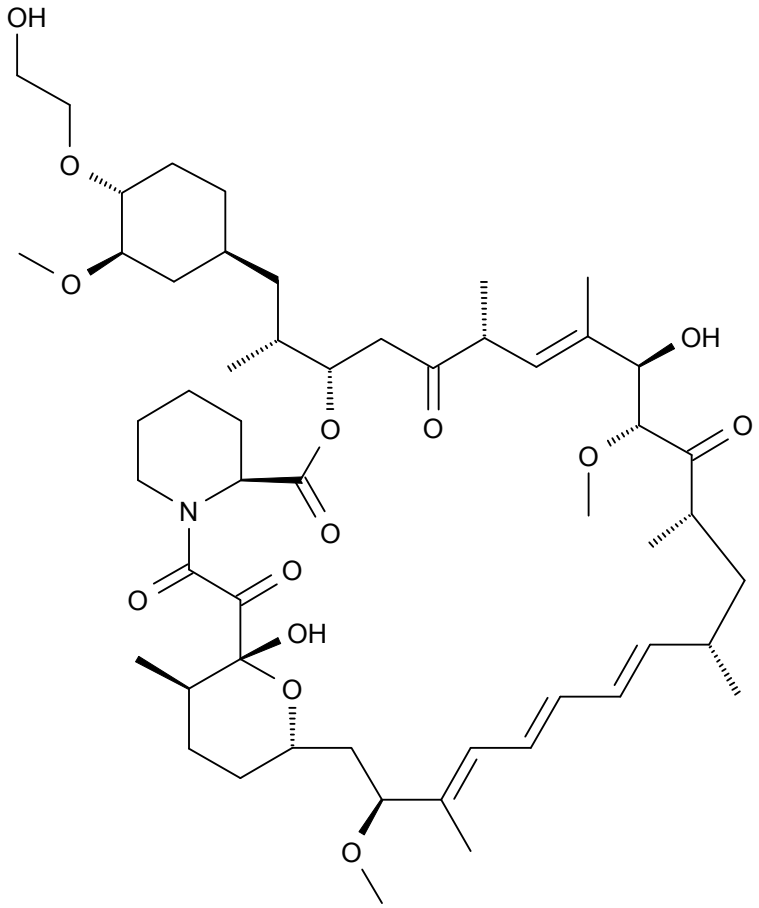
AFINITOR®
(everolimus)

NAME OF THE MEDICINE

The active ingredient of Afinitor is everolimus.

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:



DESCRIPTION

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

CAS number: 159351-69-6

Excipients: (Tablets) Butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, lactose anhydrous.

Excipients: (dispersible tablets) Butylated hydroxytoluene, magnesium stearate, lactose monohydrate, hypromellose, crospovidone, mannitol, cellulose microcrystalline, and silica colloidal anhydrous.

PHARMACOLOGY

Pharmacodynamics

Mechanism of Action

Everolimus is a signal transduction inhibitor targeting mTOR (mammalian target of rapamycin), or more specifically, mTORC1 (mammalian 'target of rapamycin' complex 1). mTOR is a key serine-threonine kinase playing a central role in the regulation of cell growth, proliferation and survival. The regulation of mTORC1 signalling is complex, being modulated by mitogens, growth factors, energy and nutrient availability. mTORC1 is an essential regulator of global protein synthesis downstream on the PI3K/AKT pathway, which is dysregulated in the majority of human cancers.

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.

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. In tuberous sclerosis syndrome, a genetic disorder, inactivating mutations in either the TSC1 or the TSC2 gene lead to hamartoma formation throughout the body.

Pharmacodynamic properties

Everolimus exerts its activity through high affinity interaction with the intracellular receptor protein FKBP12. The FKBP12/everolimus complex binds to mTORC1, inhibiting its signalling capacity. mTORC1 signalling is effected through modulation of the phosphorylation of downstream effectors, the best characterised of which are the translational regulators S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-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). Everolimus is an inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood vessel-associated smooth muscle cells.

In a mouse neuronal model of TSC in which TSC1 is ablated in most neurons during cortical development, everolimus was shown to markedly improve survival and neurological function following repeated intraperitoneal administration.

Pharmacokinetics

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 AUC0-∞ 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 Cmax 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 cyclosporin.

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.

Elimination

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 cyclosporin, 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.

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. 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. $AUC_{(0-inf)}$) 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 Dosage and Administration 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 Dosage and Administration) or in paediatric patients with TSC who have renal angiomyolipoma in the absence of SEGA. In patients with TSC who have SEGA receiving Afinitor tablets, everolimus Cmin 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 Cmin 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.

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 Precautions).

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

Exposure-response relationships

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

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

CLINICAL TRIALS

Hormone receptor-positive advanced breast cancer

BOLERO-2 (Study CRAD001Y2301) a randomized, double-blind, multicentre phase III study of Afinitor + exemestane versus placebo + exemestane was conducted in postmenopausal women with oestrogen receptor-positive, HER 2-neu/non-amplified advanced breast cancer (ABC) with recurrence[1] or progression[2] following prior therapy with letrozole or anastrozole. A total of 724 patients were randomized 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). Randomization was stratified by documented sensitivity to prior hormonal therapy (yes vs. no) and by the presence of visceral metastasis (yes vs. no). Sensitivity to prior hormonal therapy was defined as either (1) documented clinical benefit (complete response [CR], partial response [PR], stable disease ≥ 24 weeks) to at least one prior hormonal therapy in the advanced setting or (2) at least 24 months of adjuvant hormonal therapy prior to recurrence.

The primary endpoint for the trial was progression-free survival (PFS) evaluated by Response Evaluation Criteria in Solid 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 1 and Figure 1). The independent assessment was supportive.

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

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

Table 1 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

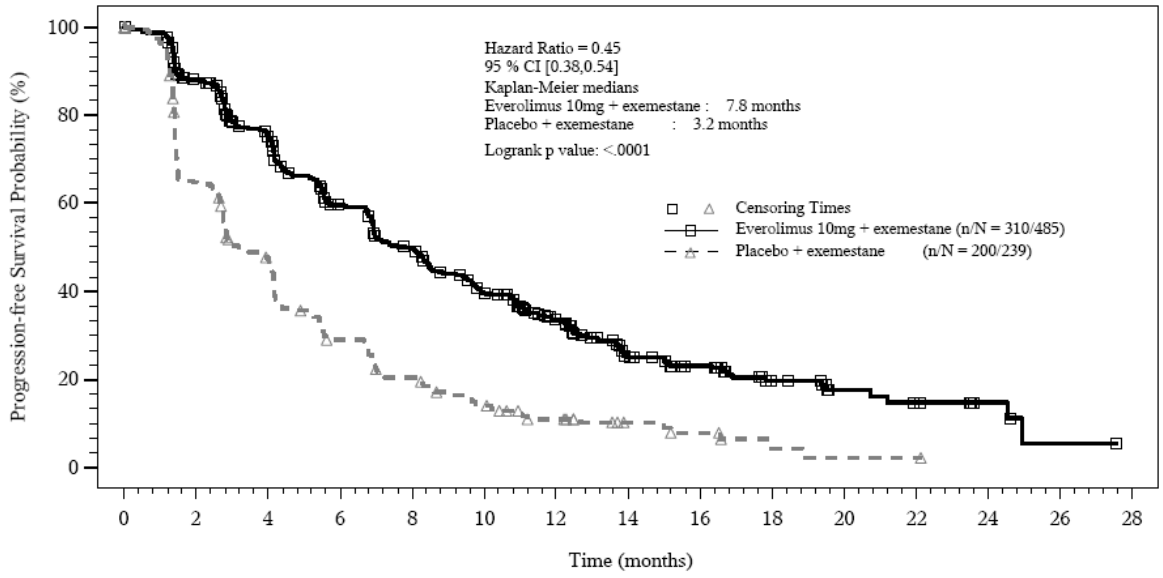
c Clinical benefit rate = proportion of patients with CR or PR or SD ≥ 24 weeks

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

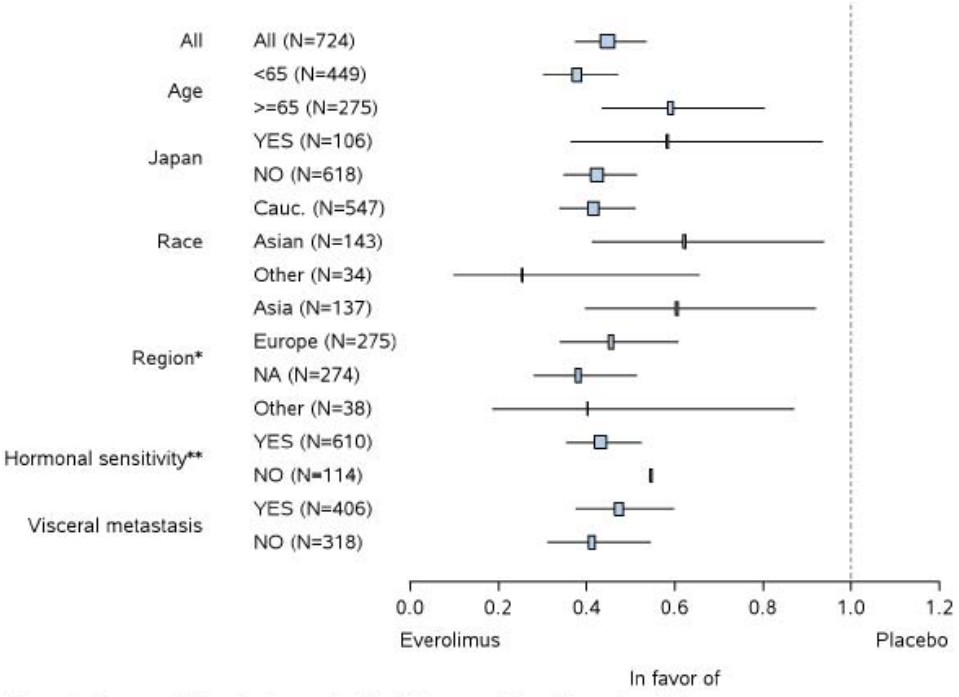
Time (wks)	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	102	108	114	120
Everolimus	485	436	366	304	257	221	185	158	124	91	66	50	35	24	22	13	10	8	2	1	0
Placebo	239	190	132	96	67	50	39	30	21	15	10	8	5	3	1	1	1	0	0	0	0

-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.

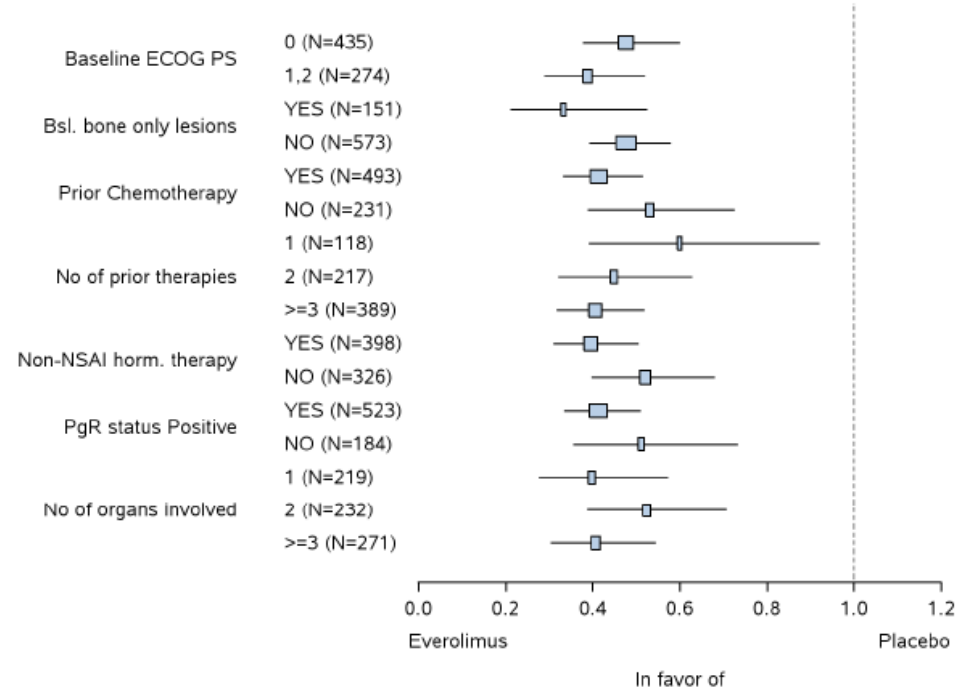
The estimated PFS treatment effect was supported by planned subgroup analysis of PFS per investigator assessment. For all analyzed subgroups, a positive treatment effect was seen with Afinitor + exemestane with an estimated hazard ratio vs. placebo + exemestane ranging from 0.25 to 0.62 (see Figure 2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

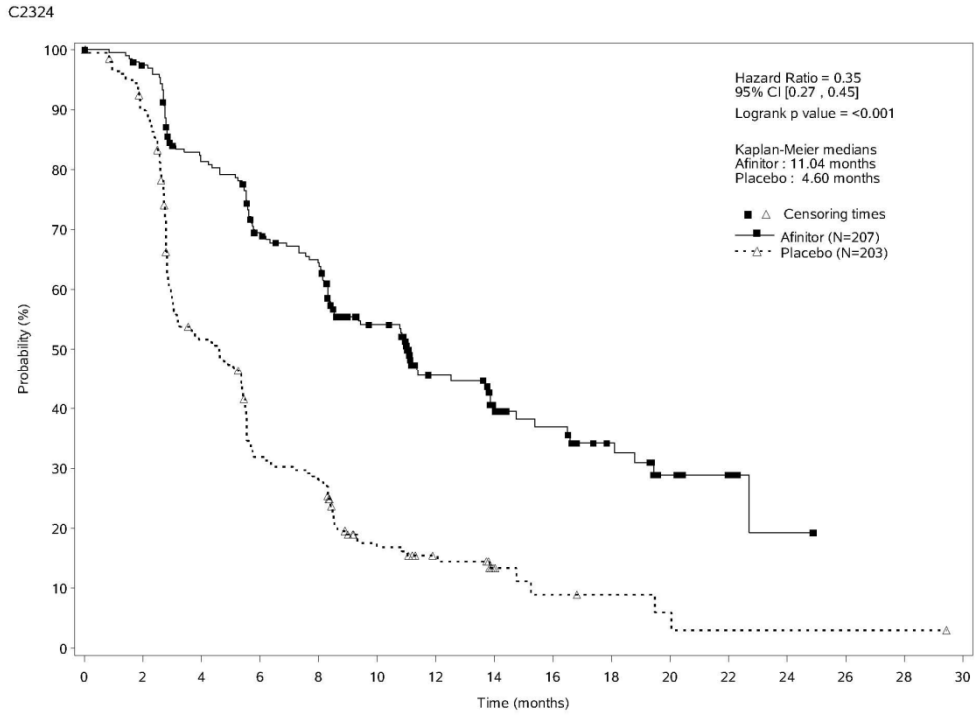
Table 2 RADIANT-3 – Progression Free Survival results

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 non-pancreatic origin

RADIANT-2 (Study CRAD001C2325), a randomised, double-blind, multicentre phase III study of Afinitor plus depot octreotide (Sandostatin LAR®) versus placebo plus depot octreotide in patients with advanced neuroendocrine tumours (carcinoid tumour) primarily of gastrointestinal or lung origin showed evidence of borderline clinical efficacy of Afinitor over placebo by a 5.1-month prolongation in median PFS (16.43 months versus 11.33 months; HR 0.77; 95%CI: 0.59 to 1.00; one sided p=0.026), resulting in a 23% risk reduction in primary PFS (see Table 3 and Figure 5). The efficacy data shown are insufficient in the context of the product's safety profile and lack of evidence of overall survival benefit in RADIANT-2 to support approval in patients with non-pancreatic advanced neuroendocrine tumours.

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

The primary endpoint is PFS evaluated by RECIST (version 1.0) as per Independent radiological review. After documented radiological progression, patients could be unblinded by the investigator: those randomised to placebo were then able to receive open-label Afinitor.

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

In total, 429 patients were randomised 1:1 to receive either Afinitor 10mg/day (n=216) or placebo (n=213), in addition to depot octreotide (Sandostatin LAR®, administered intramuscularly) 30 mg every 28 days. Notable imbalances were evident for several important baseline prognostic factors, mainly in favour of the placebo group.

Table 3 RADIANT-2 – Progression Free Survival results

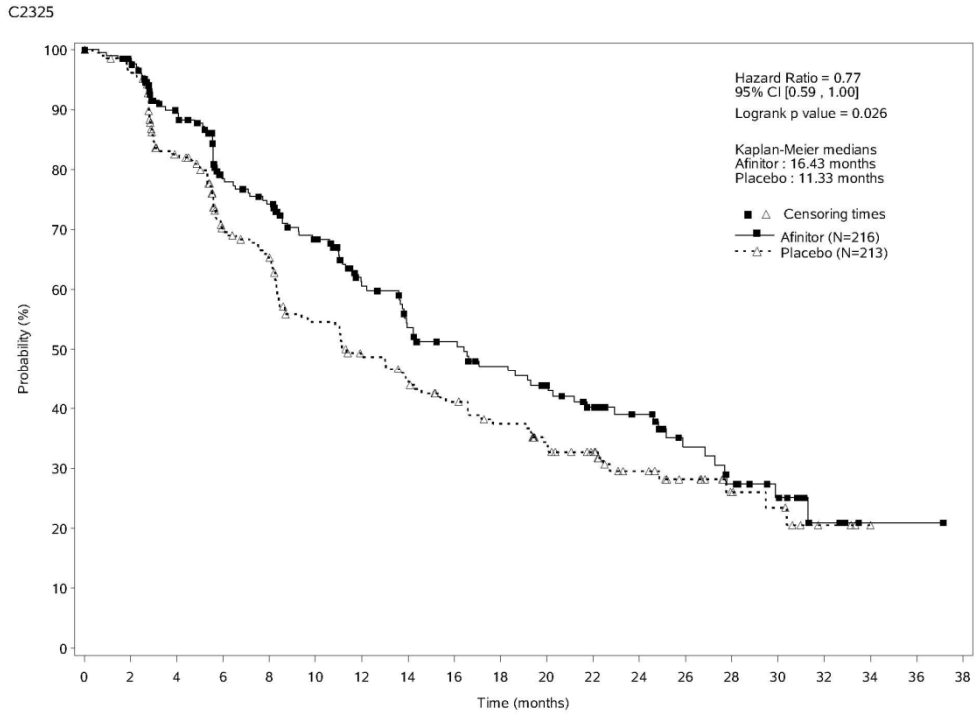
Analysis	N	Afinitor[a] N=216	Placebo[a] **N=213**	**Hazard Ratio (95%CI)**	**p-value**[c]
	429	Median progression-free survival (months) (95% CI)			
Independent radiological review[b]		16.43 (13.67 to 21.19)	11.33 (8.44 to 14.59)	0.77 (0.59 to 1.00)	0.026
Investigator radiological review		11.99 (10.61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

[a] Plus depot octreotide (Sandostatin LAR®)

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

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

Figure 5 RADIANT-2 – Kaplan-Meier progression-free survival curves (independent radiologic review)



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

The overall survival results are not yet mature and no statistically significant difference in OS was noted (HR for pre-specified adjusted analysis =1.05 (95% CI 0.79 to 1.39) in an updated analysis). Crossover of >58% of patients from placebo to open-label Afinitor following disease progression likely confounded the detection of any treatment-related difference in OS.

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.

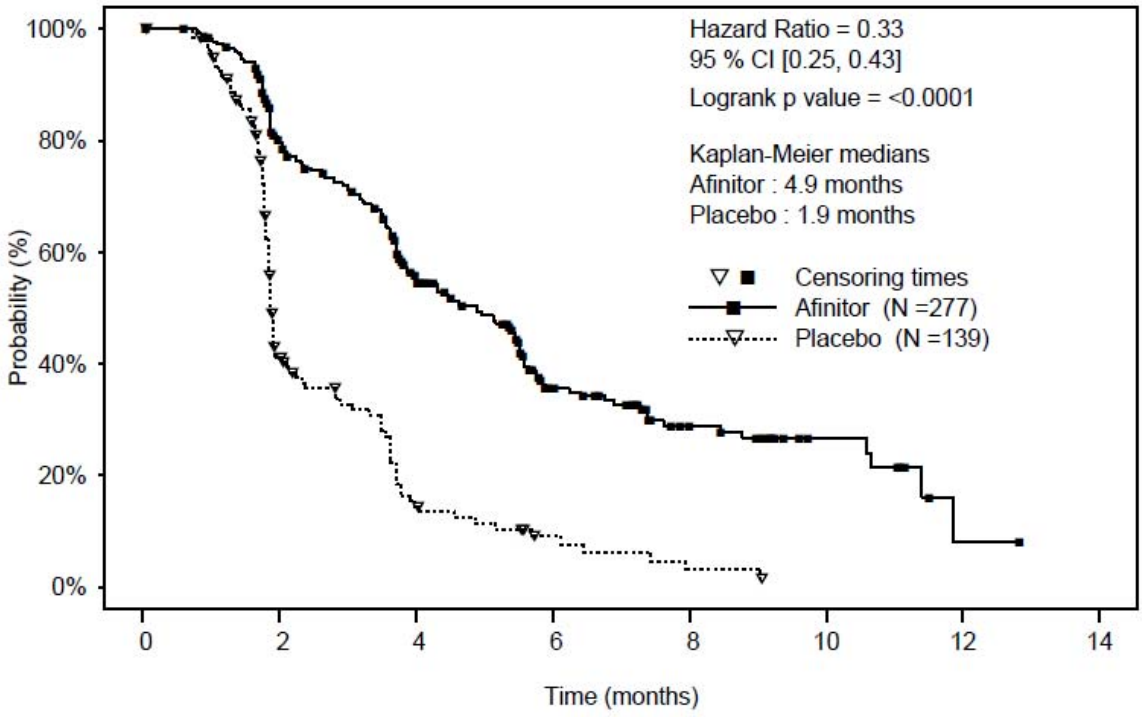
Results from a planned interim analysis showed that Afinitor was superior to placebo for the primary endpoint of progression-free survival, with a statistically significant 67% reduction in the risk of progression or death (see Table 4 and Figure 6).

Table 4 RECORD-1 - Progression Free Survival results

Population	**N**	**Afinitor N=277**	**Placebo N=139**	**Hazard Ratio (95%CI)**	**p-value**
		Median progression-free survival (months) (95% CI)			
Primary analysis					
All (blinded independent central review)	416	4.9 (4.0 to 5.5)	1.9 (1.8 to 1.9)	0.33 (0.25 to 0.43)	<0.001 [a]
Supportive/sensitivity analyses					
All (local review by investigator)	416	5.5 (4.6 to 5.8)	1.9 (1.8 to 2.2)	0.32 (0.25 to 0.41)	<0.001 [a]
MSKCC prognostic score					
Favourable risk	120	5.8 (4.0 to 7.4)	1.9 (1.9 to 2.8)	0.31 (0.19 to 0.50)	<0.001 [b]
Intermediate risk	235	4.5 (3.8 to 5.5)	1.8 (1.8 to 1.9)	0.32 (0.22 to 0.44)	<0.001 [b]
Poor risk	61	3.6 (1.9 to 4.6)	1.8 (1.8 to 3.6)	0.44 (0.22 to 0.85)	0.007 [b]
Prior VEGFR-TKI therapy					
Sunitinib only	184	3.9 (3.6 to 5.6)	1.8 (1.8 to 1.9)	0.34 (0.23 to 0.51)	<0.001 [b]
Sorafenib only	124	5.9 (4.9 to 11.4)	2.8 (1.9 to 3.6)	0.25 (0.16 to 0.42)	<0.001 [b]
Sunitinib and sorafenib	108	4.0 (3.6 to 5.4)	1.8 (1.8 to 2.0)	0.32 (0.19 to 0.54)	<0.001 [b]

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

Figure 6 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.

<u>Tuberous sclerosis complex (TSC) with renal angiomyolipoma</u>

EXIST-2 (Study CRAD001M2302), a randomized, 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 embolization/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 5). Response rates were 41.8% (95% CI: 30.8, 53.4) for the Afinitor arm compared with 0% (95% CI: 0.0, 9.0) for the placebo arm (Table 5). No patient receiving Afinitor required surgery or embolization, while one patient on placebo required bilateral renal embolization. Due to the limited duration of the study core phase, reduction in bleeding complications, avoidance of nephrectomy or embolization, and long-term preservation of renal function have not been demonstrated.

Table 5 EXIST-2 - Angiomyolipoma response

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

[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.

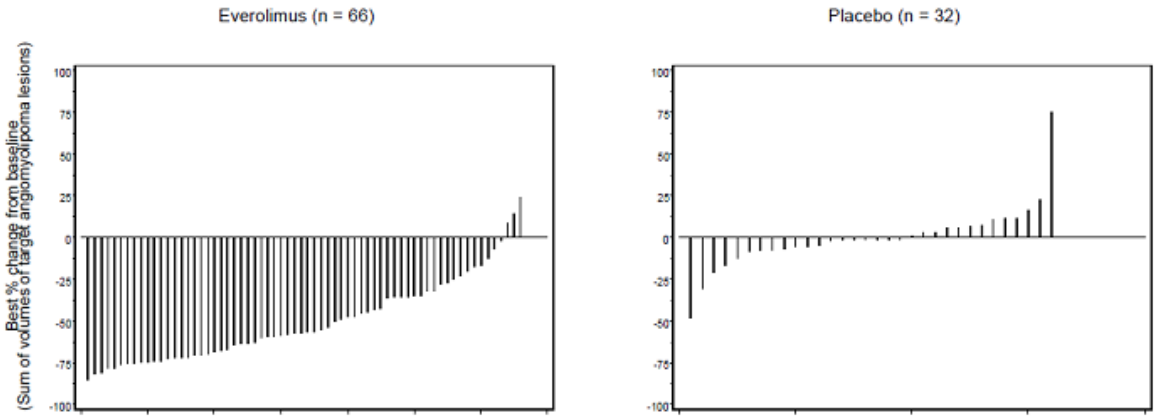
Consistent treatment effects were observed across all subgroups evaluated (i.e., EIAED use vs. EIAED non-use, sex, age, and race) (Table 6).

Table 6 EXIST-2 - Angiomyolipoma response by subgroup

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 7); 95.5% of patients in the Afinitor arm experienced angiomyolipoma shrinkage versus 59.4% in the placebo arm.

Figure 7 EXIST-2 - Angiomyolipoma shrinkage: best percentage change from baseline[1,2]



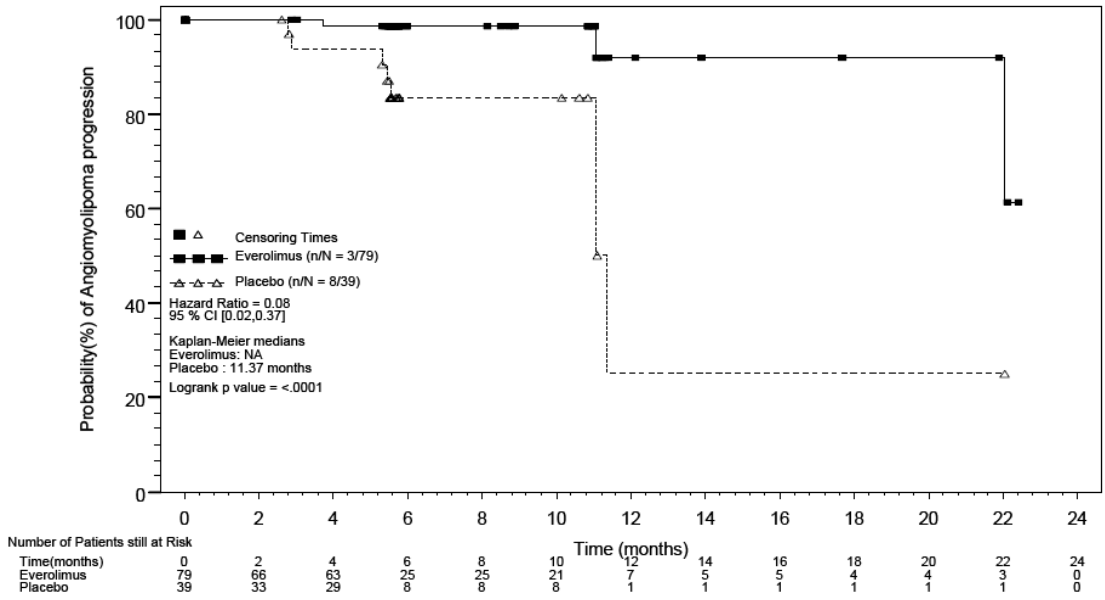
[1] Per independent central radiology review

[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.

Angiomyolipoma shrinkage was evident within the initial 12 weeks of treatment with Afinitor: 75.7% of patients had ≥ 30% reductions and 41.9% had ≥ 50% reductions at the time of the first radiological evaluation (Week 12). Sustained reductions were evident at subsequent time points; at Week 24, 80.3% of patients had ≥ 30% reductions and 54.9% had ≥ 50% reductions.

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 8). 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% of patients in the Afinitor arm compared with 20.5% 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.

Figure 8 Kaplan-Meier plot of time to angiomyolipoma progression[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.

Afinitor also demonstrated clinically meaningful and statistically significant improvements in skin lesion response (p=0.0002), with response rates of 26.0% (95% CI: 16.6, 37.2) for the Afinitor arm and 0% (95% CI: 0.0, 9.5) for the placebo arm (Table 7).

Table 7 EXIST-2 - Best overall skin lesion response

	Afinitor N=77	**Placebo N=37**	**p-value [1]**
Skin lesion response rate [1,2,3,4] - %	**26.0**	**0**	**0.0002**
95% CI	(16.6, 37.2)	(0.0, 9.5)	
Best overall skin lesion response – %			
Complete clinical response	0	0	
Partial response	26.0	0	
Stable disease	71.4	97.3	
Progressive disease	0	0	
Not evaluable	2.6	2.7	

[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.

Tuberous sclerosis complex (TSC) with Subependymal giant cell astrocytoma (SEGA)

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 angiomyolipomas (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 8). 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 8). In addition, all 8 patients on the Afinitor arm who had radiographic evidence of hydrocephalus at baseline had a decrease in ventricular volume and no patient required surgical intervention during the course of this study.

Table 8 EXIST-1 – SEGA response

	AFINITOR N=78	Placebo N=39	p-value
Primary analysis			
SEGA response rate1,2 - (%)	34.6	0	<0.0001
95% CI	24.2, 46.2	0.0, 9.0	
Best overall SEGA response - (%)			
Response	34.6	0	
Stable disease	62.8	92.3	
Progression	0	7.7	
Not evaluable	2.6	0	

[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

Consistent treatment effects were observed across all subgroups evaluated (i.e., EIAED use vs. EIAED non-use, sex, and age) (Table 9).

Table 9 EXIST-1 - SEGA response by subgroup

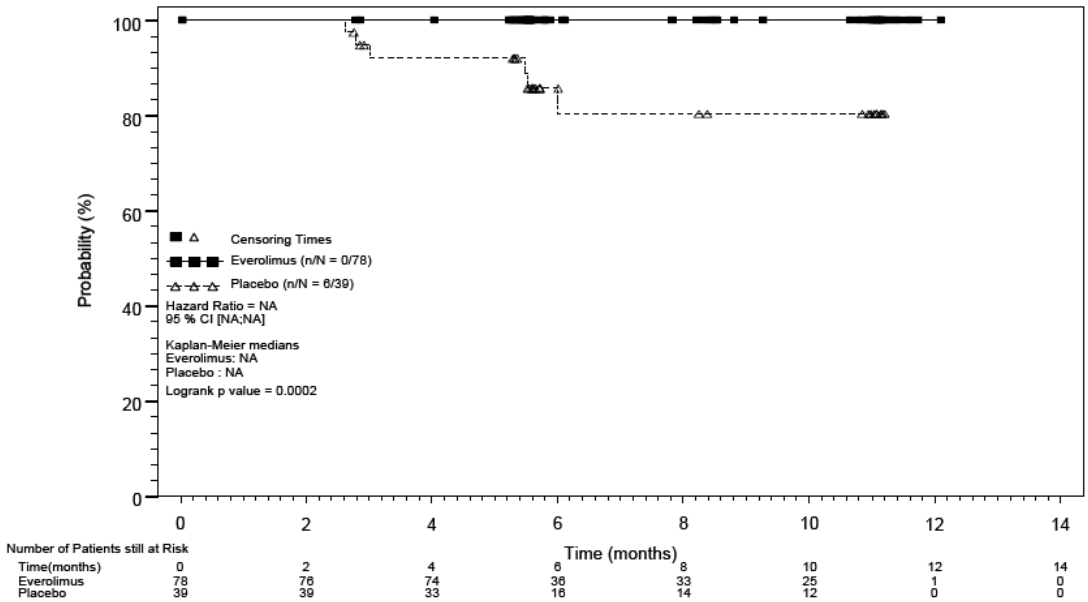
Subgroup	Afinitor N	Afinitor Responders %	Placebo N	Placebo Responders %	Difference in response rates (95% CI)
All patients	78	34.6	39	0	34.6 (15.1, 52.4)
Modified strata					
EIAED use	15	26.7	7	0	26.7 (-16.9, 64.7)
No EIAED use	63	36.5	32	0	36.5 (15.4, 55.1)
Sex					
Male	49	24.5	18	0	24.5 (-2.4, 49.5)
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)

SEGA shrinkage was evident within the initial 12 weeks of treatment with Afinitor: 73.0% of patients had ≥ 30% reductions and 29.7% had ≥ 50% reductions at the time of the first radiological evaluation (Week 12). Sustained reductions were evident at subsequent time points; at Week 24, 78.4% of patients had ≥ 30% reductions and 41.9% had ≥ 50% reductions.

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 9). Estimated progression-free rates at 6 months were 100% for the Afinitor arm and 85.7% for the placebo arm.

Figure 9 EXIST-1 - Kaplan-Meier plot of time to SEGA progression[1,2]



[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

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 10).

Table 10 EXIST-1 - best overall skin lesion response

	Afinitor N=72	Placebo N=38	p-value
Skin lesion response rate[1,2,3,4] - %	41.7	10.5	0.0004
95% CI	(30.2, 53.9)	(2.9, 24.8)	
Best overall skin lesion response - %			
Complete clinical response	0	0	
Partial response	41.7	10.5	
Stable disease	58.3	86.8	
Progression	0	0	
Not evaluable	0	2.6	

[1] Complete clinical response or partial response

[2] Per investigator

[3] Skin lesion response was determined for the 110 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.

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 3-34), 61% male, 86% Caucasian. Thirteen patients (46%) had a secondary smaller SEGA including 12 patients with SEGA in the contralateral ventricle. Four patients had surgical resection of their SEGA lesions with subsequent re-growth prior to receiving Afinitor treatment. Long-term follow-up to a median duration of 34.2 months (range: 4.7 to 47.1) demonstrated sustained efficacy.

Afinitor was associated with a clinically relevant and statistically significant reduction in primary SEGA volume at 6 months relative to baseline ($p<0.001$). At 6 months, 9 out of 28 patients (32%, 95% CI: 16% to 52%) had a ≥ 50% reduction in the tumor volume of their largest SEGA lesion (Table 11).

Three of 4 patients who had prior surgery experienced a ≥ 50% reduction in the tumor 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 11 C2485 - Response of primary SEGA lesion to Afinitor therapy

SEGA volume (cm^3)	Independent central review							
	Baseline N=28	**Month 3 N=26**	**Month 6 N=27**	**Month 12 N=26**	**Month 18 N=26**	**Month 24 N=24**	**Month 30 N=17**	**Month 36 N=9**
Primary tumor volume								
Mean (standard deviation)	2.45 (2.813)	1.47 (1.646)	1.33 (1.497)	1.26 (1.526)	1.28 (1.110)	1.19 (1.042)	1.49 (1.469)	1.17 (0.796)
Median	1.74	0.84	0.93	0.84	0.81	0.94	1.05	0.97
Range	0.49 - 14.23	0.25 - 8.32	0.31 - 7.98	0.29 - 8.18	0.33 - 5.20	0.20 - 4.63	0.40 - 6.27	0.39 - 2.70
Reduction from baseline								
Mean (standard deviation)		1.08 (1.338)	1.19 (1.433)	1.07 (1.276)	1.25 (1.887)	1.25 (1.994)	1.47 (2.123)	1.73 (1.710)
Median		0.63	0.83	0.85	0.69	0.71	1.04	1.34
Range		-0.12 - 5.91	0.06 - 6.25	0.02 - 6.05	-0.24 - 9.03	-0.55 - 9.60	-0.78 - 7.96	0.15 - 4.75
Percentage reduction from baseline, n (%)								
≥ 50%		10 (38.5)	9 (33.3)	9 (34.6)	11 (42.3)	12 (50.0)	7 (41.2)	5 (55.6)
≥ 30%		17 (65.4)	21 (77.8)	20 (76.9)	18 (69.2)	19 (79.2)	11 (64.7)	7 (77.8)
> 0%		25 (96.2)	27 (100.0)	26 (100.0)	24 (92.3)	23 (95.8)	15 (88.2)	9 (100.0)
No change		0	0	0	1 (3.8)	0	0	0
Increase		1 (3.8)	0	0	1 (3.8)	1 (4.2)	2 (11.8)	0

INDICATIONS

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.
- Progressive, unresectable or metastatic, well or moderately differentiated neuroendocrine tumours (NETs) of pancreatic origin.
- Advanced renal cell carcinoma after failure of treatment with sorafenib or sunitinib.
- Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not candidates for curative surgical resection.
- Patients with tuberous sclerosis complex (TSC) who have renal angiomyolipoma not requiring immediate surgery.

CONTRAINDICATIONS

Afinitor is contraindicated in patients with hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients (see Precautions).

PRECAUTIONS

Non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking Afinitor (see Adverse 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. 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 of pancreatic origin 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 of pancreatic origin 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.

The development of pneumonitis has been reported at a reduced dose (see Dosage and Administration).

Infections

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

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.

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 Contraindications).

Oral ulceration

Mouth ulcers, stomatitis and oral mucositis have been seen in patients treated with Afinitor (see Adverse Effects). In such cases topical treatments are recommended, but alcohol, hydrogen peroxide-, iodine-, or thyme-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed (see Interactions with Other Medicines).

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 ADVERSE EFFECTS section, see also Laboratory tests and monitoring).

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 Dosage and Administration and Precautions).

Afinitor is not recommended for use in patients with severe hepatic impairment (Child-Pugh C) for the treatment of hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumours of pancreatic origin, advanced renal cell carcinoma, or TSC who have renal angiomyolipoma unless the potential benefit outweighs the risk (see Dosage and Administration and Pharmacokinetics).

Afinitor is not recommended for use in patients < 18 years of age with TSC who have SEGA and concomitant hepatic impairment (Child-Pugh A, B or C) or in patients > 18 years of age with severe hepatic impairment (Child-Pugh C) (see Dosage and Administration and Pharmacology).

Effects on fertility

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

Everolimus completely impaired male rat fertility at an everolimus dose that resulted in a drug exposure (blood AUC) that was slightly below[3] the expected maximum human value, and sperm number and motility were reduced. 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). There was evidence for partial recovery of fertility over a period approximately equivalent to the treatment period. In animal reproductive studies

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

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

The potential for everolimus to cause infertility in male and female patients is unknown. However, menstrual irregularities, secondary amenorrhea and associated luteinising hormone (LH)/follicle stimulating hormone (FSH) imbalance have been observed in female patients.

Use in Pregnancy (Category C)

There are no adequate data from the use of everolimus in pregnant women and the potential risk to the foetus is unknown. In a rat study in which oral treatment started before mating and continued to the end of the period of organogenesis, treatment resulted in increased pre- and post-implantation losses. There was a low incidence of foetal cleft sternum, the significance of which is uncertain because it occurred at a dose giving a high foetal resorption rate. Systemic drug exposures (blood AUC) with the doses used in this study were below the expected human value at 10 mg/day. Treatment of pregnant rabbits during the period of organogenesis slightly increased late fetal resorptions but did not otherwise affect foetal development. The highest dose used in this study gave a systemic drug exposure (blood AUC) that was below the expected human value[4] at 10 mg/day. Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving Afinitor and up to 8 weeks after treatment has been stopped.

Afinitor should not be given to pregnant women unless the potential benefit outweighs the potential risk to the fetus. Male patients taking Afinitor should not be prohibited from attempting to father children.

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 in an increase in late resorptions.

Use in Lactation

It is not known whether everolimus is excreted in human milk. In animal studies, everolimus and/or its metabolites readily passed into the milk of lactating rats. Women taking Afinitor should not breast-feed.

[4] AUC=225.6 ng.hr/mL at high dose. Vs human AUC of 560 ng.hr/mL at 10 mg/day.

Paediatric Use

- There is no indication for use of Afinitor in the paediatric cancer population (see Dosage and Administration) or in paediatric patients with TSC who have renal angiomyolipoma in the absence of SEGA.
- Afinitor has not been studied in pediatric patients <1 year of age with TSC who have SEGA.
- Dosing recommendations for paediatric patients with TSC who have SEGA are consistent with those for the corresponding adult population with the exception of those patients with hepatic impairment. Afinitor is not recommended for patients <18 years of age with TSC who have SEGA and hepatic impairment.

Use in 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.

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 [5] the expected human value at 10 mg/day in mice, but were less than the expected maximum human value in rats.

Effect on laboratory tests

Renal Function

Elevations of serum creatinine, usually mild, and proteinuria have been reported in patients taking Afinitor (see Adverse 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 Adverse Effects). Monitoring of fasting serum glucose is recommended prior to the start of Afinitor therapy and

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

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 Adverse Effects). Monitoring of complete blood count is recommended prior to the start of Afinitor therapy and periodically thereafter.

INTERACTIONS WITH OTHER MEDICINES

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, cyclosporin, 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 Dosage and 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; Cmax and AUC increased by 2.0- and 4.4-fold, respectively).
- verapamil (a moderate CYP3A4 inhibitor and a PgP inhibitor; Cmax and AUC increased by 2.3-and 3.5-fold, respectively).
- cyclosporin (a CYP3A4 substrate and a PgP inhibitor; Cmax 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).

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 (Cmax 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 Interactions with Other Medicines). If Afinitor must be co-administered with a strong CYP3A4 or PgP inducer (eg 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 Dosage and 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 Cmax 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, 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 cyclosporin and was a mixed inhibitor of the CYP2D6 substrate dextromethorphan. The mean steady-state of everolimus Cmax 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.

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 pediatric patients with SEGA 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.

ADVERSE EFFECTS

Oncology- Summary of the safety profile

Adverse drug reactions (ADR) information is based on pooled safety data in patients receiving Afinitor (N=1175) in randomized, double-blind, placebo-or active comparator controlled phase III trials which serve as the basis for the approved indications (see Indications).

Table 12 Afinitor oncology studies in the pooled safety data

Indication	Study Name	Active Treatment Arm	Comparator/Control Arm
Advanced Renal Cell Carcinoma	RECORD-1 (C2240)	everolimus, N=274	placebo, N=137
Neuroendocrine Tumors – Pancreatic	RADIANT-3 (C2324)	everolimus, N=204	placebo, N=203
Neuroendocrine Tumors – Gastrointestinal, Lung (Not an approved indication)	RADIANT-2 (C2325)	everolimus+octreotide, N=215	placebo+octreotide, N=211
ER+ Breast Cancer	BOLERO-2 (Y2301)	everolimus+exemestane N=482	placebo+exemestane, N=238

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, nausea, decreased appetite, infections, anemia, dysgeusia, pneumonitis, weight decreased, peripheral oedema, asthenia, epistaxis, pruritis, vomiting, headache, hyperglycemia, cough, hypercholesterolemia, thrombocytopenia, and dyspnoea. 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, hyperglycemia, anemia, fatigue, infections, pneumonitis, diarrhoea, thrombocytopenia, neutropenia, dyspnea, lymphopenia, hypophosphatemia, asthenia, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, and rash.

Tabulated summary of adverse drug reactions from clinical trials in oncology

Table 13 presents the frequency category of ADRs reported in the pooled 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 adverse reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse reaction: 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).

Table 13 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	Anemia, thrombocytopenia
Common	Neutropenia, leukopenia, lymphopenia
Uncommon	Pancytopenia, pure red cell aplasia
Immune system disorders	
Not known	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Decreased appetite, hyperglycemia, hypercholesterolemia
Common	Hypertriglyceridemia, hyperlipidemia, hypophosphatemia, diabetes mellitus, hypokalemia, dehydration
Psychiatric disorders	
Common	Insomnia
Nervous system disorders	
Very common	Dysgeusia, headache
Uncommon	Ageusia
Cardiac disorders	
Uncommon	Congestive cardiac failure
Vascular disorders	
Common	Hypertension, hemorrhage[b]
Uncommon	Deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	
Very common	Pneumonitis[c], epistaxis, cough, dyspnea
Uncommon	Hemoptysis, pulmonary embolism, acute respiratory distress syndrome
Gastrointestinal disorders	
Very common	Stomatitis[d], diarrhea, nausea, vomiting
Common	Dry mouth, abdominal pain, oral pain, dyspepsia, dysphagia
Skin and subcutaneous tissue disorders	
Very common	Rash, pruritus
Common	Dry skin, nail disorder, erythema, acne, hand-foot syndrome[e]
Musculoskeletal and connective tissue disorders	
Common	Arthralgia
Renal and urinary disorders	
Common	Renal failure

Uncommon	Increased daytime urination, proteinuria, acute renal failure
Reproductive system and breast disorders	
Uncommon	Menstruation irregular, amenorrhea
General disorders and administration site conditions	
Very common	Fatigue, peripheral edema, asthenia,
Common	Pyrexia, mucosal inflammation
Uncommon	Non-cardiac chest pain, impaired wound healing
Investigations	
Very common	Weight decreased
Common	Alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased

[a]*Includes all reactions within the 'infections and infestations' system organ class including common: pneumonia and uncommon: herpes zoster, sepsis and isolated cases of opportunistic infections (e.g. aspergillosis, candidiasis and hepatitis B)*

[b]*Includes different bleeding events not listed individually*

[c]*Includes very common: pneumonitis and common: interstitial lung disease, lung infiltration, alveolitis, pulmonary alveolar hemorrhage, 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*

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):

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

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

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

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

Adverse drug reaction (ADR) information is based on pooled data from patients with TSC receiving Afinitor (N=241) in two randomized, double-blind, placebo-controlled, phase III studies and one non-randomized, open-label, single-arm phase II study (including open label treatment) which serve as the basis for the listed indications (see Table 14 and Indications):

Table 14 Afinitor TSC studies in the pooled safety data

Indication	Study Name	Active Treatment Arm	Comparator or Control Arm
TSC - Renal Angiomyolipoma	EXIST-2 (M2302)	everolimus, N=79	placebo, N=39
TSC - SEGA	EXIST-1 (M2301))	everolimus, N=78	placebo, N=39
TSC – SEGA[1]	CRAD001C2485	everolimus, N=28	n/a

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

The most frequent ADRs (incidence ≥1/10 and suspected to be related to treatment by the investigator) from the pooled safety database are (in decreasing order): stomatitis, upper respiratory tract infections, and hypercholesterolemia.

The most frequent grade 3/4 adverse reactions (incidence ≥1/100 to <1/10 and suspected to be related to treatment by the investigator) were stomatitis, neutropenia, amenorrhea, and gastroenteritis viral.

Tabulated summary of adverse reactions from clinical trials in TSC

Table 15 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). 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 15 Adverse drug reactions from clinical trials in TSC reported at a higher rate in the Afinitor arm than in the placebo arm in TSC studies

Infections and infestations	
Very common	Upper respiratory tract infection
Common	Sinusitis, otitis media, nasopharyngitis, urinary tract infection, pharyngitis, cellulitis, pneumonia, gastroenteritis viral, pharyngitis streptococcal
Uncommon	Herpes zoster, bronchitis viral
Blood and lymphatic system disorders	
Common	Anemia, neutropenia, leukopenia, thrombocytopenia, lymphopenia
Immune system disorders	
Uncommon	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Hypercholesterolemia
Common	Decreased appetite, hyperlipidemia, hypophosphatemia, hypertriglyceridemia
Psychiatric disorders	
Uncommon	Insomnia, aggression
Nervous system disorders	
Common	Headache, dysgeusia
Vascular disorders	
Common	Hypertension
Respiratory, thoracic and mediastinal disorders	
Common	Cough, epistaxis
Uncommon	Pneumonitis

Gastrointestinal disorders	
Very common	Stomatitis[a]
Common	Diarrhea, nausea, vomiting, abdominal pain, oral pain, flatulence, constipation, gastritis
Skin and subcutaneous tissue disorders	
Common	Acne, rash[b], dermatitis acneiform, dry skin
Renal and urinary disorders	
Common	Proteinuria
Reproductive system and breast disorders	
Common	Amenorrhea, menstruation irregular, menorrhagia, vaginal hemorrhage, menstruation delayed
General disorders and administration site conditions	
Common	Fatigue, pyrexia, irritability
Investigations	
Common	Blood lactate dehydrogenase increased, blood luteinizing hormone increased
Uncommon	Blood follicle stimulating hormone increased
[a]Includes very common: stomatitis, mouth ulceration; common: aphthous stomatitis; uncommon: gingival pain, glossitis, lip ulceration.	
[b]Includes common: rash; uncommon: erythema, rash erythematous, rash macular, rash maculo-papular, rash generalized.	

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):

- Hematology: partial thromboplastin time increased, hemoglobin decreased, white blood cells decreased, neutrophils decreased, platelet count decreased, and lymphocytes decreased.
- Clinical chemistry: cholesterol increased, triglycerides increased, AST increased, phosphate decreased, ALT increased, alkaline phosphatase increased, and potassium decreased.

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

- Hematology: neutrophils decreased, partial thromboplastin time increased and lymphocytes decreased (all common).
- Clinical chemistry: phosphate decreased, alkaline phosphatase increased (common); AST increased, cholesterol increased, and ALT 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 Precautions).

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

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

Special populations

Paediatrics

Paediatric use of Afinitor is recommended for patients with TSC who have SEGA and do not require immediate surgery. The safety and effectiveness of Afinitor have not been established in paediatric patients with renal angiomyolipoma with TSC in the absence of SEGA or in paediatric cancer patients.

The safety of Afinitor in paediatric patients with SEGA was demonstrated in two clinical trials.

In EXIST-1, the overall nature, type, and frequency of ADRs across the age groups evaluated were similar, with the exception of a higher per patient incidence of infectious serious ADRs in patients < 3 years of age. A total of 2 of 13 patients (15.4%) < 3 years of age had at least one serious ADR due to infection, compared to 0 of 7 patients (0%) treated with placebo. No patient in any age group discontinued Afinitor due to infection.

In Study CRAD001C2485, the frequency of ADRs across the age groups was generally similar. The long term effects of Afinitor on growth and pubertal development are unknown.

Everolimus clearance normalized to body surface area was higher in paediatric patients than in adults with SEGA (see Pharmacology). The recommended starting dose and subsequent requirement for therapeutic drug monitoring to achieve and maintain trough concentrations of 3 to 15 ng/mL are the same for adult and paediatric patients with SEGA (see Dosage and administration).

Geriatrics

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

The number of patients with an ADR leading to discontinuation of Afinitor was higher in patients ≥ 65 years of age (23% vs. 14%). The most common ADRs leading to discontinuation were pneumonitis, fatigue, dyspnea, and stomatitis.

DOSAGE AND 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 Pharmacokinetics). Afinitor is available in two formulations: tablets (Afinitor Tablets) and dispersible tablets (Afinitor Dispersible Tablets).

Afinitor Tablets may be used in all approved indications.

Afinitor Tablets and Afinitor Dispersible Tablets may be used for the treatment of patients with TSC who have SEGA in conjunction with therapeutic drug monitoring (see Therapeutic drug monitoring for patients treated for TSC with SEGA and Pharmacology).

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. Use one dosage form or the other.

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 Therapeutic drug monitoring for patients treated for TSC with SEGA below).

Adults

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

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

Dosing in TSC with SEGA

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 centimeters:

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

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.

Therapeutic drug monitoring of everolimus blood concentrations is required for patients treated for TSC with SEGA (see Therapeutic drug monitoring for patients treated for TSC with SEGA). Everolimus whole blood trough concentrations should be assessed approximately 2 weeks after commencing treatment. Dosing should be titrated to attain trough concentrations of 3 to 15 ng/mL.

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 Pharmacokinetics).

Once a stable 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

Adverse drug reactions:

Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption and dose reduction of Afinitor therapy (see Precautions). 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 16 summarizes recommendations for dose reduction, interruption or discontinuation of Afinitor in the management of ADRs. General management recommendations are also provided as applicable. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Table 16 Afinitor dose adjustment and management recommendations for adverse drug reactions

Adverse Drug Reaction	Severity[1]	Afinitor Dose Adjustment[2] and Management Recommendations
Non-infectious pneumonitis	Grade 1 Asymptomatic, radiographic findings only	No dose adjustment required. Initiate appropriate monitoring.
	Grade 2 Symptomatic, not interfering with ADL[3]	Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to Grade ≤ 1. Re-initiate Afinitor at a lower dose. Discontinue treatment if failure to recover within 4 weeks.
	Grade 3 Symptomatic, interfering with ADL[3] O_2 indicated	Interrupt Afinitor 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, ventilatory support indicated	Discontinue Afinitor, rule out infection, and consider treatment with corticosteroids.
Stomatitis	Grade 1 Minimal symptoms, normal diet	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouthwash several times a day.
	Grade 2 Symptomatic but can eat and swallow modified diet	Temporary dose interruption until recovery to Grade ≤1. Re-initiate Afinitor at the same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤1. Re-initiate Afinitor at a lower dose. Manage with topical analgesic mouth treatments (e.g., benzocaine, butyl aminobenzoate, tetracaine hydrocholoride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[4]
	Grade 3 Symptomatic and unable to adequately eat or hydrate orally	Temporary dose interruption until recovery to Grade ≤1. Re-initiate Afinitor at a lower dose. Manage with topical analgesic mouth treatments (e.g., benzocaine, butyl aminobenzoate, tetracaine hydrocholoride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[4]
	Grade 4 Symptoms associated with	Discontinue Afinitor and treat with appropriate medical therapy.

Adverse Drug Reaction	Severity[1]	Afinitor Dose Adjustment[2] and Management Recommendations
	life-threatening Consequences	
Other non-hematologic toxicities (excluding metabolic events)	Grade 1	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor. If toxicity becomes intolerable, temporary dose interruption until recovery to Grade ≤1. Re-initiate Afinitor at the same dose. If toxicity recurs at Grade 2, interrupt Afinitor until recovery to Grade ≤1. Re-initiate Afinitor at a lower dose.
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Initiate appropriate medical therapy and monitor. Consider re-initiating Afinitor at a lower dose. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue Afinitor and treat with appropriate medical therapy.
Metabolic events (e.g. hyperglycemia, dyslipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.
	Grade 3	Temporary dose interruption. Re-initiate Afinitor at a lower dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue Afinitor and treat with appropriate medical therapy.
Thrombocytopenia	Grade 2 (<75, ≥50x10^9/l)	Temporary dose interruption until recovery to Grade ≤1 (≥75x10^9/l). Re-initiate Afinitor at same dose.
	Grade 3 & 4 (<50x10^9/l)	Temporary dose interruption until recovery to Grade ≤1 (≥75x10^9/l). Re-initiate Afinitor at 5 mg daily.
Neutropenia	Grade 2 (≥1x10^9/l)	No dose adjustment required.
	Grade 3 (<1, ≥0.5x10^9/l)	Temporary dose interruption until recovery to Grade ≤2 (≥1x10^9/l). Re-initiate Afinitor at same dose.
	Grade 4 (<0.5x10^9/l)	Temporary dose interruption until recovery to Grade ≤2 (≥1x10^9/l). Re-initiate Afinitor at 5 mg daily.
Febrile neutropenia	Grade 3	Temporary dose interruption until recovery to Grade ≤2 (≥1.25x10^9/l) and no fever. Re-initiate Afinitor at 5 mg daily.
	Grade 4	Discontinue Afinitor

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

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

[3] Activities of daily living (ADL)

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

Moderate CYP3A4 or PgP inhibitors:

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

- **Hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumors of pancreatic origin, advanced renal cell carcinoma, and TSC with renal**

angiomyolipoma: If the moderate inhibitor is discontinued, consider a washout period of at least 2 to 3 days (average for most commonly used moderate inhibitors) should be allowed 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 Precautions).

- **TSC with SEGA:** Everolimus trough concentrations should be assessed approximately 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 Precautions and Therapeutic drug monitoring for patients treated for TSC with SEGA).

Strong CYP3A4 inducers:
Avoid the use of concomitant strong CYP3A4 inducers.

- **Hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumors of pancreatic origin, 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 Precautions).
- **TSC with SEGA**: Patients receiving concomitant strong CYP3A4 inducers (e.g., the enzyme inducing antiepileptic drugs carbamazepine, phenobarbital, and phenytoin) 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 two weeks after doubling the dose. Further adjust the dose if necessary to maintain the trough within the 3 to 15 ng/mL range. If the strong inducer is discontinued, the Afinitor dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer and the everolimus trough concentrations should be assessed approximately 2 weeks later (see Precautions and Therapeutic drug monitoring for patients treated for TSC with SEGA).

Therapeutic drug monitoring for patients treated for TSC with SEGA

Therapeutic drug monitoring of everolimus blood concentrations is required for patients treated for TSC with SEGA 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 2 weeks after the initial dose, after any change in dosage form, after an initiation or change in co-administration of CYP3A4/PgP inducers and/or inhibitors (see Precautions) or after any change in hepatic (Child-Pugh) status. Dosing should be titrated with the objective of attaining everolimus trough concentrations of 3 to 15 ng/mL, subject to tolerability (see Pharmacokinetics). 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 in the absence of SEGA.
- Afinitor has not been studied in pediatric patients <1 year of age with TSC who have SEGA.
- Dosing recommendations for paediatric patients with TSC who have SEGA are consistent with those for the corresponding adult population with the exception of those patients with hepatic impairment. Afinitor is not recommended for patients <18 years of age with TSC who have SEGA and hepatic impairment.

Elderly patients (≥ 65 years)

No dosage adjustment is required (see Pharmacokinetics).

Renal impairment

No dosage adjustment is required (see Pharmacokinetics).

Hepatic impairment

- Hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumours of pancreatic origin 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**:
    - **Patients ≥18 years of age**
        - Mild hepatic impairment (Child-Pugh A) – 75% of the dose calculated based on BSA (rounded to the nearest strength).
        - Moderate hepatic impairment (Child-Pugh B) – 25% of the dose calculated based on BSA (rounded to the nearest strength).
        - Severe hepatic impairment (Child-Pugh C) – not recommended.

      Everolimus whole blood trough concentrations should be assessed approximately 2 weeks after commencing treatment or after any change in hepatic (Child-Pugh) status. Dosing should be titrated to attain trough concentrations of 3 to 15 ng/mL (see Therapeutic drug monitoring for patients treated for TSC with SEGA). Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment (see Pharmacokinetics).

- **Patients <18 years of age**

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

OVERDOSAGE

In animal studies, everolimus showed a low acute toxic potential. No lethality or severe toxicity was observed in either mice or rats given single oral doses of 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.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

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. Packs of 30, 50, 60 and 100, 120 tablets.

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. Packs of 30, 50, 60 and 100, 120 tablets.

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. Packs of 30, 50, 60, 100 and 120 tablets.

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. Packs of 30, 50, 60 and 100, 120 tablets.

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. Packs of 30, 50, 60 and 100, 120 tablets.

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. Packs of 30, 50, 60 and 100, 120 tablets.

Not all pack sizes may be marketed.

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

NAME AND ADDRESS OF THE SPONSOR

Novartis Pharmaceuticals Australia Pty Limited
(ABN No: 18 004 244 160)
54 Waterloo Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4).

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

6 August 2009

DATE OF MOST RECENT AMENDMENT

19 August 2013

® = Registered Trademark

For Internal Use Only
Afi190813i based on the CDS 27Mar2012 incorporating new indication ABC (CDS 14Oct2011) and CDS 24 January 2013 (corrected 18 February 2013).