AUSTRALIAN PI – AFINITOR (EVEROLIMUS) TABLETS AND DISPERSIBLE TABLETS

1 NAME OF THE MEDICINE

Everolimus.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Afinitor tablet contains either 2.5 mg, 5 mg or 10 mg everolimus.

Each Afinitor dispersible tablet contains either 2 mg, 3 mg or 5 mg everolimus.

Excipients with known effect: tablets only - contains sugars as lactose.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

2.5 mg tablet: White to slightly yellowish, elongated tablet with a bevelled edge and no score engraved with “LCL” on one side and “NVR” on the other.

5 mg tablet: White to slightly yellowish, elongated tablet with a bevelled edge and no score engraved with “5” on one side and “NVR” on the other.

10 mg tablet: White to slightly yellowish, elongated tablet with a bevelled edge and no score engraved with “UHE” on one side and “NVR” on the other.

2 mg dispersible tablet: White to slightly yellowish, round, flat tablets with a bevelled edge and no score. The tablets are engraved with “D2” on one side and “NVR” on the other.

3 mg dispersible tablet: White to slightly yellowish, round, flat tablets with a bevelled edge and no score. The tablets are engraved with “D3” on one side and “NVR” on the other.

5 mg dispersible tablet: White to slightly yellowish, round, flat tablets with a bevelled edge and no score. The tablets are engraved with “D5” on one side and “NVR” on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Afinitor is indicated for the:

- Treatment of postmenopausal women with hormone receptor-positive, HER2 negative advanced breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole.
- Treatment of progressive, unresectable or metastatic, well or moderately differentiated neuroendocrine tumours (NETs) of pancreatic origin.
- Treatment of progressive, unresectable or metastatic, well-differentiated, non-functional neuroendocrine tumours (NET) of gastrointestinal or lung origin in adults.
- Treatment of advanced renal cell carcinoma after failure of treatment with sorafenib or sunitinib.

- Treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not candidates for curative surgical resection.
- Treatment of patients with tuberous sclerosis complex (TSC) who have renal angiomyolipoma not requiring immediate surgery.
- Adjunctive treatment of patients aged 2 years and older with TSC and associated refractory seizures.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Afinitor should be administered orally once daily at the same time every day (preferably in the morning), either consistently with or consistently without food (see section 5.2 'Pharmacokinetic properties'). Afinitor is available in two formulations: tablets (Afinitor Tablets) and dispersible tablets (Afinitor Dispersible Tablets).

Afinitor Tablets may be used in all oncology indications and in the TSC with SEGA and TSC with renal angiomyolipoma indications. Afinitor Tablets have not been studied and are not recommended for use in patients with TSC and refractory seizures.

Afinitor Dispersible Tablets may be used for the treatment of patients with TSC who have SEGA and patients with TSC and refractory seizures in conjunction with therapeutic drug monitoring (see section 4.2 'Dose and method of administration-Therapeutic drug monitoring').

If a dose is missed, the patient should take the next dose at the next scheduled time. Patients should not take two doses to make up for the one that they missed.

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

Afinitor Tablets

Afinitor tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed.

For patients with TSC who have SEGA and are unable to swallow tablets whole, Afinitor tablets can be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring until the tablet(s) is fully disintegrated (approximately 7 minutes), 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.

Afinitor Dispersible tablets

Afinitor Dispersible Tablets are to be taken as a suspension only and should not be swallowed whole, chewed, or crushed. The suspension can be prepared in an oral syringe or in a small drinking glass. Care should be taken to ensure the entire dose is administered.

Administer the suspension immediately after preparation. Discard the suspension if not administered within 60 minutes of preparation. Prepare the suspension in water only.

Using an oral syringe:

- Place the prescribed dose of Afinitor Dispersible Tablets into a 10-mL syringe. Do not exceed a total of 10 mg per syringe. If higher doses are required, prepare an additional syringe. Do not break or crush tablets.
- Draw approximately 5 mL of water and 4 mL of air into the syringe.
- Place the filled syringe into a container (tip up) for 3 minutes, until the Afinitor Dispersible Tablets are in suspension.
- Gently invert the syringe 5 times immediately prior to administration.
- After administration of the prepared suspension, draw approximately 5 mL of water and 4 mL of air into the same syringe, and swirl the contents to suspend remaining particles. Administer the entire contents of the syringe.

Using a small drinking glass:

- Place the prescribed dose of Afinitor Dispersible Tablets into a small drinking glass (maximum size 100 mL) containing approximately 25 mL of water. Do not exceed a total of 10 mg of Afinitor Dispersible Tablets per glass. If higher doses are required, prepare an additional glass. Do not break or crush tablets.
- Allow 3 minutes for suspension to occur.
- Stir the contents gently with a spoon, immediately prior to drinking.
- After administration of the prepared suspension, add 25 mL of water and stir with the same spoon to re-suspend remaining particles. Administer the entire contents of the glass.

Switching dosage forms:

The two dosage forms (Afinitor Tablets and Afinitor Dispersible Tablets) are not interchangeable. Do not combine the two dosage forms to achieve the desired dose. Consistently use the same dosage form, as appropriate for the indication being treated.
When switching dosage forms, the dose should be adjusted to the closest milligram strength of the new dosage form and the everolimus trough concentration should be assessed approximately 2 weeks later (see section 4.2 'Dose and method of administration-Therapeutic drug monitoring').

Adults

Dosing in hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumours, advanced renal cell carcinoma, and TSC with renal angiomyolipoma

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

BSA based Dosing in TSC with SEGA and TSC with refractory seizures

Individualise dosing based on the body surface area (BSA, in m^2) using the Dubois formula, where weight (W) is in kilograms and height (H) is in centimetres:

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

Starting dose and target trough concentrations in TSC with SEGA

The recommended starting dose of Afinitor for treatment of patients with TSC who have SEGA is 4.5 mg/m^2, rounded to the nearest strength of Afinitor Tablets or Afinitor Dispersible Tablets. Different strengths of Afinitor Tablets can be combined to attain the desired dose. Likewise, different strengths of Afinitor Dispersible Tablets can be combined to attain the desired dose. The two dosage forms should not be combined to achieve the desired dose.

Dosing should be titrated to attain trough concentrations of 3 to 15 ng/mL.

Starting dose and target trough concentrations in TSC with refractory seizures

The recommended starting daily dose for Afinitor Dispersible Tablets for the treatment of patients with seizures is shown in Table 1. The starting dose should be rounded to the nearest available strength of Afinitor Dispersible Tablets. Different strengths of Afinitor Dispersible Tablets can be combined to attain the desired dose. Dosing should be titrated to attain trough concentrations of 5 to 15 ng/mL.

Table 1 Afinitor starting dose in TSC with refractory seizures

Age	Starting dose without co-administration of CYP3A4/PgP inducer	Starting dose with co-administration of CYP3A4/PgP inducer
<6 years	6 mg/m^2	9 mg/m^2
≥6 years	5 mg/m^2	8 mg/m^2

Dose Monitoring

Therapeutic drug monitoring of everolimus blood concentrations is required for patients with TSC who have SEGA or patients with TSC and seizures (see section 4.2 'Dose and method of administration - Therapeutic drug monitoring'). Everolimus whole blood trough concentrations should be assessed approximately 1 to 2 weeks after commencing treatment or any change in dose.

Titration

Individualized dosing should be titrated by increasing the dose by increments of 1 to 4 mg to attain the target trough concentration for optimal clinical response. Efficacy, safety, concomitant medication, and the current trough concentration should be considered when planning for dose titration. Individualized dose titration can be based on simple proportion:

New everolimus dose = current dose x (target concentration/current concentration)

For example, a patient's current dose based on BSA is 4 mg with a steady state concentration of 4 ng/mL. In order to achieve a target concentration above the lower Cmin limit of 5 ng/mL, e.g. 8 ng/mL, the new everolimus dose would be 8 mg (an increase of 4 mg to the current daily dose). The trough concentration should then be assessed 1 to 2 weeks after this change in dose.

Long-term dose monitoring

For patients with TSC who have SEGA, evaluate SEGA volume 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 5 'Pharmacological properties').

For patients with TSC who have SEGA and patients with TSC and seizures, once a stable desired dose is attained, monitor trough concentrations every 3 to 6 months in patients with changing body surface area or every 6 to 12 months in patients with stable body surface area for the duration of treatment.

Dose Modifications due to adverse drug reactions:

Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption (with or without dose reduction) or discontinuation of Afinitor therapy (see section 4.4 'Special warnings and precautions for use'). If dose reduction is required, the suggested dose is approximately 50% lower than the daily dose previously administered. For dose reductions below the lowest available tablet strength, alternate day dosing should be considered.Table 2 summarizes recommendations for dose interruption, reduction, 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 2 Afinitor dose adjustment and management recommendations for adverse drug reactions

Adverse Drug Reaction	**Severity[a]**	**Afinitor Dose Adjustment[b] and Management Recommendations**
Non-infectious pneumonitis	Grade 1 Asymptomatic, clinical or diagnostic observations only; intervention not indicated	No dose adjustment required. Initiate appropriate monitoring.
	Grade 2 Symptomatic, medical intervention indicated; limiting instrumental with ADL[c]	Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to Grade ≤ 1. Re-initiate treatment at a lower dose. Discontinue treatment if failure to recover within 4 weeks.
	Grade 3 Severe symptoms; limiting self-care ADL[c]; oxygen indicated	Interrupt treatment until symptoms resolve to Grade ≤ 1. Rule out infection and consider treatment with corticosteroids. Consider re-initiating Afinitor at a lower dose. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4 Life-threatening , respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Discontinue treatment, rule out infection, and consider treatment with corticosteroids.
Stomatitis	Grade 1 Asymptomatic or mild symptoms, intervention not indicated	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouthwash several times a day.
	Grade 2 Moderate pain; not interfering with oral intake; modified diet indicated	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at the same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤1. Re-initiate treatment at a lower dose. Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]

Adverse Drug Reaction	Severity[a]	Afinitor Dose Adjustment[b] and Management Recommendations
	Grade 3 Severe pain; interfering with oral intake	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at a lower dose. Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue treatment and treat with appropriate medical therapy.
Other non-haematologic 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 treatment at the same dose. If toxicity recurs at Grade 2, interrupt treatment until recovery to Grade ≤1. Re-initiate treatment at a lower dose.
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Initiate appropriate medical therapy and monitor. Consider re-initiating treatment at a lower dose. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue treatment 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 treatment at a lower dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue treatment and treat with appropriate medical therapy.
Thrombocytopenia (Platelet count decreased)	Grade 1 (<LLN[e] – 75,000/mm^3; <LLN[e] – 75.0 x 10^9/L)	No dose adjustment required
	Grade 2 (<75,000 – 50,000/mm^3; <75.0 – 50.0 x10^9/L)	Temporary dose interruption until recovery to Grade 1. Re-initiate treatment at same dose.
	Grade 3 (<50,000 – 25,000/mm^3; <50.0 - 25.0 x10^9/L) or Grade 4 (<25,000/mm^3; <25.0 x10^9/L)	Temporary dose interruption until recovery to Grade 1. Re-initiate treatment at a lower dose.
Neutropenia (Neutrophil count decreased)	Grade 1 (<LLN[e] – 1,5000/mm^3; <LLN[e] – 1.5 x10^9/L) or Grade 2 (<1,500/mm^3 – 1,000/mm^3; <1.5 - 1.0 x10^9/L)	No dose adjustment required.
	Grade 3 (<1,000 – 500/mm^3; <1.0 – 0.5 x10^9/L)	Temporary dose interruption until recovery to Grade 2. Re-initiate treatment at same dose.

Adverse Drug Reaction	Severity[a]	Afinitor Dose Adjustment[b] and Management Recommendations
	Grade 4 (<500/mm^3; <0.5x10^9/L)	Temporary dose interruption until recovery to Grade 2. Re-initiate treatment at a lower dose.
Febrile neutropenia	Grade 3 ANC[f] < 1 with a single temperature of > 38.3 ºC or a sustained temperature of ≥38 ºC for more than one hour	Temporary dose interruption until recovery to Grade 2 and no fever. Re-initiate treatment at a lower dose.
	Grade 4 Life threatening consequences; urgent intervention indicated	Discontinue treatment

[a] Severity Grade description: 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms. Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

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

[c] Activities of daily living (ADL)

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

[e] Lower limit of normal (LLN)

[f] Absolute Neutrophil Count (ANC)

Moderate CYP3A4 or PgP inhibitors:

Use caution when administering Afinitor in combination with moderate CYP3A4 or PgP inhibitors. If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, reduce the Afinitor daily dose by approximately 50%. Further dose reduction may be required to manage adverse drug reactions. For dose reductions below the lowest available strength, alternate day dosing should be considered (see section 4.4 'Special warnings and precautions for use').

- **Hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumours, advanced renal cell carcinoma, and TSC with renal angiomyolipoma:** If the moderate CYP3A4/PgP inhibitor is discontinued, consider a washout period of at least 2 to 3 days (average for most commonly used moderate inhibitors) before the Afinitor dose is increased. The Afinitor dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor (see section 4.4 'Special warnings and precautions for use').
- **TSC with SEGA:** Everolimus trough concentrations should be assessed approximately 1 to 2 weeks after the addition of a moderate CYP3A4 or PgP inhibitor. If the inhibitor is discontinued the Afinitor dose should be returned to the dose used prior to initiation of the inhibitor and the everolimus trough concentration should be re-assessed approximately 2 weeks later (see section 4.4 'Special warnings and precautions for use' and 4.2 'Dose and method of administration - Therapeutic drug monitoring').

Strong CYP3A4 inducers:

Avoid the use of concomitant strong CYP3A4 inducers.

- **Hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumours, advanced renal cell carcinoma, and TSC with renal angiomyolipoma:** If patients require co-administration of a strong CYP3A4 inducer, consider doubling the daily dose of Afinitor (based on pharmacokinetic data), using increments of 5 mg or less. 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, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction), before the Afinitor dose is returned to the dose used prior to initiation of the strong CYP3A4 inducer (see section 4.4 'Special warnings and precautions for use').

- **TSC with SEGA and TSC with refractory seizures**:
  - Patients with SEGA receiving concomitant strong CYP3A4 inducers (e.g., the enzyme inducing antiepileptic drugs carbamazepine, phenobarbital (phenobarbitone), and phenytoin) at the start of treatment may require an increased Afinitor dose to attain trough concentrations of 3 to 15 ng/mL. Double the daily dose of Afinitor and assess tolerability. Assess the everolimus trough level approximatively two weeks after doubling the dose. Further adjust the dose by increments of 1 to 4 mg as necessary to maintain the target trough concentration.
  - Patients with seizures receiving concomitant strong CYP3A4 inducers (e.g., enzyme inducing antiepileptic drugs carbamazepine, phenobarbital (phenobarbitone), and phenytoin) require an increased starting dose to attain trough concentrations of 5 to 15 ng/mL (see recommendations outlined in Table 1). Further adjust the dose by increments of 1 to 4 mg as necessary to maintain the target trough concentration.
  - The addition of another concomitant strong CYP3A4 inducer may not require additional dose adjustment. Assess the everolimus trough level two weeks after initiating the additional inducer. Adjust the dose in 1 to 4 mg increments as necessary to maintain the target trough concentration.
  - Discontinuation of one of multiple strong CYP3A4 inducers may not require additional dose adjustment. Assess the everolimus trough level two weeks after discontinuation of one of multiple strong CYP3A4 inducers. If all strong inducer are discontinued, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction) before the Afinitor dose is returned to the dose used prior to initiation of the strong CYP3A4 inducer. Assess the everolimus trough concentration approximately two weeks later (see section 4.2 'Dose and method of administration - Therapeutic drug monitoring', section 4.4 'Special warnings and precautions for use' and section 4.5 'Interactions with other medicines').

Therapeutic drug monitoring

Therapeutic drug monitoring of everolimus blood concentrations is required for patients treated for TSC with SEGA or refractory seizures using a validated bioanalytical LC/MS method. When possible, use the same assay and laboratory for therapeutic drug monitoring throughout treatment.

Trough concentrations should be assessed approximately 1 to 2 weeks after the initial dose, after any change in dosage form, after an initiation or change in co-administration of CYP3A4/PgP inhibitors (see section 4.4 'Special warnings and precautions for use') or after any change in hepatic (Child-Pugh) status. Trough concentrations should be assessed approximately 2 weeks after initiation or change in co-administration of CYP3A4/PgP inducers (see section 4.4 'Special warnings and precautions for use' and 4.5 'Interactions with other medicines'). Dosing should be titrated with the objective of attaining everolimus trough concentrations of 3 to 15 ng/mL for patients with TSC who have SEGA and 5 to 15 ng/mL for patients with TSC and refractory seizures, subject to tolerability (see section 5.2

'Pharmacokinetic properties'). The dose may be increased to attain a higher trough concentration within the target range to obtain optimal efficacy, subject to tolerability.

Special Populations

Paediatric 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.
- Afinitor has not been studied in paediatric patients <1 year of age with TSC who have SEGA.
- Afinitor has not been studied in paediatric patients <2 years of age with TSC and refractory seizures.
- 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.
- Dosing recommendations for paediatric patients with TSC and refractory seizures are consistent with those for the corresponding adult population with the exception of the starting dose for patients <6 years of age.
- Afinitor is not recommended for patients <18 years of age with hepatic impairment and TSC with SEGAor TSC with seizures.

Elderly patients (65 years of age or older)

No dosage adjustment is required (see section 5.2 'Pharmacokinetic properties').

Renal impairment

No dosage adjustment is required (see section 5.2 'Pharmacokinetic properties').

Hepatic impairment

- **Hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumours and, 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 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 and TSC with refractory seizures**:
    - **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. If the desired benefit outweighs the risk, 25% of the dose calculated based on BSA (rounded to the nearest strength) must not be exceeded.

Everolimus whole blood trough concentrations should be assessed approximately 1 to 2 weeks after commencing treatment or after any change in hepatic (Child-Pugh) status. For patients with SEGA, dosing should be titrated to attain trough concentrations of 3 to 15 ng/mL (see section 4.2 'Dose and method of administration - Therapeutic drug monitoring'). For patients with seizures, dosing should be titrated to attain trough concentrations of 5 to 15 ng/mL (see section 4.2 'Dose and method of administration - Therapeutic drug monitoring'). Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment (see section 5.2 'Pharmacokinetic properties').

- **Patients <18 years of age**
  - Afinitor is not recommended for patients <18 years of age with TSC with SEGA or seizures and hepatic impairment.

4.3 CONTRAINDICATIONS

Afinitor is contraindicated in patients with hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients (see section 4.4 'Special warnings and precautions for use').

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 4.8 Adverse effects (undesirable effects)). 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 section 4.4 'Special warnings and precautions for use – 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:

- In patients with hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumours or advanced renal cell carcinoma, Afinitor may be reintroduced at 5 mg daily.
- In patients with SEGA, 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:

- In patients with hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumours or advanced renal cell carcinoma, therapy with Afinitor may be re-initiated at a reduced dose of 5 mg daily depending on the individual clinical circumstances.
- In patients with SEGA, therapy with Afinitor may be re-initiated at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances.

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 4.2 'Dose and method of administration').

Infections

Afinitor has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens (see section 4.8 Adverse effects (undesirable effects)). 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 paediatric patients (see section 4.8 Adverse effects (undesirable effects)). 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, Afinitor should be promptly and permanently discontinued and the patient treated with appropriate antifungal therapy.

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.

Impaired Wound Healing

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

Radiation therapy complications

Severe radiation reactions (including radiation esophagitis, radiation pneumonitis and radiation skin injury) have been reported when everolimus was used during, or shortly after radiation therapy.

Caution should therefore be exercised for patients using everolimus in close temporal relationship with radiation therapy.

Additionally, radiation recall syndrome has been reported in patients on everolimus who have received prior radiotherapy.

Hypersensitivity

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnoea, flushing, chest pain or angioedema (eg swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus (see section 4.3 '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 4.8 Adverse effects (undesirable effects)). 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 4.2 Dose and method of administration). Antifungal agents should not be used unless fungal infection has been diagnosed (see section 4.5 'Interactions with other medicines').

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 4.8 Adverse effects (undesirable effects)).

The study used 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). No food or drink was to be consumed for at least 1 hour after swishing and spitting the dexamethasone oral solution.

Ethnicity

In Asian patients, with NETs, the reported adverse events of hypertension were 1.95 fold higher (17.6% vs. 9.0%), of pneumonitis 1.88 fold higher (13.2% vs. 7.0%), and of hyperglycaemia 1.59 fold higher (29.4% vs. 18.4%) than in Caucasian patients.

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 4.8 Adverse effects (undesirable effects), section 4.4 'special warnings and precautions for use - Effects on Laboratory tests' and section 4.2 Dose and method of administration - Therapeutic drug monitoring').

Functional carcinoid tumours

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

Prognostic factors in neuroendocrine tumours of gastrointestinal or lung origin

In patients with non-functional gastrointestinal or lung neuroendocrine tumours and good prognostic baseline factors, e.g. ileum as primary tumour origin and normal chromogranin A values or without bone involvement, an individual benefit-risk assessment should be performed prior to the start of Afinitor therapy. In the subgroup of patients with ileum as primary tumour origin, PFS benefit was uncertain (see section 5.1 'Pharmacodynamic properties- Clinical trials'), RADIANT-4, Figure 6).

Use in hepatic impairment

Exposure to everolimus was increased in patients with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment (see section 4.2 'Dose and method of administration' and 4.4 'special warnings and precautions for use').

Afinitor is not recommended for use in patients ≥18 years of age with severe hepatic impairment (Child-Pugh C) unless the potential benefit outweighs the risk (see section 4.2 'Dose and method of administration' and 5.2 'Pharmacokinetic properties').

Afinitor is not recommended for use in patients < 18 years of age with TSC who have SEGA or refractory seizures and concomitant hepatic impairment (Child-Pugh A, B or C) (see section 4.2 'Dose and method of administration' and 5 'Pharmacological properties').

Use in the elderly

In patients over 65 years, with NETs, the reported incidences of dehydration, hypomagnesaemia and pneumonitis was more than 1.4 fold higher than for patients 65 years or younger.

Paediatric use

- There is no indication for use of Afinitor in the paediatric cancer population (see section 4.2 'Dose and method of administration) or in paediatric patients with TSC who have renal angiomyolipoma.
- Afinitor has not been studied in paediatric patients <1 year of age with TSC who have SEGA.
- Afinitor has not been studied in paediatric patients <2 years of age with TSC and refractory seizures.
- 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 hepatic impairment and TSC with SEGA or TSC with seizures.
- The starting dose for paediatric patients < 6 years of age with TSC and refractory seizures is slightly higher than for adults (see section 4.2 'Dose and method of administration').

Effects on laboratory tests

Renal Function

Elevations of serum creatinine, usually mild, and proteinuria have been reported in patients taking Afinitor (see section 4.8 Adverse effects (undesirable effects)). 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 4.8 Adverse effects (undesirable effects)). 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 hyperglycaemia. The appropriate optimal glycaemic control must be achieved before starting a patient on Afinitor.

Octreotide has been associated with a rise in blood glucose which may increase the hyperglycaemic effect of everolimus.

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.

Haematological parameters

Decreased haemoglobin, lymphocytes, neutrophils and platelets have been reported in patients treated with Afinitor (see section 4.8 Adverse effects (undesirable effects)). Monitoring of complete blood count is recommended prior to the start of Afinitor therapy and periodically thereafter.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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.

Moderate CYP3A4 or PgP inhibitors

Concomitant treatment with moderate inhibitors of CYP3A4 including but not limited to erythromycin, verapamil, ciclosporin, fluconazole, diltiazem, amprenavir, fosamprenavir, aprepitant, or posaconazole and PgP requires caution. If Afinitor must be co-administered with a moderate CYP3A4 or PgP inhibitor, the patient should be carefully monitored for undesirable effects and the dose reduced if necessary (see section 4.2 'Dose and method of administration').

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).

Other moderate inhibitors of CYP3A4 and PgP that may increase everolimus blood concentrations include certain antifungal agents (e.g. fluconazole) and calcium channel blockers (e.g. diltiazem).

Co-administration of cannabidiol with the P-glycoprotein and CYP3A4 substrate everolimus in a healthy volunteer study led to an increase in everolimus exposure of approximately 2.5-fold for both Cmax and AUC. Everolimus and cannabidiol should be co-administered with caution, closely monitoring for side effects. Monitor everolimus whole blood trough concentrations and reduce the everolimus dose as necessary.

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

Strong CYP3A4 or PgP inhibitors

Concurrent treatment with strong inhibitors of CYP3A4 or PgP (including but not limited to ketoconazole, itraconazole, ritonavir and clarithromycin) 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). An interaction with topically administered ketoconazole cannot be excluded.

Agents that may decrease everolimus blood concentrations

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

Strong CYP3A4 inducers

Concurrent treatment with strong inducers of CYP3A4 or PgP should be avoided (see section 4.5 'Interactions with other medicines'). If Afinitor must be co-administered with a strong CYP3A4 or PgP inducer (e.g. rifampicin and rifabutin), the patient should be carefully monitored for clinical response.

Consider a dose increase of Afinitor when co-administered with strong inducers of CYP3A4 or PgP if alternative treatment is not possible (see section 4.2 'Dose and method of administration').

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.

Pre-treatment of healthy subjects with multiple doses of rifampicin (a 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 that may increase the metabolism of everolimus and decrease everolimus blood levels include St. John's wort (*Hypericum perforatum*), corticosteroids (e.g. dexamethasone, prednisone, prednisolone), anticonvulsants (e.g. carbamazepine, phenobarbital (phenobarbitone), 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 was therefore considered to be unlikely.

A study in healthy subjects demonstrated that co-administration of an oral dose of midazolam 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.

Everolimus increased pre-dose concentrations of the antiepileptic drugs (AEDs) carbamazepine, clobazam, and the clobazam metabolite N-desmethylclobazam by about 10%. The increase in the pre-dose concentrations of these AEDs may not be clinically significant but 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 and zonisamide). Everolimus had no impact on the pre-dose concentration of other AEDs, including valproic acid, topiramate, oxcarbazepine, phenobarbital (phenobarbitone) and phenytoin.

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. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines. For paediatric patients with TSC who have SEGA or seizures and that do not require immediate treatment, complete the recommended childhood series of live virus vaccinations prior to the start of therapy according to local treatment guidelines.

Lactose

Patients with rare hereditary problems of galactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Based on non-clinical findings, male and female fertility may be compromised by treatment with Afinitor.

Animal data

Testicular atrophy was observed in all animal species tested (mouse, rat, minipigs and monkey) at drug exposures similar to the expected clinical exposure (blood AUC). Everolimus completely impaired male rat fertility at an everolimus dose that resulted in a drug exposure (blood AUC) that was slightly below[1] the expected maximum human value. 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 for partial recovery of fertility over a period approximately equivalent to the treatment period. In animal reproductive studies female fertility was not affected. However, oral doses of everolimus in female rats at ≥0.1 mg/kg (approximately 4% the AUC_{0-24h} in patients receiving the 10 mg daily dose) resulted in increased incidence of pre-implantation loss.

Human data

Both male and female fertility may be compromised by treatment with everolimus.

Menstrual irregularities, secondary amenorrhea and associated luteinizing hormone (LH)/follicle stimulating hormone (FSH) imbalance have been observed in female patients receiving everolimus.

[1] At high dose (5 mg/kg/day), AUC0-24 hr=414.8 ng.hr/mL vs human AUC=560 at 10 mg/day.

Blood levels of FSH and LH increased, blood levels of testosterone decreased, and azoospermia have been observed in male patients receiving everolimus.

Use in pregnancy – Pregnancy Category C

Risk Summary

There are no adequate data from the use of everolimus in pregnant women and the potential risk to the fetus is unknown.

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 AUC0-24h 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 as an increase in late resorptions that occurred at an oral dose of 0.8 mg/kg. (approximately 45% of the $AUC_{0\text{-}24h}$ in patients receiving the 10 mg daily dose). 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.

Use in lactation.

It is not known whether everolimus is transferred 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 based on AUC. Women taking Afinitor should not breast-feed during treatment and for 2 weeks after the last dose.

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 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. However, adverse effects of this medicine include fatigue, asthenia and insomnia which could affect the ability to drive or use machines (see section 4.8 Adverse effects (undesirable effects)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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=2672) in randomised, double-blind, placebo-or active comparator controlled phase III and phase-II studies related to the trials which serve as the basis for the approved indications in oncology (see section 4.1 'Therapeutic indications').

The most common adverse reactions (incidence ≥1/10 and suspected to be related to treatment by the investigator) from the pooled safety data of the double-blind treatment portion of each of the phase-III, controlled studies were (in decreasing order): stomatitis, rash, fatigue, diarrhoea, infections, nausea, decreased appetite, anaemia, dysgeusia, pneumonitis, oedema peripheral, hyperglycaemia, asthenia, pruritus, weight decreased, hypercholesterolaemia, epistaxis, vomiting, cough, 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 3 presents the frequency category of ADRs reported in the pooled safety analysis from the double-blind treatment phase of each of the phase-III, controlled studies noted above.

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 3 Adverse drug reactions from oncology trials reported at a higher rate in the Afinitor arm than in the comparator arm

Infections and infestations	
Very common	Infections[a]
Blood and lymphatic system disorders	

Very common	Anaemia
Common	Thrombocytopenia, neutropenia, leucopenia, lymphopenia
Uncommon	Pancytopenia
Rare	Pure red cell aplasia
Immune system disorders	
Uncommon	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Decreased appetite, hyperglycemia, 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, lymphoedema[g]
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], diarrhea, 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, acne, erythema, 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 very common: pneumonitis and common: interstitial lung disease, lung infiltration, 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

[g]ADR was determined based on postmarketing reports. Frequency was determined based on oncology trials 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 decreased, and neutrophils decreased (or collectively as pancytopenia).
- Clinical chemistry: glucose (fasting) increased, cholesterol increased, triglycerides increased, AST increased, phosphate decreased, ALT increased, creatinine increased, potassium decreased and albumin decreased.

Most of the observed abnormalities (≥1/100) 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 events (irrespective of causality) presented below are based on pooled data from patients with TSC receiving Afinitor (N=404) or placebo (N=197) in the double-blind treatment phase of the three phase-III, controlled studies (see section 4.1 'Therapeutic indications'). Table 4 presents the most frequent adverse events (incidence ≥1/10) from this pooled safety data.

Table 4 Adverse events assessed from clinical trials in TSC in the Afinitor and placebo arms (incidence ≥1/10)

	Everolimus N= 404	**Placebo N=197**
Preferred term	**n (%)**	**n (%)**
Stomatitis	137 (33.9)	15 (7.6)
Mouth ulceration	96 (23.8)	9 (4.6)
Nasopharyngitis	75 (18.6)	43 (21.8)
Diarrhoea	72 (17.8)	10 (5.1)
Pyrexia	67 (16.6)	16 (8.1)
Upper respiratory tract infection	58 (14.4)	26 (13.2)
Vomiting	56 (13.9)	18 (9.1)
Cough	54 (13.4)	15 (7.6)
Aphthous ulcer	41 (10.1)	7 (3.6)

Adverse drug reaction (ADR, assessed as related to treatment by the sponsor) information is based on pooled data from the 3 controlled studies mentioned above but including cumulative data (N=608, including 408 patients <18 years of age) from the double-blind plus open-label treatment phases and in addition from one non-randomised, open-label, single-arm phase II study (see Table 5 and section 4.1 'Therapeutic indications'):

Table 5 Afinitor TSC studies in the pooled safety data for ADR assessment

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[b]	357[d]
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)	11.1 (0-26.9)[c]
Exposure in Patient-Years	146	391	391	353

[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] *One patient discontinued during the first week of treatment and was recorded as "0" months.*

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

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

The most frequent grade 3/4 adverse reactions (incidence ≥1/100 to <1/10 suspected to be related to treatment by the sponsor) were pneumonia, stomatitis, amenorrhea, neutropenia, pyrexia, menstruation irregular, hypophosphataemia, diarrhoea and cellulitis.

Tabulated summary of adverse drug reactions from clinical trials in TSC

Table 6 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 6 Adverse drug reactions assessed from clinical trials in TSC in the Afinitor arm

Infections and infestations	
Very common	Nasopharyngitis, upper respiratory tract infection, pneumonia, urinary tract infection, sinusitis, pneumonia, pharyngitis
Common	Otitis media, cellulitis, pharyngitis streptococcal, gastroenteritis viral, gingivitis
Uncommon	Sepsis, herpes zoster, bronchitis viral
Blood and lymphatic system disorders	
Common	Anemia, neutropenia, leucopenia, thrombocytopenia, lymphopenia
Immune system disorders	
Common	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Decreased appetite, hypercholesterolemia
Common	Hypertriglyceridemia, hyperlipidemia, hypophosphatemia, hyperglycemia
Psychiatric disorders	
Common	Insomnia, aggression, irritability
Nervous system disorders	
Very common	Headache
Uncommon	Dysgeusia
Vascular disorders	
Very common	Hypertension
Common	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	Amenorrhea[c], menstruation irregular[c]
Common	Menorrhagia, ovarian cyst, vaginal haemorrhage
Uncommon	Menstruation delayed[c]
General disorders and administration site conditions	
Very common	Pyrexia, fatigue
Investigations	
Common	Blood lactate dehydrogenase increased, blood luteinizing hormone increased
Uncommon	Blood follicle stimulating hormone increased

[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, erythema; uncommon: rash generalised, 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, haemoglobin 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 haematology and chemistry abnormalities included:

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

Adverse Reactions of special interest

In clinical trials and post-marketing spontaneous reports, 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 (see section 4.2 'Special warnings and precautions for use').

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 4.2 'Special warnings and precautions for use').

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 4.2 'Special warnings and precautions for use').

In clinical trials and post-marketing spontaneous reports, angioedema has been reported with and without concomitant use of ACE inhibitors (see section 4.2 'Special warnings and precautions for use').

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

Paediatric patients (below 18 years)

The safety of Afinitor in paediatric patients with TSC who have SEGA was demonstrated in two clinical trials (EXIST-1 and Study CRAD001C2485) and in paediatric patients with TSC and refractory seizures in one clinical trial (EXIST-3).

The overall type, frequency and severity of ADRs across the age groups evaluated were similar, with the exception of infections, which were reported at a higher frequency and severity in patients below the age of 6 years. A total of 49 out of 137 patients (36%) <6 years had Grade 3/4 infections, compared to 53 out of 272 patients (19%) 6 to <18 years and 27 out of 203 patients (13%) ≥18 years. Two fatal cases due to infection were reported in patients <18 years receiving everolimus.

Geriatric 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 (including interstitial lung disease), stomatitis, fatigue, and dyspnoea.

Post-marketing experience

The following adverse reactions have been identified during post approval use of AFINITOR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate frequency or establish a causal relationship to drug exposure.

Blood and lymphatic disorders: Thrombotic microangiopathy.

Injury, poisoning and procedural complications: radiation recall syndrome.

4.9 OVERDOSE

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 2000 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Everolimus is an inhibitor targeting mTOR (mammalian target of rapamycin), or more specifically, mTORC1 (mammalian 'target of rapamycin' complex 1). It exerts its activity through high affinity interaction with the intracellular receptor protein FKBP12. The FKBP12/everolimus complex binds to mTORC1, inhibiting its signaling capacity. 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.

mTORC1 signaling is effected through modulation of the phosphorylation of downstream effectors, the best characterized of which are the translational regulators S6 ribosomal protein kinase (S6K1) and eukaryotic initiation factor 4E-binding protein (4E-BP). 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) in multiple tumours such as RCC and angiomyolipoma). 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 estrogen receptor, which is responsible for ligand-independent receptor activation.

Everolimus is an 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.

Clinical trial results did not show an impact of Afinitor on growth and pubertal development.

Constitutive activation of the PI3K/Akt/mTOR pathway can contribute to endocrine resistance in breast cancer. *In vitro* studies show that oestrogen-dependent and HER2+ breast cancer cells are sensitive to the inhibitory effects of everolimus, and that combination of everolimus with Akt, HER2, or aromatase inhibitors synergistically enhances the anti-tumour effect of everolimus.

In tuberous sclerosis syndrome, a genetic disorder, inactivating mutations in either the TSC1 or the TSC2 gene lead to hamartoma formation throughout the body, including seizure and epileptogenesis. The mTOR regulates protein synthesis and multiple downstream cellular functions that may influence neuronal excitability and epileptogenesis. Overactivation of mTOR results in neuronal dysplasia, aberrant axonogenesis and dendrite formation, increased excitatory synaptic currents, reduced myelination, and disruption of the cortical laminar structure causing abnormalities in neuronal development and function. Preclinical studies in models of mTOR dysregulation in the brain demonstrated that treatment with an mTOR inhibitor such as everolimus could prolong survival, suppress seizures, prevent the development of new-onset seizures, and prevent premature death. In summary, everolimus is highly active in this neuronal model of TSC, with benefit apparently attributable to effects on mTORC1 inhibition.

Pharmacodynamic properties/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 eIF-4G was complete at all C_{min} values after the 10 mg daily dose.

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%) tumour size reduction from baseline, which was statistically significant at a 5% level.

In patients with TSC and refractory seizures, a conditional logistic regression analysis for the probability of seizure response vs. Time Normalized(TN)-C_{min} stratified by age subgroup indicated that a 2-fold increase in TN-C_{min} was associated with a 2.172-fold increase (95% CI: 1.339, 3.524) in the odds for a seizure response. Baseline seizure frequency was also a significant factor in the seizure response (with an odds ratio of 0.978 [95% CI: 0.959, 0.998]).

Clinical trials

Hormone receptor-positive advanced breast cancer

BOLERO-2 (Study CRAD001Y2301) a randomised, double-blind, multicentre phase III study of Afinitor + exemestane versus placebo + exemestane was conducted in postmenopausal women with oestrogen receptor-positive, HER 2-neu/non-amplified advanced breast cancer (ABC) with recurrence[2] or progression[3] following prior therapy with letrozole or anastrozole. A total of 724 patients were randomised in a 2:1 ratio to receive either Afinitor (10 mg daily) plus exemestane (25 mg daily) (n=485) or placebo plus exemestane (25 mg daily) (n=239). Randomisation was stratified by documented sensitivity to prior hormonal therapy (yes vs. no) and by the presence of visceral metastasis (yes vs.

[2] Recurrence while on or within 12 months of end of adjuvant treatment with letrozole or anastrozole.

[3] Progression while on or within one month of the end of letrozole or anastrozole treatment for ABC.

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 Tumours (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.

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 median progression-free survival by investigator assessment at the time of the final PFS analysis was 7.8 months and 3.2 months in the Afinitor and placebo arms, respectively. Patients in the placebo+exemestane arm did not cross-over to Afinitor at the time of progression. The median duration of treatment was 29.5 weeks (range 1.0-123.3 weeks) for patients receiving Afinitor + exemestane and 14.1 weeks (range 1.0-101.0 weeks) for the placebo + exemestane group.

The study demonstrated a statistically significant increase in PFS with Afinitor + exemestane compared with placebo + exemestane based on the investigator assessment (Table 7 and Figure 1). The independent assessment was supportive.

Table 7 BOLERO-2 – efficacy results

Analysis	**Afinitor[a] N = 485**	**Placebo[a] N = 239**	**Hazard ratio**	**P-value**
Median progression-free survival (months, 95% CI)				
Investigator radiological review	7.8 (6.9 to 8.5)	3.2 (2.8 to 4.1)	0.45 (0.38 to 0.54)	<0.0001
Independent radiological review	11.0 (9.7 to 15.0)	4.1 (2.9 to 5.6)	0.38 (0.31 to 0.48)	<0.0001
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

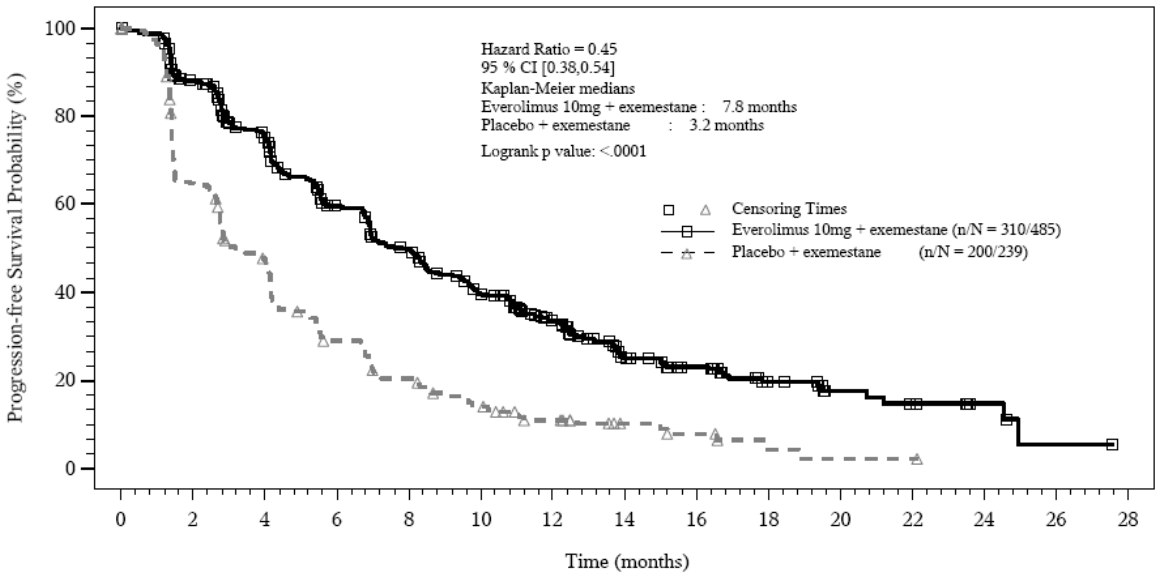
[c] Clinical benefit rate = proportion of patients with CR or PR or SD ≥ 24 weeks

[d] not applicable

[e] p-value is obtained from the exact CMH test using a stratified version of the Cochran-Armitage permutation test

Overall Survival (OS) data are not mature at the time of the interim analysis and no statistically significant treatment-related difference in OS was noted [HR=0.77 (95% CI: 0.57, 1.04)].

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



No. of patients still at risk

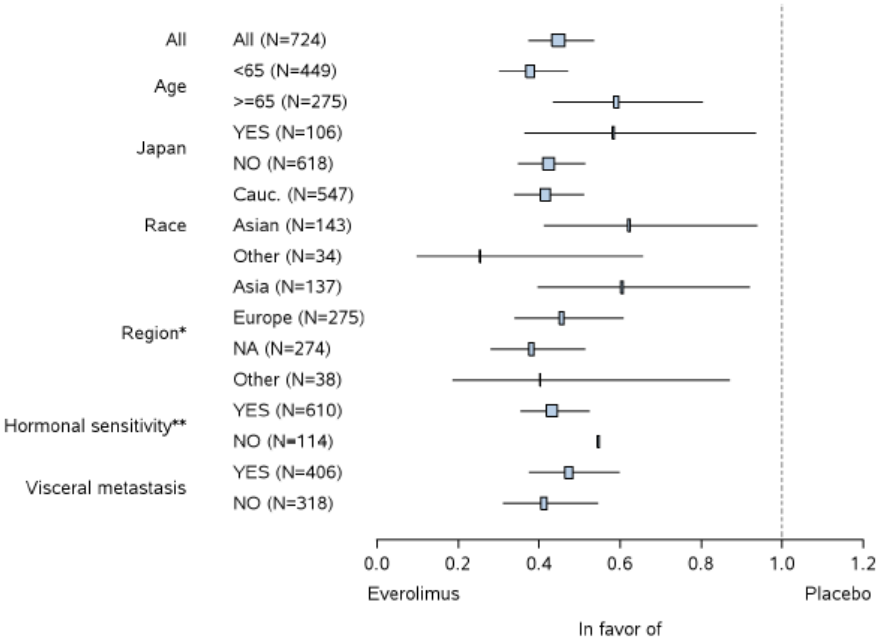
Time (wks)	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	102	108	114	120
Everolimus	485	436	366	304	257	221	185	158	124	91	66	50	35	24	22	13	10	8	2	1	0
Placebo	239	190	132	96	67	50	39	30	21	15	10	8	5	3	1	1	1	0	0	0	0

-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 44% of patients receiving Afinitor + exemestane compared with 16% in the placebo + exemestane arm at a median follow-up of 17.7 months.

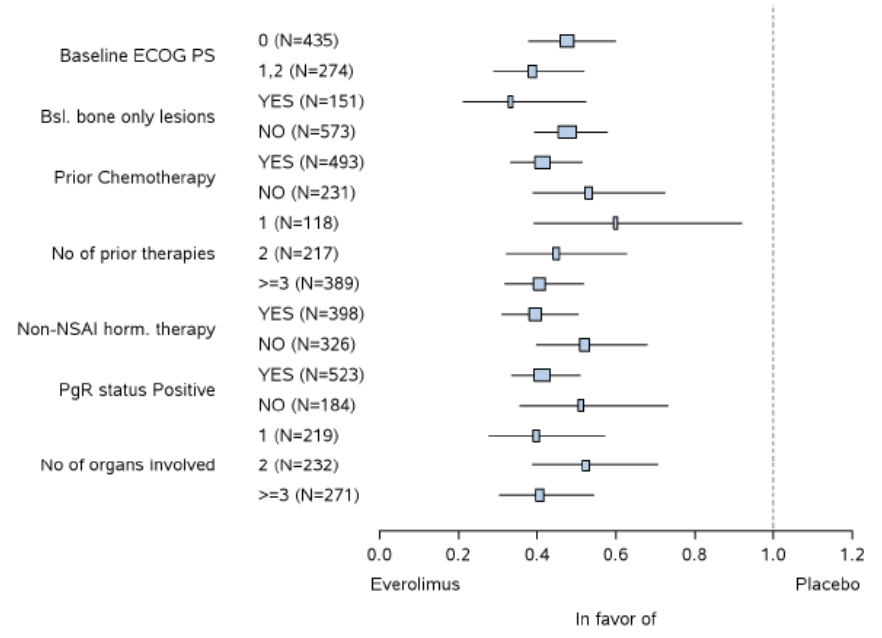
The estimated PFS treatment effect was supported by planned subgroup analysis of PFS per investigator assessment. For all analysed subgroups, a positive treatment effect was seen with Afinitor + exemestane with an estimated hazard ratio vs. placebo + exemestane ranging from 0.25 to 0.62 (see Figure 2 and Figure 3). 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.

Figure 2 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 3 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

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.

Advanced neuroendocrine tumours of pancreatic origin

RADIANT-3 (Study CRAD001C2324), a randomised, double-blind, multicentre phase III study of Afinitor plus best supportive care (BSC) versus placebo plus BSC in patients with progressive, unresectable or metastatic, well or moderately differentiated pancreatic neuroendocrine tumours (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; one sided p<0.0001) (see Table 8 and

Figure 4).

RADIANT-3 enrolled patients with advanced pNET whose disease had progressed within the prior 12 months, was well or moderately differentiated, and unresectable or metastatic. 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 Tumours, version 1.0) as per investigator 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, 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, 55.4% male, 78.5% Caucasian).

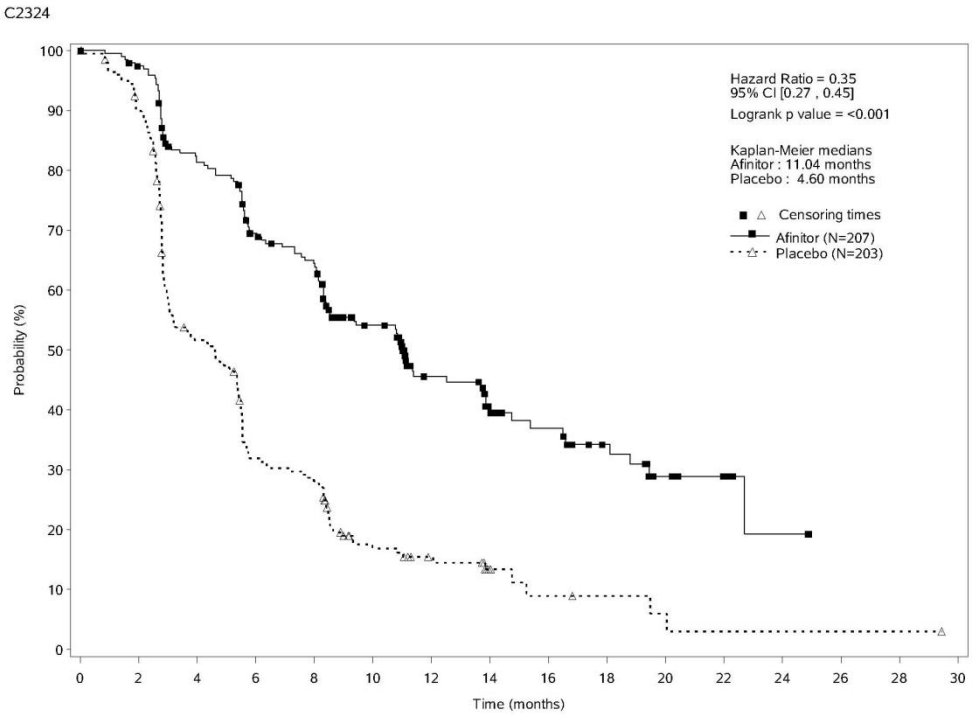
Table 8 RADIANT-3 – Progression Free Survival results

Analysis	**N**	**Afinitor N=207**	**Placebo N=203**	**Hazard Ratio (95%CI)**	**p-value[b]**
	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 4 **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 overall survival results are not yet mature and no statistically significant difference in OS was noted (HR=0.99 (95% CI 0.68 to 1.43) in an updated analysis). Crossover of >74% of patients from placebo to open-label Afinitor following disease progression likely confounded the detection of any treatment-related difference in OS.

Advanced neuroendocrine tumours of gastrointestinal or lung origin

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 well-differentiated (Grade 1 or Grade 2) non-functional neuroendocrine tumours (NET) of gastrointestinal or lung origin without a history of and no active symptoms related to carcinoid syndrome. Randomisation was stratified by prior somatostatin analog (SSA) use, tumour origin and WHO performance status.

The primary endpoint for the study was progression-free survival (PFS) evaluated by Response Evaluation Criteria in Solid Tumours (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 (approximately 50% of patients had received prior SSA treatment in each arm). 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 <0.001) per independent assessment (see Table 9 and Figure 5).

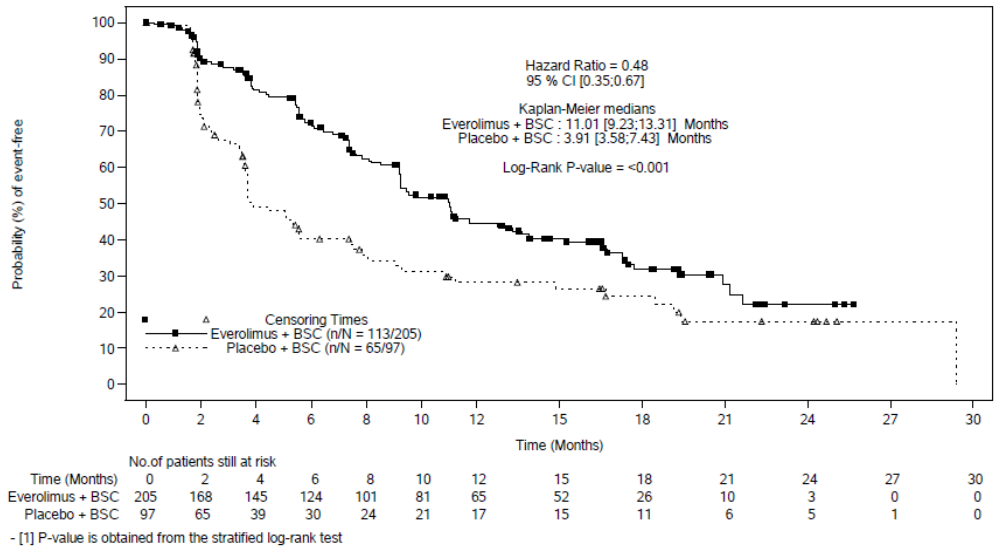
The analysis of PFS based on local investigator assessment was supportive and showed a 2.6-fold prolongation in median progression-free-survival (14.39 months versus 5.45 months), resulting in a 60% risk reduction of progression or death (HR 0.40; 95% CI: 0.29, 0.55; one-sided stratified log-rank test p-value<0. 001) (see Table 9).

Table 9 **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)	<0.001
Investigator radiological review		14.39 (11.24 to 17.97)	5.45 (3.71 to 7.39)	0.40 (0.29 to 0.55)	<0.001

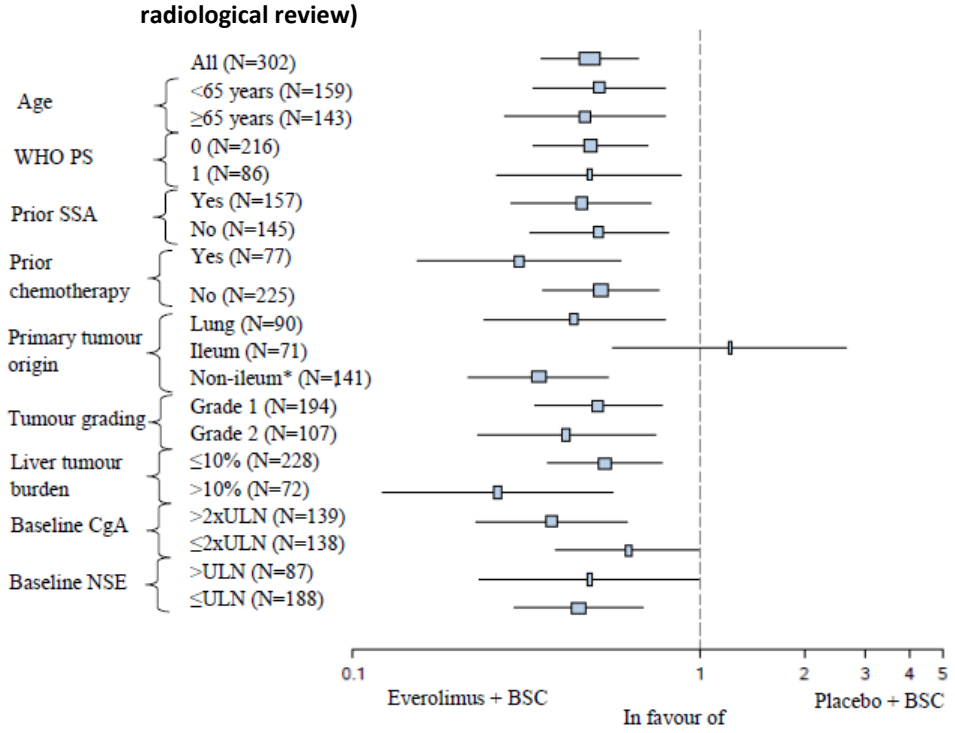
[a] *One-sided p-value from a stratified log-rank test*

Figure 5 **RADIANT-4 – Kaplan-Meier progression-free survival curves (independent radiological review)**



In supportive analyses, positive treatment effect has been observed in all subgroups with the exception of the subgroup of patients with ileum as primary site of tumour origin (Ileum: HR=1.22 [95% CI: 0.56 to 2.65]; Non-ileum: HR=0.34 [95% CI: 0.22 to 0.54]; Lung: HR=0.43 [95% CI: 0.24 to 0.79]) (see Figure 6).

Figure 6 **RADIANT-4 – Progression free survival results by pre-specified patient subgroup (independent radiological review)**



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

ULN: Upper limit of normal

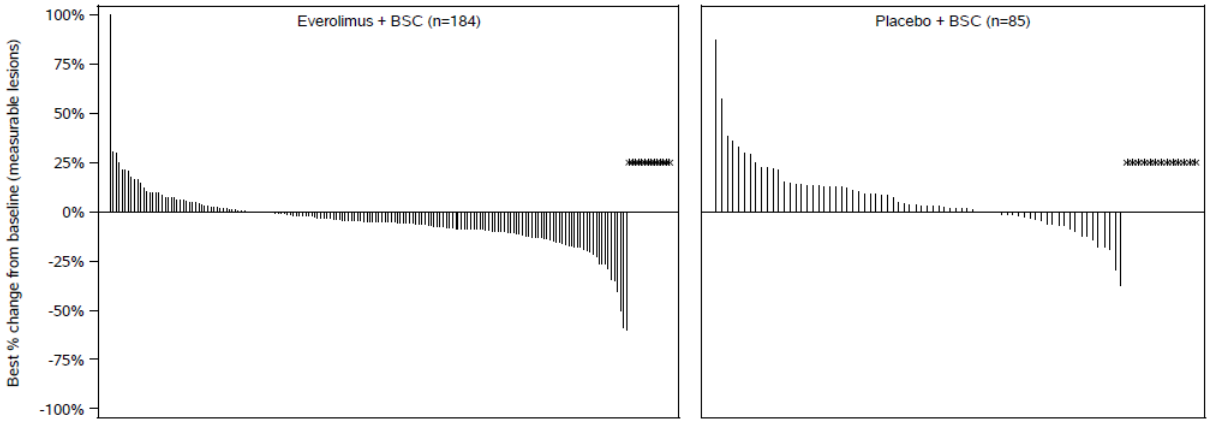
CgA: Chromogranin A

NSE: Neuron specific enolase

Hazard ratio (95% CI) from stratified Cox model

The 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. Tumour reduction was also evident from the corresponding waterfall plot. Results indicate that 63.6% of patients in the everolimus arm experienced tumour shrinkage versus 25.9% for placebo (Figure 7).

Figure 7 **Tumour shrinkage: best percentage change from baseline in sum of longest diameters as per independent radiological assessment**

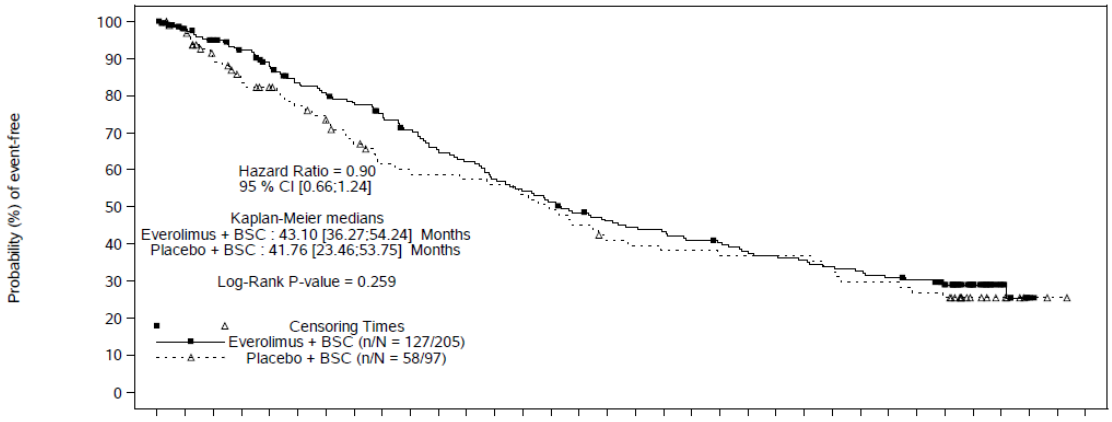


	Everolimus + BSC	Placebo + BSC
Decrease in best percentage change from baseline	63.6%	25.9%
Increase/zero change in best percentage change from baseline	28.8%	58.8%
* % change in target lesion contradicted by overall lesion response = PD	7.6%	15.3%

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 final overall survival (OS) analysis did not show statistically significant difference between those patients who received Afinitor or placebo during the blinded treatment period of the study [HR= 0.90 (95% CI: 0.66 to 1.24)] (Figure 8).

Figure 8 RADIANT-4 - Kaplan-Meier plot of overall survival (Full Analysis Set)



No.of patients still at risk

Time (Months)	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75	78	81	84	87	90	93	96	99
Everolimus + BSC	205	190	182	173	163	151	145	140	133	124	115	109	101	95	90	84	79	76	74	70	68	64	62	60	57	55	52	50	44	28	10	2	0	0
Placebo + BSC	97	93	80	71	67	62	57	51	45	43	43	42	41	39	36	33	29	28	27	27	26	26	26	26	24	21	21	19	18	9	6	2	1	0

Clinically or statistically significant differences were not observed between the two treatment arms in terms of time to deterioration of WHO PS (HR: 1.02; 95% CI: 0.65, 1.61) and time to deterioration of FACT-G total score (HR: 0.74; 95% CI: 0.50, 1.10).

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, cytokines and chemotherapy 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.

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 9).

Table 10 RECORD-1 - Progression Free Survival results

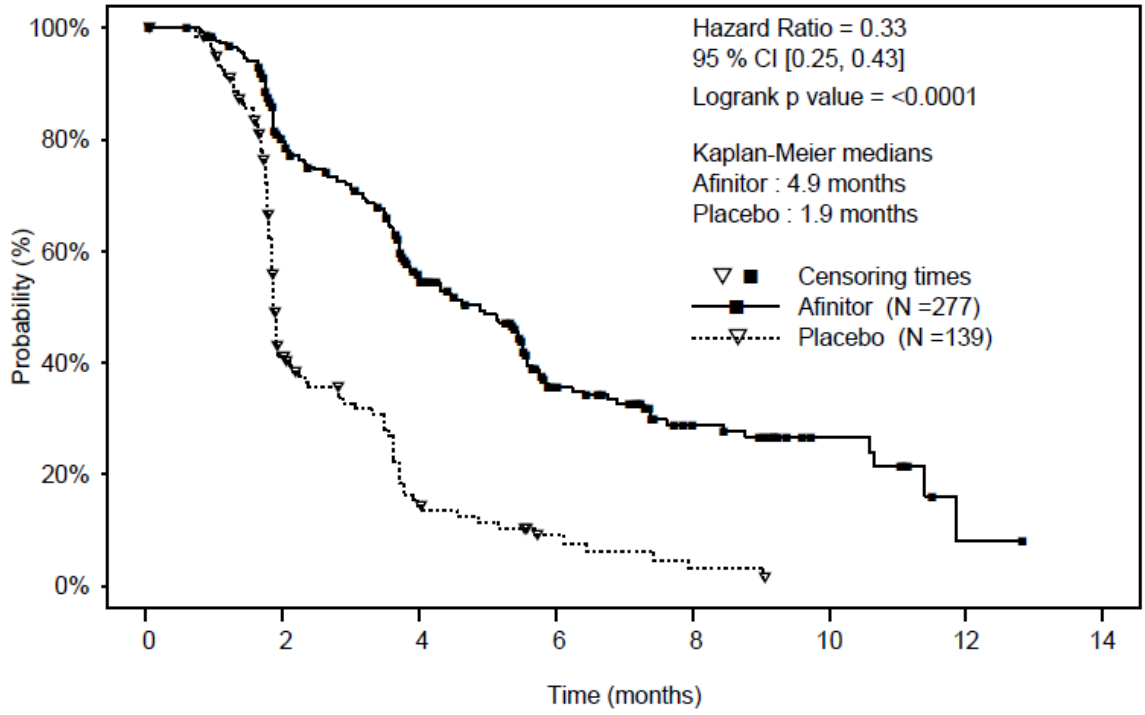
Population	**N**	**Afinitor N=277**	**Placebo N=139**	**Hazard Ratio (95%CI)**	**p-value**
		Median progression-free survival (months) (95% CI)			
Primary analysis					
All (blinded independent central review)	416	4.9 (4.0 to 5.5)	1.9 (1.8 to 1.9)	0.33 (0.25 to 0.43)	<0.001 [a]
Supportive/sensitivity 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]

Population	N	Afinitor N=277	Placebo N=139	Hazard (95%CI)	Ratio	p-value

[a] Log-rank test stratified by prognostic score

[b] Unstratified one-sided log-rank test

Figure 9 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).

No statistically significant treatment-related difference in overall survival was noted, although there was a trend in favour of Afinitor (HR 0.82; 95% CI: 0.57 to 1.17; p=0.137). Crossover to open-label Afinitor following disease progression for patients allocated to placebo confounded the detection of any treatment-related difference in overall survival.

Subgroup analyses by age (<65 years and ≥65 years) indicated that the Afinitor treatment effect was consistent.

No difference in health-related quality of life was observed in patients receiving Afinitor compared to placebo patients.

Tuberous sclerosis complex (TSC) with refractory seizures

EXIST-3 (Study CRAD001M2304), a randomised, double-blind, multicenter, three-arm, parallel-group, phase-III study of Afinitor Dispersible Tablets versus placebo as adjunctive therapy was conducted in TSC patients with refractory seizures. Patients were treated with concomitant and stable dose of 1-3 antiepileptic drug(s) (AEDs) prior to study entry. The study consisted of three phases: an 8-week baseline observation phase; an 18-week double-blind, placebo-controlled core treatment phase (composed of titration and maintenance periods) and an extension phase in which all patients received everolimus.

The primary endpoint was the response rate defined as at least a 50% reduction from baseline in seizure frequency during the maintenance period of the core phase.

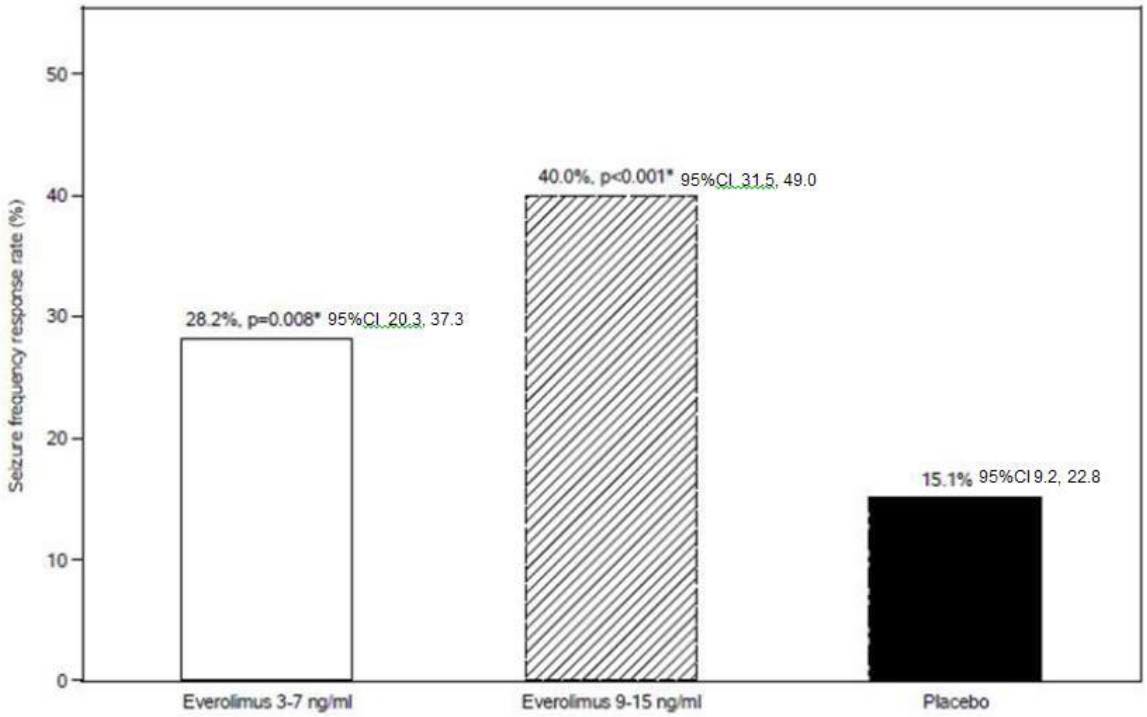
The percentage reduction from baseline in seizure frequency during the maintenance period of the core phase was a supporting endpoint.

Secondary endpoints included seizure freedom, proportion of patients with ≥25% seizure frequency reduction from baseline, distribution of reduction from baseline in seizure frequency (≤-25%, >-25% to <25%; ≥25% to <50%; ≥50% to <75%; ≥75% to <100%; 100%), long-term evaluation of seizure frequency and overall quality-of-life.A total of 366 TSC patients with refractory seizures were randomised in an 1:1.09:1 ratio to Afinitor (n=117) low trough (LT) range (3 to 7 ng/mL), Afinitor (n=130) high trough (HT) range (9 to 15 ng/mL) or placebo (n=119) added to each patient's concomitant AED therapy. Median age was 10.1 years (range: 2.2-56.3; 28.4% <6 years, 30.9% 6 to <12 years, 22.4% 12 to <18 years and 18.3% >18 years); 51.9% were male and 64.8% were Caucasian. Median duration of treatment was 18 weeks for all three arms.

At baseline, 19.4% of patients had focal seizures with retained awareness (sensory with electroencephalogram (EEG) or motor), 45.1% had focal seizures with impaired awareness (predominantly non-motor), 69.1% had focal motor seizures, and 1.6% had generalised onset seizures (previously confirmed by EEG). The median baseline seizure frequency across the treatment arms was 35, 38, and 42 seizures per 28 days for the Afinitor LT, Afinitor HT, and placebo groups, respectively. The majority of patients (67%) failed 5 or more AEDs prior to the study and 41.0% and 47.8% of patients were taking 2 and ≥ 3 AEDs during the study.

The study met its primary objective for seizure frequency response rate, as per EMA recommendation, in the two everolimus trough + concomitant AEDs arms over the placebo + concomitant AEDs arm. The response rate, defined as at least 50% reduction from baseline in seizure frequency was 28.2% (95% CI: 20.3, 37.3) in the Afinitor LT arm (p=0.008), 40.0% (95% CI: 31.5, 49.0) in the Afinitor HT arm (p<0.001) and 15.1% (95% CI: 9.2, 22.8) in the placebo arm (Figure 10). Odds Ratios vs placebo (95% CIs): Afinitor LT arm 2.21 (1.16, 4.20), Afinitor HT arm 3.93 (2.10, 7.32).

Figure 10 **EXIST-3 - Seizure frequency response rate (Full Analysis Set)**



** Statistically significant difference versus placebo, based on Cochran-Mantel-Haenszel tests stratified by age subgroup and a Bonferroni-Holm procedure to ensure a family-wise Type I error rate of 2.5% one-sided*

Table 11 **EXIST-3 - Seizure frequency response rate**

	Everolimus		**Placebo**
	LT target of 3-7 ng/mL	**HT target of 9-15 ng/mL**	
Statistic	**N=117**	**N=130**	**N=119**
Responders – n (%)	33 (28.2)	52 (40.0)	18 (15.1)
Response rate 95% CI [a]	20.3, 37.3	31.5, 49.0	9.2, 22.8
Odds ratio (versus placebo) [b]	2.21	3.93	
95% CI	1.16, 4.20	2.10, 7.32	
p-value (versus placebo) [c]	0.008	<0.001	
Statistically significant per Bonferroni-Holm procedure [d]	Yes	Yes	
Non-responders – n (%)	84 (71.8)	78 (60.0)	101 (84.9)

[a] *Exact 95% CI obtained using Clopper-Pearson method*

[b] *Odds ratio and its 95% CI obtained using logistic regression stratified by age subgroup. Odds ratio >1 favors everolimus arm.*

[c] *p-values computed from the Cochran-Mantel-Haenszel test stratified by age subgroup*

[d] *Family-wise error rate of 2.5% one-sided*

Percentage reduction from baseline in seizure frequency was a supporting analysis.

The median percentage reduction from baseline in seizure frequency was 29.3% (95% CI: 18.8, 41.9) in the Afinitor LT arm (p = 0.003), 39.6% (95% CI: 35.0, 48.7) in the Afinitor HT arm (p < 0.001) and 14.9% (95% CI: 0.1, 21.7) in the placebo arm.

The seizure free rate (the frequency of seizure-free days per 28 days during the maintenance phase) was 5.1% (95% CI: 1.9, 10.8) and 3.8% (95% CI: 1.3, 8.7) in the Afinitor LT and HT arms, respectively, versus 0.8% (95% CI: 0.0, 4.6) in the placebo arm.

The proportion of patients with at least 25% reduction in seizure frequency was 52.1% (95% CI: 42.7, 61.5) in the Afinitor LT and 70.0% (95% CI: 61.3, 77.7) in the Afinitor HT arms, respectively, versus 37.8% (95% CI: 29.1, 47.2) on placebo.

Higher proportions of responders were evident for all response categories in the everolimus LT and HT arms relative to placebo. Furthermore, approximately twice as many patients in the placebo arm experienced seizure exacerbation relative to the everolimus LT and HT arms.

A homogeneous and consistent everolimus effect was observed across all subgroups evaluated for the primary efficacy endpoints by: age categories (Table 12), gender, race and ethnicity, seizure types, seizures frequency at Baseline, number and name of concomitant AEDs, and TSC features (angiomyolipoma, SEGA, cortical tuber status).

Table 12 EXIST-3 - Response rate by age

	Everolimus		**Placebo**
	LT target of 3-7 ng/mL	**HT target of 9-15 ng/mL**	
Age category	**N=117**	**N=130**	**N=119**
<6 years	**n=33**	**n=37**	**n=34**
Response rate (95% CI) [a]	30.3 (15.6, 48.7)	59.5 (42.1, 75.2)	17.6 (6.8, 34.5)
6 to <12 years	**n=37**	**n=39**	**n=37**
Response rate (95% CI) [a]	29.7 (15.9, 47.0)	28.2 (15.0, 44.9)	10.8 (3.0, 25.4)
12 to <18 years	**n=26**	**n=31**	**n=25**
Response rate (95% CI) [a]	23.1 (9.0, 43.6)	32.3 (16.7, 51.4)	16.0 (4.5, 36.1)
≥ 18 years	**n=21**	**n=23**	**n=23**
Response rate (95% CI) [a]	28.6 (11.3, 52.2)	39.1 (19.7, 61.5)	17.4 (5.0, 38.8)

[a] *Exact 95% CI obtained using Clopper-Pearson method*
[b] *95% CI of the median based on bootstrap percentiles*

Tuberous sclerosis complex (TSC) with renal angiomyolipoma

EXIST-2 (Study CRAD001M2302), a randomised, double-blind, multicentre phase III study of a once daily oral dose of Afinitor 10 mg 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 Tablets 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

embolisation/nephrectomy; 96.6% had skin lesions at baseline and 44.1% had target SEGAs (at least one SEGA ≥ 1 cm in longest diameter). The median duration of blinded study treatment was 48.1 weeks (range 2 to 115) for patients receiving Afinitor and 45.0 weeks (range 9 to 115) for those receiving placebo.

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 (see footnote 2 in Table 13). Best overall response rate was 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 13).

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 randomisation), 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 embolisation were reported.

Table 13 EXIST-2 - Angiomyolipoma response

	Primary Analysis[3]			**Final analysis[4]**
	Afinitor	**Placebo**	**p-value**	**Afinitor**
	N=79	**N=39**		**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 14).

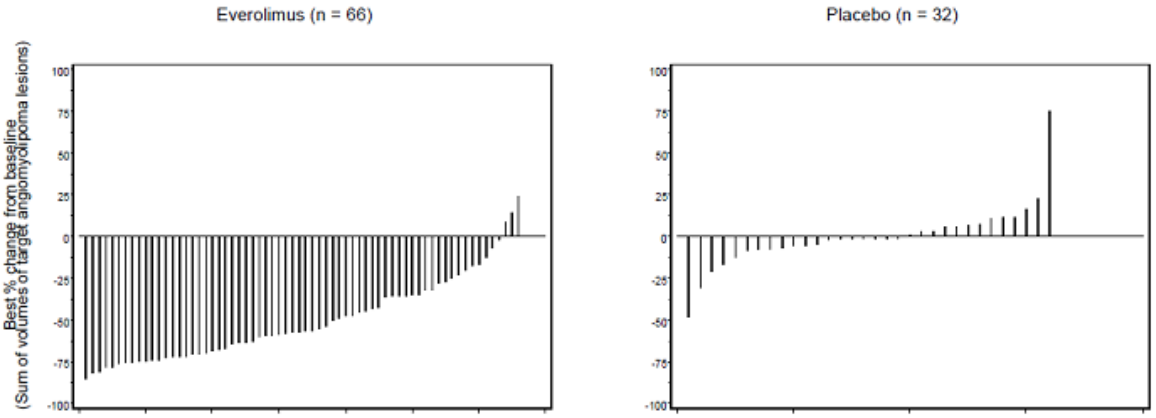
Table 14 EXIST-2 - Angiomyolipoma response by subgroup at primary analysis

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)

The waterfall plots provide a graphical representation of the reduction in angiomyolipoma volume (Figure 11) at primary analysis; 95.5% of patients in the Afinitor arm experienced angiomyolipoma shrinkage versus 59.4% in the placebo arm.

Figure 11 **EXIST-2 - Angiomyolipoma shrinkage: best percentage change from baseline at primary analysis[1,2]**



[1] Per independent central radiology review

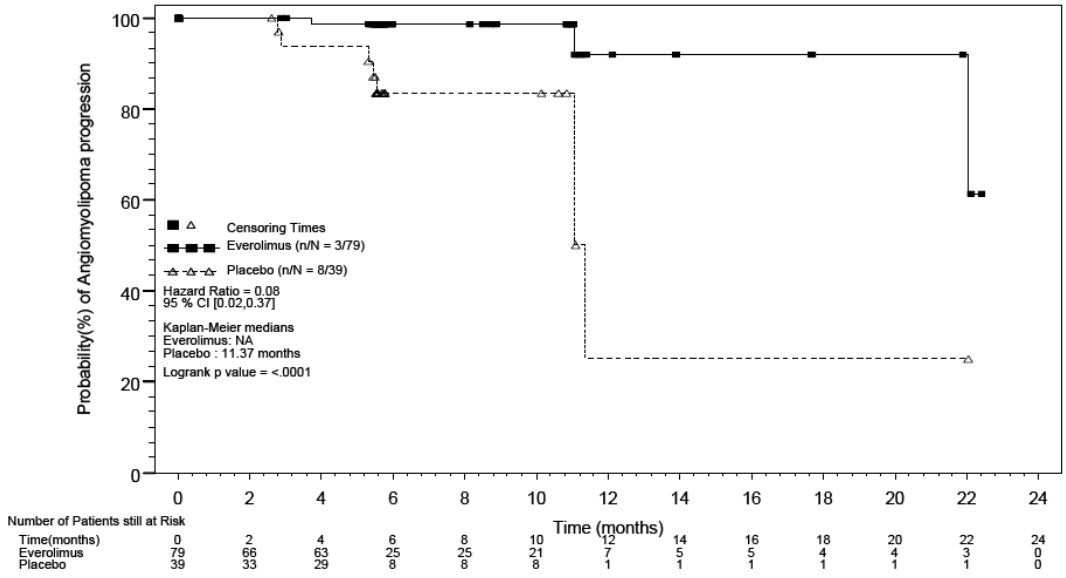
[2] Patients for whom the best % change in sum of volumes of target angiomyolipoma lesions was not available and patients with overall angiomyolipoma response = Not evaluable were excluded from the graph.

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 12) 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 (Figure 13).

Figure 12 **EXIST-2 Kaplan-Meier plot of time to angiomyolipoma progression at primary analysis[1,2]**

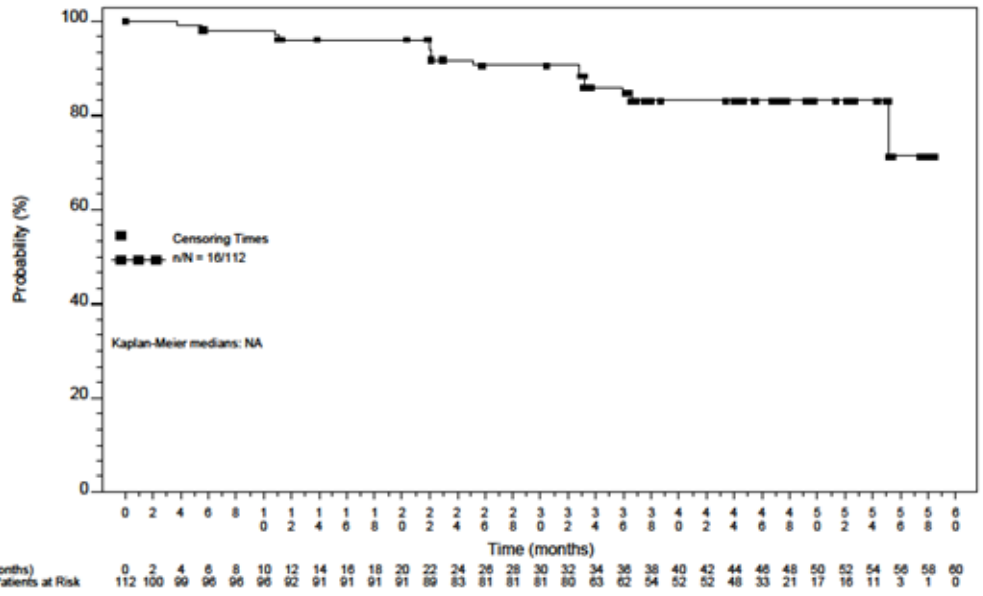


[1] p-value is obtained from the one-sided stratified log-rank test.
[2] Hazard ratio <1 implies reduced risk of angiomyolipoma progression in the Everolimus group.

[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 13 **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 (Table 15). At the final analysis, the skin lesion response rate had increased to 68.2% (73/107) (95% CI: 58.5%, 76.9%) (Table 15), with one patient reporting a confirmed complete clinical skin lesion response and no patients experiencing progressive disease as their best response.

Table 15 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 randomised to placebo with a SEGA lesion at baseline) and increased to 48.0% (24/50) at the final analysis.

In EXIST-2, of 34 patients eligible for follow-up after completion of everolimus treatment, 16 were able to be evaluated for efficacy. 12 of 16 evaluable patients evaluated for angiomyolipoma volume for up to 1 year after discontinuation of everolimus, experienced an increase in tumour volume compared to their most recent tumour 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).

<u>Tuberous sclerosis complex (TSC) with Subependymal giant cell astrocytoma (SEGA)</u>

Phase III trial in patients with TSC who have SEGA

EXIST-1 (Study CRAD001M2301), a randomised, double-blind, multicentre phase III study of Afinitor versus placebo was conducted in patients with TSC who have SEGA, irrespective of age. The study required the titration of Afinitor from an initial starting dose of 4.5 mg/m^2/day, subject to tolerability,

with the objective of attaining trough concentrations consistent with the revised 5 to 15 ng/mL range. 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.

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 52.2 weeks (range 24 to 89) for patients receiving Afinitor and 46.6 weeks (range 14 to 88) for those receiving placebo.

Results showed that Afinitor was superior to placebo for the primary endpoint of best overall SEGA response ($p<0.0001$) (see footnote 2 in Table 16). 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 (Table 16). 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 16 EXIST-1 – SEGA response

	Primary analysis[3]			Final analysis[4]
	Afinitor N=78	**Placebo N=39**	**p-value**	**Afinitor N=111**
SEGA response rate[1,2] - (%)	34.6	0	<0.0001	57.7
95% CI	24.2, 46.2	0.0, 9.0		47.9, 67.0
Best overall SEGA response - (%)				
Response	34.6	0		57.7
Stable disease	62.8	92.3		39.6
Progression	0	7.7		0
Not evaluable	2.6	0		2.7

[1] Per independent central radiology review

[2] SEGA responses were confirmed with a repeat scan. Response was defined as: ≥ 50% reduction in the sum of SEGA volume relative to baseline, plus no unequivocal worsening of non-target SEGA lesions, plus absence of new SEGA ≥ 1 cm in longest diameter, plus no new or worsening hydrocephalus

[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 204.9 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 17).

Table 17 EXIST-1 - SEGA response by subgroup at 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)

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%

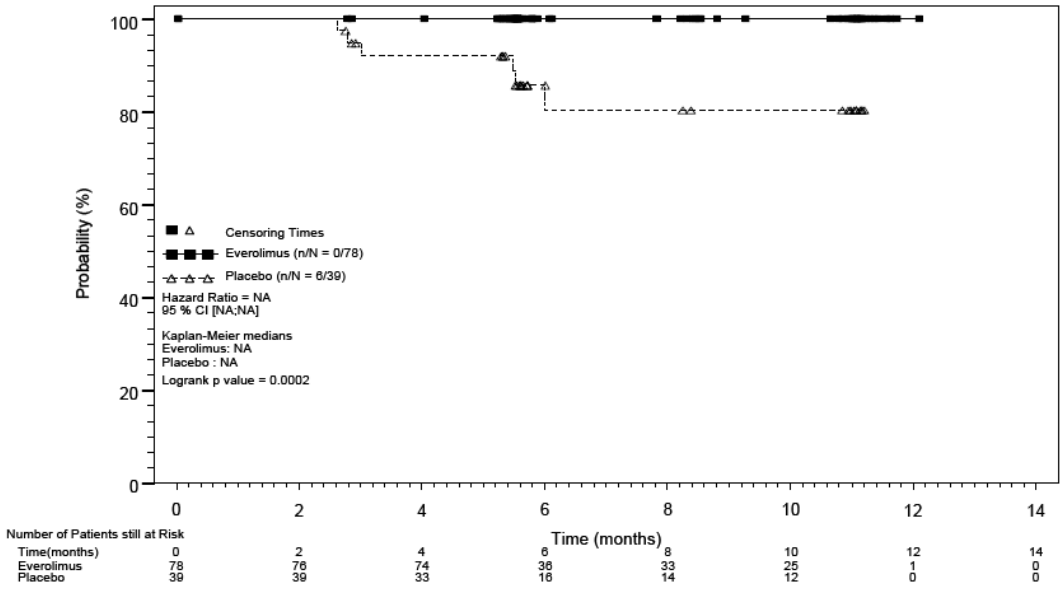
(31/74) of patients had ≥50% reductions and 78.4% (58/74) of patients had ≥ 30% reductions in SEGA volume.

In the everolimus treated population (N=111) of the study, including patients who crossed over from the placebo group, tumour 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 14). 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 randomised to everolimus and patients randomised to placebo who thereafter crossed over to everolimus demonstrated durable responses (Figure 15).

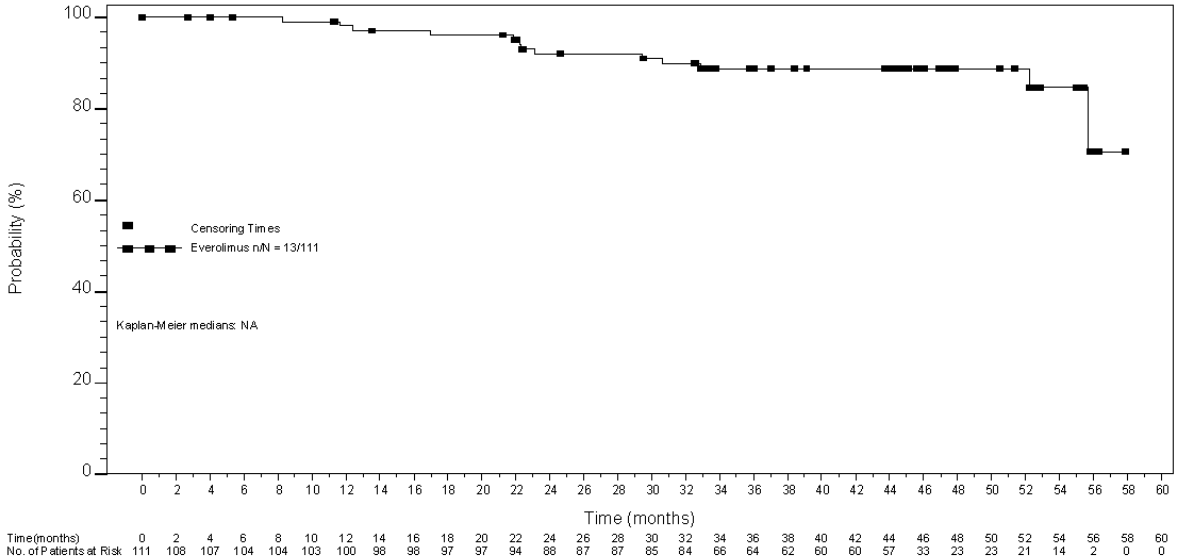
Figure 14 EXIST-1 - Kaplan-Meier plot of time to SEGA progression[1,2] at primary analysis



[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 15 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 (Table 18). At the final analysis, the skin lesion response rate increased to 58.1% (95% CI: 48.1, 67.7) (Table 18).

Table 18 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 tumour 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

Study CRAD001C2485, a prospective, open-label, single-arm trial was conducted to evaluate the safety and efficacy of Afinitor in patients with SEGA associated with TSC. Serial radiological evidence of SEGA growth was required for entry.

Change in SEGA volume at the end of the core 6-month treatment phase was assessed via an independent central radiology review, was the primary efficacy endpoint. After the core treatment phase, patients could continue to receive Afinitor treatment as part of an 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 67.8 months (range: 4.7 to 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 time points (Table 19). At 6 months, 9 out of 28 patients (32%, 95% CI: 16% to 52%) had a ≥ 50% reduction in the tumour volume of their largest SEGA lesion (Table 19).

Three of 4 patients who had prior surgery experienced a ≥ 50% reduction in the tumour volume of their largest SEGA lesion. One of these three patients responded by month 6. No patient developed new lesions, worsening hydrocephalus, increased intracranial pressure, and none required surgical resection or other therapy for SEGA.

Table 19 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 tumour 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

Long-term follow-up to a median duration of 67.8 months (range: 4.7 to 83.2 months) 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).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After administration of Afinitor Tablets 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 with daily dosing between 5 and 10 mg. AUC shows dose-proportionality over the 5 to 70 mg dose range.

Effects of Food

In healthy subjects, high fat meals reduced systemic exposure to Afinitor 10 mg (as measured by AUC) by 22% and the peak plasma concentration C_{max} by 54%. Light fat meals reduced AUC by 32% and C_{max}

by 42%. Food, however, had no apparent effect on the post absorption phase concentration-time profile.

Relative bioavailability of dispersible tablets

The $AUC_{0-\infty}$ of the Afinitor Dispersible Tablets when administered as a suspension in water was equivalent to that of Afinitor Tablets (85% to 91% of that associated with Afinitor Tablets). The predicted trough concentrations of everolimus at steady-state after daily administration were similar for both dosage forms. The C_{max} of everolimus associated with the Afinitor Dispersible Tablets was, however, somewhat lower (64% to 80% relative to that associated with Afinitor Tablets).

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 10 mg/day of Afinitor. Plasma protein binding is approximately 74% both in healthy subjects and 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, and exposure of everolimus in brain was enhanced by co-administration with ciclosporin.

Metabolism

Everolimus is a substrate of CYP3A4 and P-glycoprotein (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.

Excretion

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

Steady-state pharmacokinetics

After 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 with a daily dosing regimen. Steady-state was achieved within two weeks. C_{max} is dose-proportional between 5 and 10 mg. t_{max} occurs at 1 to 2 hours post-dose. There was a significant correlation between $AUC_{0-\tau}$ and pre-dose trough concentration at steady-state on a daily regimen. Mean elimination half-life is approximately 30 hours.

Special population

Hepatic impairment

The safety, tolerability and pharmacokinetics of Afinitor were evaluated in two single oral dose studies of Afinitor Tablets in 8 and 34 subjects with impaired hepatic function relative to subjects with normal hepatic function. In one study, the average AUC of everolimus in 8 subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in 8 subjects with normal hepatic function. In a second study of 34 subjects with different impaired hepatic function compared to normal subjects, there was a 1.6-fold, 3.3-fold, and 3.6-fold increase in exposure (i.e. $AUC_{(0\text{-}inf)}$) 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 section 4.2 'Dose and method of administration and 4.4 'Special warning and precautions').

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.

Paediatrics

There is no relevant indication for use of Afinitor in the paediatric cancer population (see section 4.2 'Dose and method of administration') or in paediatric patients with TSC who have renal angiomyolipoma. In patients with TSC who have SEGA receiving Afinitor tablets, 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 receiving Afinitor tablets, the everolimus geometric mean C_{min} values normalised 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.

In patients with TSC and refractory seizures receiving Afinitor Dispersible Tablets, a trend was observed toward lower C_{min} normalised to dose (as mg/m^2) in younger patients. Median C_{min} normalised to mg/m^2 dose was lower for the younger age groups, indicating that everolimus clearance (normalised to body surface area) was higher in younger patients.

Elderly

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

Ethnicity

Asian patients with neuroendocrine tumours (NETs) showed a consistent pattern of reduced clearance, and higher AUC values, with higher C_{min} values compared to non-Asian patients (see section 4.2 'Special warnings and precautions for use').

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Everolimus did not show genotoxicity in *in vitro* tests for gene mutation (bacteria and mammalian cells), and in an *in vitro* test and an *in vivo* mouse micronucleus assay for clastogenic activity.

Carcinogenicity

Long-term carcinogenicity studies have been carried out in mice and rats and no oncogenic responses were observed. Drug exposures (blood AUC) were up to 4-times [4] the expected human value at 10 mg/day in mice, but were less than the expected maximum human value in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablets: Butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, lactose.

Dispersible tablets: Butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, mannitol, microcrystalline cellulose, and colloidal anhydrous silica.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the ARTG. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C in the original packaging. Protect from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

2.5 mg tablet: PA/Al/PVC/Al Packs of 10, 30 and 90 tablets.
5 mg tablet: PA/Al/PVC/Al Packs of 30, 50, 60 and 100, 120 tablets.
10 mg tablet: PA/Al/PVC/Al Packs of 30, 50, 60, 100 and 120 tablets.
2 mg dispersible tablet: PA/Al/PVC/Al Packs of 30, 50, 60 and 100, 120 tablets.
3 mg dispersible tablet: PA/Al/PVC/Al Packs of 30, 50, 60 and 100, 120 tablets.
5 mg dispersible tablet: PA/Al/PVC/Al Packs of 30, 50, 60 and 100, 120 tablets.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

[4] AUC0-24 hr=2231 ng.hr/mL in mice vs AUC=560 in human at 10 mg/day.

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

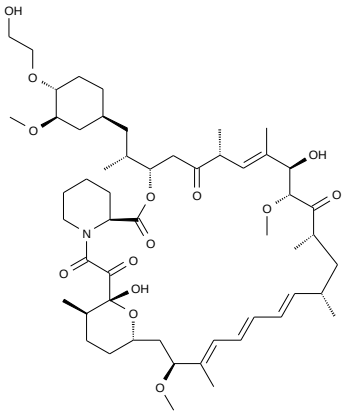
6.7 PHYSICOCHEMICAL PROPERTIES

Everolimus is a white to faintly yellow powder practically insoluble in water but soluble in organic solvents such as ethanol and methanol.

Chemical structure

The chemical name is 40-O-(2-hydroxyethyl)-rapamycin or 40-O-(2-hydroxyethyl)-sirolimus. Its molecular formula is $C_{53}H_{83}NO_{14}$ and its molecular weight is 958.2.

The structural formula of everolimus is:



CAS number

159351-69-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Medicine schedule (Poisons Standard) Prescription Only Medicine (Schedule 4).

8 SPONSOR

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
Header	Deletion of black triangle symbol and related text.
4.5	Addition of interaction with cannabidiol.

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