasikan sesuai dengan pedoman pengobatan setempat sebelum memulai terapi AFINITOR.

Penggunaan obat-obatan lain

AFINITOR dapat berinteraksi dengan beberapa obat lain, sehingga mungkin diperlukan untuk memodifikasi dosis AFINITOR.

Mohon beritahukan kepada dokter, apoteker atau tenaga profesional kesehatan Anda sebelum menggunakan AFINITOR, jika Anda sedang menggunakan atau baru saja menggunakan obat-obatan lain, termasuk menggunakan obat-obatan tanpa resep, sebagai berikut:

- Beberapa obat-obatan yang digunakan untuk pengobatan infeksi, termasuk pengobatan penyakit jamur (antijamur seperti ketokonazol, itrakonazol, atau flukonazol), atau obat-obatan yang digunakan untuk mengobati infeksi bakteri (antibiotik seperti klaritromisin, telitromisin, atau eritromisin)
- Beberapa obat-obatan yang digunakan untuk mengobati penyakit tuberkulosis seperti rifampisin atau rifabutin
- St. John's Wort – produk herbal yang digunakan untuk mengobati depresi dan kondisi lainnya (juga diketahui sebagai *Hypericum Perforatum*)
- Beberapa kortikosteroid seperti deksametason, prednison, atau prednisolon
- Obat-obatan untuk mengatasi kejang (antiepilepsi seperti fenitoin, karbamazepin, atau fenobarbital)
- Beberapa obat-obatan yang digunakan untuk mengobati AIDS/HIV seperti ritonavir, amprenavir, fosamprenavir, efavirenz, atau nevirapin
- Beberapa obat-obatan yang digunakan untuk mengobati kondisi jantung atau tekanan darah tinggi (penghambat chanel kalsium seperti verapamil atau diltiazem)
- Siklosporin, obat yang digunakan untuk mengatasi reaksi penolakan tubuh terhadap organ

transplantasi

- Aprepitant, obat yang digunakan untuk mencegah mual dan muntah
- midazolam, obat yang digunakan untuk mengatasi kejang akut, atau digunakan sebagai sedatif sebelum atau selama menjalani operasi atau suatu prosedur medis.

Obat-obatan diatas sebaiknya dihindari selama pengobatan dengan AFINITOR. Jika Anda sedang menggunakan salah satu dari obat-obatan diatas, dokter Anda mungkin dapat meresepkan obat lain untuk menghentikan efek samping akibat penggunaan kombinasi obat-obat tersebut dengan AFINITOR. Untuk pasien dengan SEGA yang sedang menggunakan pengobatan anti kejang, perubahan dosis obat anti kejang yang digunakan (naik atau turun) mungkin harus diikuti dengan perubahan dosis AFINITOR.

Jika Anda sedang menggunakan pengobatan dengan AFINITOR, Anda tidak diperbolehkan memulai penggunaan obat baru yang lain tanpa terlebih dahulu meminta saran kepada dokter yang meresepkan AFINITOR. Obat-obatan baru yang dimaksud ini mencakup obat dengan resep, obat tanpa resep (OTC) dan obat herbal atau alternatif.

Penggunaan AFINITOR bersamaan dengan makanan atau minuman

Pengobatan menggunakan AFINITOR setiap hari sebaiknya dilakukan pada saat yang sama, baik bersamaan ataupun tanpa makanan. Mohon untuk tidak meminum jus atau memakan buah ***grapefruit* (sejenis jeruk), belimbing atau jeruk Seville.** Buah-buahan tersebut dapat meningkatkan kadar AFINITOR dalam darah, sehingga dapat mencapai kadar yang membahayakan.

Pasien usia lanjut **(usia 65 tahun ke atas)**

Jika Anda berusia 65 tahun keatas, Anda dapat menggunakan AFINITOR dengan dosis yang sama dengan pasien dewasa.

Pasien anak-anak atau remaja (di bawah usia 18 tahun)

Pengobatan kanker payudara hormon reseptor-positif tahap lanjut, neurokendokrin tumor tahap lanjut atau kanker ginjal tahap lanjut

AFINITOR tidak dapat digunakan pada anak-anak atau remaja.

Pengobatan TSC dengan angiomyolipoma pada ginjal

AFINITOR tidak dapat digunakan pada anak-anak atau remaja yang mengalami TSC dengan angiomyolipoma pada ginjal, jika tidak terdapat SEGA.

Pengobatan TSC dengan SEGA

AFINITOR dapat digunakan pada anak-anak atau remaja yang memiliki fungsi hati normal.

Kehamilan dan menyusui

Mohon tanyakan kepada dokter, apoteker atau tenaga profesional kesehatan Anda sebelum Anda menggunakan obat apapun. AFINITOR dapat membahayakan bayi dalam kandungan atau bayi yang sedang menyusui.

- AFINITOR tidak direkomendasikan penggunaannya selama kehamilan. Jika Anda sedang hamil atau kemungkinan hamil, mohon beritahukan kepada dokter Anda sehingga dokter Anda dapat menjelaskan potensi resiko penggunaan AFINITOR selama kehamilan.
- Menyusui tidak direkomendasikan selama pengobatan dengan AFINITOR dan dua minggu setelah dosis terakhir AFINITOR. Mohon beritahukan kepada dokter Anda jika Anda sedang dalam masa menyusui.

Wanita yang berpotensi untuk melahirkan dan pasien laki-laki

Anda harus menggunakan motode kontrasepsi yang efektif (seperti kondom atau pil) selama pengobatan dengan AFINITOR dan sampai dengan 8 bulan setelah pengobatan dihentikan. Jika Anda berpikir Anda tengah hamil, mohon agar meminta saran kepada dokter Anda sebelum melanjutkan penggunaan AFINITOR.

AFINITOR dapat berdampak pada kesuburan pria maupun wanita. Tidak terjadinya menstruasi pada wanita yang sebelumnya mengalami mestruasi amenore sekunder) pernah terlapor pada beberapa wanita yang menggunakan AFINITOR.

3 Bagaimana cara menggunakan AFINITOR

Mohon agar mengikuti petunjuk dokter dengan hati-hati. Mohon untuk tidak menggunakan obat lebih banyak dari yang disarankan oleh dokter Anda.

Berapa banyak penggunaan AFINITOR

Dokter Anda akan menjelaskan berapa banyak jumlah tablet AFINITOR yang Anda gunakan. Jangan mengubah dosis tanpa memberitahukan kepada dokter Anda.

Jika Anda sedang menggunakan AFINITOR untuk pengobatan TSC dengan SEGA, dokter Anda mungkin akan meresepkan AFINITOR tablet kepada Anda.

Jika Anda mengalami efek samping terkait dengan penggunaan AFINITOR, maka dokter Anda mungkin perlu untuk mengurangi dosis AFINITOR; atau menginterupsi atau menghentikan pengobatan Anda dengan AFINITOR.

Jangan menghentikan pengobatan dengan AFINITOR jika tidak disarankan oleh dokter Anda.

Pengobatan kanker payudara hormon reseptor-positif tahap lanjut, neurokendokrin tumor tahap lanjut, kanker ginjal tahap lanjut atau TSC dengan angiomyolipoma pada ginjal

Dosis penggunaan tablet AFINITOR adalah 10 mg, digunakan satu kali dalam sehari.

Dosis yang lebih tinggi maupun lebih rendah dapat direkomendasikan oleh dokter Anda berdasarkan kebutuhan pengobatan tiap individu, contohnya: jika Anda mengalami gangguan hati atau sedang menggunakan tambahan obat-obatan tertentu.

Pengobatan TSC dengan SEGA

Dokter Anda akan menentukan dosis tablet AFINITOR yang harus Anda gunakan berdasarkan berat badan Anda, kondisi kesehatan hati dan obat-obatan lain yang sedang Anda gunakan. Pemeriksaan darah penting dilakukan pada saat pengobatan dengan AFINITOR untuk mengukur kadar AFINITOR dalam darah Anda dan menentukan dosis harian yang tepat untuk Anda. Mohon agar mengikuti petunjuk dokter dengan hati-hati mengenai berapa banyak AFINITOR yang harus digunakan.

AFINITOR tidak dapat digunakan pada anak-anak dan remaja (dibawah 18 tahun) yang mengalami gangguan hati.

Kapan menggunakan AFINITOR

Mohon agar menggunakan AFINITOR satu kali dalam sehari, pada saat yang sama setiap hari. Penggunaan AFINITOR di waktu yang sama setiap hari sangat penting, sehingga dapat memberikan kadar obat yang stabil di dalam aliran darah.

Bagaimana cara menggunakan AFINITOR

Tablet AFINITOR

Tablets AFINITOR diminum melalui mulut.

Pengobatan menggunakan AFINITOR setiap hari sebaiknya dilakukan pada saat yang sama, baik bersamaan ataupun tanpa makanan.

Mohon untuk menelan tablet dengan menggunakan segelas air. Mohon untuk tidak mengunyah atau menggerus tablet.

Jika Anda menggunakan tablet AFINITOR untuk pengobatan TSC dengan SEGA namun Anda tidak dapat menelan tablet tersebut, Anda dapat melarutkan tablet dalam segelas air sebagai berikut:

- Letakkan tablet yang diinginkan ke dalam segelas air (yang berisi kira-kira 30 mL)
- Larutkan tablets secara perlahan dalam air sampai dengan tablet hancur (selama kira-kira 7 menit) dan minumlah dengan segera.

- Bilaslah gelas Anda dengan menggunakan sejumlah air yang sama (kira-kira 30 mL) dan minumlah kembali keseluruhan isi gelas tersebut untuk memastikan bahwa Anda mendapatkan dosis AFINITOR secara utuh.

Instruksi cara menggunakan tablet AFINITOR

Perawat disarankan agar tidak menyentuh langsung suspensi tablet AFINITOR. Cuci tangan dengan bersih pada saat sebelum dan setelah penyiapan suspensi.

Berapa lama menggunakan AFINITOR

Mohon untuk menggunakan AFINITOR selama dokter Anda menginstruksikannya.

Jika Anda menggunakan AFINITOR lebih dari seharusnya

Jika Anda menggunakan AFINITOR terlalu banyak, atau jika orang lain tidak sengaja menggunakan obat Anda, mohon segera hubungi dokter atau rumah sakit terdekat. Mohon untuk menunjukkan kemasan AFINITOR. Penanganan medis mungkin diperlukan.

Jika Anda terlupa menggunakan AFINITOR

Jika Anda terlupa menggunakan AFINITOR, Anda masih dapat menggunakannya sampai dengan 6 jam kedepan terhitung dari waktu Anda biasanya minum obat tersebut.

Jika waktu Anda teringat telah melewati 6 jam terhitung dari waktu Anda biasanya menggunakan AFINITOR, mohon agar melewatkan dosis untuk hari tersebut. Pada hari berikutnya, mohon agar menelan tablet di waktu Anda biasa menggunakannya. Mohon tidak menggunakan dosis ganda untuk menggantikan dosis yang terlupa.

4 Kemungkinan efek samping

Seperti halnya obat-obatan lain, pasien yang diterapi dengan AFINITOR dapat mengalami efek samping, walaupun belum tentu semua akan mengalaminya. AFINITOR juga dapat berdampak pada beberapa hasil pemeriksaan darah.

Mohon HENTIKAN penggunaan AFINITOR dan segera meminta pertolongan dokter jika Anda atau anak Anda mengalami tanda-tanda reaksi alergi sebagai berikut:

- sesak napas atau sulit menelan
- Pembengkakan pada wajah, bibir, lidah atau tenggorokan
- Rasa gatal hebat pada kulit beserta ruam atau timbul bintil-bintil kemerahan pada kulit

Beberapa efek samping yang dapat menjadi serius

Jika Anda mengalami efek samping dibawah ini, **mohon segera beritahukan kepada dokter Anda** karena mungkin akan dapat membahayakan Anda.

Efek samping serius yang terjadi selama pengobatan terhadap kanker payudara reseptor hormonal positif stadium lanjut, tumor neurokendokrin stadium lanjut, atau kanker ginjal stadium lanjut

Beberapa efek samping yang sangat sering terjadi

(Efek samping ini terjadi pada lebih dari 1 dari 10 orang)

- Terjadi peningkatan suhu badan atau menggigil (tanda-tanda infeksi)
- Letih, hilang nafsu makan, mual, ikterus (kulit menjadi kekuningan), atau nyeri pada bagian kanan atas abdomen, tinja berwarna pucat atau urin berwarna gelap (mungkin merupakan tanda-tanda reaktivasi Hepatitis B)
- Demam, batuk, sesak napas, mengi, tanda-tanda inflamasi paru (pneumonitis)

Beberapa efek samping yang sering terjadi

(Efek samping ini terjadi pada sampai dengan 1 dari 10 orang)

- Rasa haus berlebihan, sering berkemih, peningkatan nafsu makan namun disertai penurunan berat badan, kelelahan (diabetes)
- Perdarahan, misalnya pada dinding usus
- Jarang berkemih (jumlah urin menurun drastis), tanda-tanda gagal ginjal

Beberapa efek samping yang tidak begitu sering terjadi

(Efek samping ini terjadi pada sampai dengan 1 dari 100 orang)

- Napas terasa pendek, sesak napas ketika dalam posisi berbaring, pembengkakan pada kaki atau tungkai, tanda-tanda gagal jantung
- Ruam, gatal, biduran, sesak napas atau sulit menelan, pusing, tanda-tanda reaksi alergi yang serius (hipersensitivitas)
- Pembengkakan dan/atau nyeri pada kaki, biasanya pada bagian betis. Kulit kemerahan atau hangat, tanda-tanda penyumbatan pembuluh darah (vena) pada tungkai yang disebabkan karena pembekuan darah.
- Napas tiba-tiba terasa pendek, nyeri dada atau batuk darah, tanda-tanda yang bisa mengarah ke emboli paru (suatu kondisi yang terjadi ketika salah satu arteri atau lebih pada paru tersumbat)
- Penurunan jumlah pengeluaran urin secara berat, pembengkakan pada kaki, rasa nyeri pada punggung, tanda-tanda kegagalan ginjal mendadak (gagal ginjal akut)

Beberapa efek samping yang jarang terjadi

(Efek samping ini terjadi pada sampai dengan 1 dari 1000 orang)

- Napas terasa pendek atau cepat seperti terengah-engah (tanda-tanda sindrom distres pernapasan akut)
- Pembengkakan jalan napas atau lidah, dengan atau tanpa gangguan pernapasan (angioedema)

Efek samping serius yang terjadi selama pengobatan terhadap TSC

Beberapa efek samping yang sangat sering terjadi

(Efek samping ini terjadi pada lebih dari 1 dari 10 orang)

- Demam, batuk, sesak napas, mengi, tanda-tanda inflamasi paru (pneumonia)

Beberapa efek samping yang sering terjadi

(Efek samping ini terjadi pada sampai dengan 1 dari 10 orang)

- Pembengkakan, tubuh terasa berat atau tertekan, nyeri, bagian-bagian tubuh sulit digerakkan, tanda-tanda yang bisa mengarah ke adanya penumpukan cairan abnormal di jaringan lunak karena penyumbatan pada sistem limfatik *(limfedema)*
- Ruam, gatal, biduran, sesak napas atau sulit menelan, pusing, tanda-tanda reaksi alergi serius (hipersensitivitas)
- Demam, batuk, sesak napas, mengi (tanda-tanda inflamasi paru, dikenal sebagai pneumonitis)

Beberapa efek samping yang tidak begitu sering terjadi

(Efek samping ini terjadi pada sampai dengan 1 dari 100 orang)

- Ruam berupa lepuh kecil-kecil berisi cairan, tampak di atas kulit yang kemerahan, tanda-tanda infeksi virus yang dapat menjadi berat (herpes zoster atau “cacar ular”)
- Pembengkakan jalan napas atau lidah, dengan atau tanpa gangguan pernapasan (angioedema)
- Demam, batuk, sesak napas, mengi, tanda-tanda inflamasi paru (pneumonitis), menggigil, napas dan denyut jantung cepat, ruam, kebingungan dan disorientasi (tanda-tanda infeksi serius, dikenal sebagai sepsis)

Efek samping lain yang mungkin terjadi

Beberapa efek samping lain yang mungkin terjadi dijelaskan di bawah ini. Jika efek samping ini terasa semakin berat, mohon beritahukan kepada dokter, apoteker atau tenaga profesional kesehatan Anda.

Hampir sebagian besar dari efek samping ini ringan sampai sedang dan akan hilang dalam beberapa hari setelah interupsi pengobatan.

Beberapa efek samping lain yang terjadi selama pengobatan terhadap kanker payudara reseptor hormonal positif stadium lanjut, tumor neurokendokrin tumor stadium lanjut atau kanker ginjal stadium lanjut

Beberapa efek samping yang sangat sering terjadi

(Efek samping ini terjadi pada lebih dari 1 dari 10 orang)

- Kadar gula yang tinggi dalam darah (hiperglikemia)
- Hilang nafsu makan
- Gangguan dalam mengecap rasa (disgeusia)
- Sakit kepala
- Batuk
- Mimisan (epistaksis)
- Luka pada mulut
- Mual
- Diare
- Ruam kulit
- Gatal (pruritus)
- Rasa lesu atau letih
- Keletihan, napas terasa pendek, pusing, kulit pucat, tanda-tanda kadar sel darah merah yang rendah (anemia)
- Pembengkakan pada lengan, tangan, kaki, pergelangan kaki atau bagian lain dari tubuh (tanda-tanda udem)
- Penurunan berat badan
- Kadar lipid (lemak) yang tinggi dalam darah (hiperkolesterolemia)

Jika Anda sangat terganggu dengan salah satu atau beberapa efek samping di atas, **mohon segera beritahukan kepada dokter Anda.**

Beberapa efek samping yang sering terjadi

(Efek samping ini terjadi pada sampai dengan 1 dari 10 orang)

- Perdarahan atau memar spontan, tanda-tanda kadar trombosit yang rendah (trombositopenia)
- Rasa haus, jarang berkemih (jumlah urin sedikit), urin berwarna gelap, kulit merah dan kering, mudah tersinggung (tanda-tanda dehidrasi)
- Susah tidur (insomnia)
- Sakit kepala, pusing, tanda-tanda tekanan darah tinggi (hipertensi)
- Demam, sakit tenggorokan atau luka pada mulut akibat infeksi, tanda-tanda kadar sel darah putih yang rendah (leukopenia, limfopenia, neutropenia)
- Sesak napas (dispnea)
- Demam
- Inflamasi pada lapisan mulut bagian dalam, lambung, usus
- Mulut kering
- Rasa panas seperti terbakar di ulu hati(dispepsia)
- Mual

- Kesulitan menelan (disfagia)
- Nyeri perut
- Jerawat
- Ruam dan nyeri pada telapak tangan atau telapak kaki (*hand foot syndrome*)
- Kulit memerah (eritema)
- Nyeri sendi
- Nyeri pada mulut
- Gangguan menstruasi, seperti mens tidak teratur
- Kadar lipid (lemak) yang tinggi dalam darah (hiperlipidemia, peningkatan trigliserida)
- Kadar kalium yang rendah dalam darah (hipokalemia)
- Kadar fosfat yang rendah dalam darah (hipofosfatemia)
- Kulit kering
- Gangguan pada kuku
- Uji fungsi hati yang abnormal (peningkatan alanin dan aspartat aminotransferase)
- Uji fungsi ginjal yang abnormal (peningkatan kreatinin)
- Adanya protein dalam urin

Jika Anda sangat terganggu dengan salah satu atau beberapa efek samping di atas, **mohon segera beritahukan kepada dokter Anda.**

Beberapa efek samping yang tidak begitu sering terjadi

(Efek samping ini terjadi pada sampai dengan 1 dari 100 orang)

- Lemah, perdarahan atau memar secara spontan dan infeksi yang sering dengan tanda-tanda demam, menggigil, sakit tenggorokan atau luka pada mulut, tanda-tanda kadar sel darah yang rendah (pansitopenia)
- Kehilangan kemampuan mengecap rasa (ageusia)
- Batuk darah (hemoptisis)
- Tidak terjadi menstruasi (amenore)
- Berkemih lebih sering di siang hari
- Nyeri dada
- Penyembuhan luka yang tidak normal

- **Beberapa efek samping yang jarang terjadi**

(Efek samping ini terjadi pada antara sampai dengan 1 dari 1000 orang)

- Kelelahan, napas terasa pendek, pusing, kulit pucat, tanda-tanda kadar sel darah merah yang rendah (suatu tipe anemia yang disebut sebagai *pure red cell aplasia*)

Jika Anda sangat terganggu dengan salah satu atau beberapa efek samping di atas**, mohon segera beritahukan kepada dokter Anda.**

Beberapa efek samping lain yang pernah terlapor selama pengobatan TSC

Beberapa efek samping yang sangat sering terjadi

(Efek samping ini terjadi pada lebih dari 1 dari 10 orang)

- Infeksi saluran napas bagian atas
- Sakit tenggorokan dan hidung meler (nasofaringitis)
- Sakit kepala, rasa tertekan pada mata, hidung atau pipi, tanda-tanda inflamasi sinus dan saluran nasal (sinusitis)
- Infeksi saluran kemih
- Kadar lipid (lemak) yang tinggi dalam darah (hiperkolesterolemia)
- Penurunan nafsu makan
- Sakit kepala
- Batuk
- Luka pada mulut
- Diare
- Mual
- Jerawat
- Ruam kulit
- Rasa kelelahan
- Demam
- Gangguan menstruasi seperti tidak terjadi mestruasi (amenore) atau mestruasi tidak teratur
- Sakit tenggorokan (faringitis)

Jika Anda sangat terganggu dengan salah satu atau beberapa efek samping di atas, **mohon segera beritahukan kepada dokter Anda.**

Beberapa efek samping yang sering terjadi

(Efek samping ini terjadi pada sampai dengan 1 dan 10 orang)

- Infeksi telinga bagian tengah
- Gusi bengkak, gusi berdarah, tanda-tanda peradangan gusi (gingivitis)
- Inflamasi kulit (selulitis)
- Perdarahan atau memar secara spontan, tanda-tanda kadar trombosit yang rendah (trombositopenia)
- Kadar fosfat yang rendah dalam darah (hipofosfatemia)
- Kadar lipid (lemak) yang tinggi dalam darah (hiperlipidemia, peningkatan trigliserida)
- Kadar gula yang tinggi dalam darah (hiperglikemia)

- Lelah, napas terasa pendek, pusing, kulit pucat, tanda-tanda kadar sel darah merah yang rendah (anemia)
- Demam, sakit tenggorokan atau luka pada mulut akibat infeksi, tanda-tanda kadar sel darah putih yang rendah (leukopenia, limfopenia, neutropenia)
- Sakit kepala, pusing, tanda-tanda peningkatan tekanan darah (hipertensi)
- Mimisan (epistaksis)
- Nyeri mulut
- Mual
- Nyeri perut
- Nyeri hebat di bagian perut bawah dan daerah panggul, dengan menstruasi yang tidak teratur (kista ovarium)
- Kelebihan gas dalam usus (flatulens)
- Konstipasi (sembelit)
- Nyeri perut, mual, muntah, diare, pembengkakan perut dan rasa kembung, tanda-tanda inflamasi pada lapisan lambung (gastritis, gastroenteritis viral)
- Inflamasi kulit yang ditandai dengan kemerahan, gatal, kista berisi cairan yang menjadi bersisik, berkulit dan mengeras (dermatitis akneiformis)
- Kulit kering
- Adanya protein dalam urin
- Gangguan menstruasi seperti mentruasi berlebihan (menoragi) atau perdarahan pada vagina
- Mudah tersinggung
- Susah tidur (insomnia)
- Agresif
- Kadar enzim laktat dehidrogenase yang tinggi dalam darah yang memberi informasi mengenai kesehatan orang-organ tertentu
- Peningkatan kadar hormon pencetus terjadinya ovulasi (peningkatan *luteinizing hormone* dalam darah)

Jika Anda sangat terganggu dengan salah satu atau beberapa efek samping di atas, **mohon segera beritahukan kepada dokter Anda.**

Beberapa efek samping yang tidak begitu sering terjadi

(Efek samping ini terjadi pada sampai dengan 1 dari 100 orang)

- Batuk berdahak, nyeri dada, demam, tanda-tanda inflamasi saluran pernapasan (bronkitis viral)
- Gangguan rasa kecap (disgeusia)
- Kadar hormon reproduksi wanita yang meningkat (peningkatan *follicle stimulating hormone* dalam darah)

Jika Anda mengetahui adanya efek samping lain yang tidak disebutkan pada brosur ini, **mohon beritahukan kepada dokter, apoteker atau tenaga profesional kesehatan Anda**.

5 Cara penyimpanan AFINITOR

- Mohon tidak menggunakan obat setelah tanggal kadaluarsa yang tercantum pada dus obat
- Kondisi penyimpanan: disimpan pada suhu tidak lebih dari 30°C
- Simpan obat di dalam kemasannya
- Mohon agar blister dibuka jika hanya tablet AFINITOR akan digunakan
- Mohon agar tablet AFINITOR tetap kering dan terhindar dari cahaya dan kelembaban
- Mohon jauhkan obat ini dari jangkauan anak-anak

6 Isi dari kemasan dan informasi lain

Apakah isi dari AFINITOR

Tablet AFINITOR

Zat aktif dari tablet AFINITOR adalah everolimus.

Zat tambahan lainnya adalah *butylated* hidrokstoluen (E321), magnesium stearat, laktosa monohidrat, hipromelose, krospovidon dan laktosa anhidrat.

Bagaimana bentuk dari AFINITOR dan isi kemasannya

Tablet AFINITOR

Tablet berwarna putih sedikit kekuningan, bentuk memanjang dengan tepi miring dan tanpa goresan ditengahnya.

Masing-masing tablet 2.5 mg mengandung everolimus 2.5 mg dan tertulis “LCL” pada satu sisi dan “NVR” pada sisi yang lain.

Masing-masing tablet 5 mg mengandung everolimus 5 mg dan tertulis “5” pada satu sisi dan “NVR” pada sisi yang lain.

Masing-masing tablet 10 mg mengandung everolimus 10 mg dan tertulis “UHE” pada satu sisi dan “NVR” pada sisi yang lain.

Tiap blister terdiri dari 10 tablet.

Kemasan:

Afinitor 5 mg

Dus, 3 blister @ 10 tablet

No. Reg. DKI1067507810A1

Afinitor 10 mg

Dus, 3 blister @ 10 tablet

No. Reg. DKI1067507810B1

HARUS DENGAN RESEP DOKTER

Pemegang Nomor Ijin Edar

PT Novartis Indonesia

Pabrik pembuat

Novartis Pharma Stein AG, Stein, Switzerland

Jika Anda memiliki pertanyaan mengenai obat ini, mohon hubungi dokter atau apoteker Anda.

PIL based on BPL 27-Mar-2017

** Disclaimer: For Afinitor 2.5 mg tablet is not registered and marketed in Indonesia*