Afinitor®

Protein kinase inhibitors

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

Tablets

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

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

Active substance

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

Certain dosage strengths and dosage forms may not be available in all countries.

Excipients

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

Information might differ in some countries.

INDICATIONS

Afinitor Tablets are indicated for the treatment of:

- Postmenopausal women with hormone receptor-positive and HER-2 negative advanced breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole.
- Patients with advanced neuroendocrine tumors of gastrointestinal, lung or pancreatic origin.
- Patients with advanced renal cell carcinoma after failure of therapy with sunitinib or sorafenib or after treatment with VEGF targeted therapy.

DOSAGE REGIMEN AND ADMINISTRATION

Afinitor Tablets may be used in all approved indications.

Dosage regimen

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

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

General target population

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

The recommended dose of Afinitor Tablets is 10 mg, to be taken once daily (see section METHOD OF ADMINISTRATION).

Dose Modifications

Adverse drug reactions:

Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption (with or without dose reduction) or discontinuation of Afinitor therapy. If dose reduction is required, the suggested dose is approximately 50% lower than the daily dose previously administered (see section WARNINGS AND PRECAUTIONS). For dose reductions below the lowest available tablet strength, alternate day dosing should be considered.

Table 1 summarizes recommendations for dose interruption, reduction, or discontinuation of Afinitor in the management of ADRs. General management recommendations are also provided as applicable. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

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

Adverse Drug Reaction	Severity[a]	Afinitor Dose Adjustment[b] and Management Recommendations
Non-infectious pneumonitis	Grade 1 Asymptomatic, clinical or diagnostic observations only; intervention not indicated	No dose adjustment required. Initiate appropriate monitoring.
	Grade 2 Symptomatic, medical intervention indicated; limiting instrumental ADL[c]	Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to Grade ≤1. Re-initiate treatment at a lower dose. Discontinue treatment if failure to recover within 4 weeks.
	Grade 3 Severe symptoms; limiting self-care ADL[c]; oxygen indicated	Interrupt treatment until symptoms resolve to Grade ≤1, Rule out infection and consider treatment with corticosteroids. Consider re-initiating treatment at a lower dose. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4 Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Discontinue treatment, rule out infection, and consider treatment with corticosteroids.
Stomatitis	Grade 1 Asymptomatic or mild symptoms intervention not indicated	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouthwash several times a day.

Adverse Drug Reaction	Severity[a]	Afinitor Dose Adjustment[b] and Management Recommendations
	Grade 2 Moderate pain; not interfering with oral intake; modified diet indicated	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at the same dose. If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤1. Re-initiate treatment at a lower dose. Manage with topical analgesic mouth treatments (e.g., benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]
	Grade 3 Severe pain; interfering with oral intake	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at a lower dose. Manage with topical analgesic mouth treatments (e.g., benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue treatment and treat with appropriate medical therapy.
Other non-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 treatment at the same dose. If toxicity recurs at Grade 2, interrupt treatment until recovery to Grade ≤1. Re-initiate treatment at a lower dose.
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Initiate appropriate medical therapy and monitor. Consider re-initiating treatment at a lower dose. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue treatment and treat with appropriate medical therapy.
Metabolic events (e.g. hyperglycemia, dyslipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.
	Grade 3	Temporary dose interruption. Re-initiate treatment at a lower dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue treatment and treat with appropriate medical therapy.
Thrombocytopenia (Platelet count decreased)	Grade 1 (<LLN[e] - 75,000/mm^3; <LLN[e] - 75.0 x 10^9/L)	No dose adjustment required.
	Grade 2 (<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at the same dose.
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Re-initiate treatment at a lower dose.

Adverse Drug Reaction	Severity[a]	Afinitor Dose Adjustment[b] and Management Recommendations
	(<50,000 - 25,000/mm^3; <50.0 - 25.0 x 10^9/L) **OR** Grade 4 (<25,000/mm^3; <25.0 x 10^9/L)	
Neutropenia (Neutrophil count decreased)	Grade 1 (<LLN[e] – 1,500/mm^3; <LLN[e] – 1.5 x 10^9/L) **OR** Grade 2 (<1,500 – 1,000/mm^3; <1.5 – 1.0 x 10^9/L)	No dose adjustment required.
	Grade 3 (<1,000 - 500/mm^3; <1.0 - 0.5 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤2. Re-initiate treatment at the same dose.
	Grade 4 (<500/ mm^3; <0.5 x 10^9/L)	Temporary dose interruption until recovery to Grade ≤2. Re-initiate treatment at a lower dose.
Febrile neutropenia	Grade 3 ANC[f] <1,000/mm^3 with a single temperature of >38.3ºC (101ºF) or a sustained temperature of ≥38ºC (100.4ºF) for more than one hour.	Temporary dose interruption until recovery to Grade ≤2 and no fever. Re-initiate treatment at a lower dose.
	Grade 4 Life-threatening consequences; urgent intervention indicated	Discontinue treatment.

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

Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

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

[c] *Activities of daily living (ADL)*

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

[e] *Lower limit of normal (LLN)*

[f] *Absolute Neutrophil Count (ANC)*

Moderate CYP3A4/PgP inhibitors

Use caution when administering Afinitor in combination with moderate CYP3A4/PgP inhibitors. If patients require co-administration of a moderate CYP3A4/PgP inhibitor, reduce the Afinitor dose by approximately 50%. Further dose reduction may be required to manage ADRs. For dose reductions below the lowest available strength, alternate day dosing should be considered (see sections WARNINGS AND PRECAUTIONS and INTERACTIONS).

If the moderate CYP3A4/PgP inhibitor is discontinued, consider a washout period of at least 2 to 3 days (average for most commonly used moderate inhibitors) before the Afinitor dose is increased. The Afinitor dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor (see sections WARNINGS AND PRECAUTIONS and INTERACTIONS).

Strong CYP3A4 inducers

Avoid the use of concomitant strong CYP3A4 inducers.

If patients require co-administration of a strong CYP3A4 inducer, 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 sections WARNINGS AND PRECAUTIONS and INTERACTIONS).

Special populations

Pediatric patients (below 18 years)

Afinitor is not recommended for use in pediatric cancer patients and do not use in patients aged <18 years due to a lack of data on safety and efficacy.

Geriatric patients (65 years of age or older)

No dosage adjustment is required (see section CLINICAL PHARMACOLOGY).

Renal impairment

No dosage adjustment is required (see section CLINICAL PHARMACOLOGY).

Hepatic impairment

- Mild hepatic impairment (Child-Pugh A) – the recommended dose is 7.5 mg daily
- Moderate hepatic impairment (Child-Pugh B) – the recommended dose is 5 mg daily; the dose may be decreased to 2.5 mg if not well tolerated.
- Severe hepatic impairment (Child-Pugh 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.

Method of administration

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

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

Missed dose

Afinitor can still be taken up to 6 hours after the time it is normally taken. After more than 6 hours, the dose should be skipped for that day. The next day, Afinitor should be taken at its usual time. Double doses should not be taken to make up for the one that was missed.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking Afinitor (see section ADVERSE DRUG REACTIONS). Some of these have been severe and on rare occasions, a fatal outcome was observed.

A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Opportunistic infections such as pneumocystis jirovecii pneumonia (PJP) should be ruled out in the differential diagnosis of non-infectious pneumonitis (see sub-section Infections).

Patients should be advised to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue Afinitor therapy without dose alteration (see section DOSAGE REGIMEN AND ADMINISTRATION, Table 1).

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

For cases of grade 3 non-infectious pneumonitis, interrupt Afinitor until resolution to less than or equal to grade 1. Afinitor may be re-initiated at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances. If toxicity recurs at grade 3, consider discontinuation of Afinitor. For cases of grade 4 non-infectious pneumonitis, Afinitor therapy should be discontinued. Corticosteroids may be indicated until clinical symptoms resolve.

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

The development of pneumonitis has also been reported at a reduced dose (see section DOSAGE REGIMEN AND ADMINISTRATION, Table 1).

Infections

Afinitor has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens (see section ADVERSE DRUG REACTIONS). Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis, candidiasis, or pneumocystis jirovecii pneumonia (PJP) and viral infections including reactivation of hepatitis B virus, have been described in patients taking Afinitor. Some of these infections have been

severe (e.g. leading to sepsis [including septic shock], respiratory or hepatic failure) and occasionally have had a fatal outcome in adult and pediatric patients (see section ADVERSE DRUG REACTIONS).

Physicians and patients should be aware of the increased risk of infection with Afinitor. Treat pre-existing infections prior to starting treatment with Afinitor. While taking Afinitor, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of Afinitor.

If a diagnosis of invasive systemic fungal infection is made, discontinue Afinitor and treat with appropriate antifungal therapy.

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

Hypersensitivity reactions

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

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

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

Stomatitis

Stomatitis, including mouth ulceration and oral mucositis, is the most commonly reported adverse drug reaction in patients treated with Afinitor (see section ADVERSE DRUG REACTIONS). Stomatitis mostly occurs within the first 8 weeks of treatment. If stomatitis occurs, topical treatments are recommended, but alcohol-, hydrogen peroxide, iodine-, or thyme-containing products should be avoided as they may exacerbate the condition (see section DOSAGE REGIMEN AND ADMINISTRATION, Table 1). Antifungal agents should not be used unless fungal infection has been diagnosed (see section INTERACTIONS).

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

Renal failure events

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

Laboratory tests and monitoring

Renal function

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

Blood glucose

Hyperglycemia has been reported in patients taking Afinitor (see section ADVERSE DRUG REACTIONS). Monitoring of fasting serum glucose is recommended prior to the start of Afinitor therapy and periodically thereafter. More frequent monitoring is recommended when Afinitor is co-administered with other drugs that may induce hyperglycemia. Optimal glycemic control should be achieved before starting a patient on Afinitor.

Blood lipids

Dyslipidemia (including hypercholesterolemia and hypertriglyceridemia) has been reported in patients taking Afinitor. Monitoring of blood cholesterol and triglycerides prior to the start of Afinitor therapy and periodically thereafter as well as management with appropriate medical therapy is recommended.

Hematological parameters

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

Interactions

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

Use caution when administered in combination with moderate CYP3A4/PgP inhibitors. If Afinitor must be co-administered with a moderate CYP3A4/PgP inhibitor, the patient should be carefully monitored for undesirable effects and the Afinitor dose reduced if necessary (see sections DOSAGE REGIMEN AND ADMINISTRATION and INTERACTIONS).

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

Exercise caution when Afinitor is taken in combination with orally administered CYP3A4 substrates with a narrow therapeutic index due to the potential for drug interactions. If Afinitor is taken with orally administered CYP3A4 substrates with a narrow therapeutic index, the patient should be monitored for undesirable effects described in the product information of the orally administered CYP3A4 substrate (see section INTERACTIONS).

Hepatic impairment

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

Afinitor is not recommended in patients ≥18 years of age with severe hepatic impairment (Child-Pugh C) unless the potential benefit outweighs the risk (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL PHARMACOLOGY).

Vaccinations

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with Afinitor (see section INTERACTIONS).

Wound healing complications

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

Radiation therapy complications

Severe radiation reactions (including radiation esophagitis, radiation pneumonitis and radiation skin injury) have been reported when everolimus was used during, or shortly after radiation therapy. Caution should therefore be exercised for patients using everolimus in close temporal relationship with radiation therapy.

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

ADVERSE DRUG REACTIONS

Oncology - Summary of the safety profile

Adverse drug reaction (ADR, suspected to be related to treatment by the investigator) information is based on pooled safety data in patients receiving Afinitor (N=2672) in clinical studies including randomized, double-blind, placebo- or active comparator-controlled phase III and phase II studies related to the approved indications in oncology:

The most common ADRs (incidence ≥1/10 and suspected to be related to treatment by the investigator) from the pooled safety data were (in decreasing order): stomatitis, rash, fatigue, diarrhoea, infections, nausea, decreased appetite, anaemia, dysgeusia, pneumonitis, oedema peripheral, hyperglycaemia, asthenia, pruritus, weight decreased, hypercholesterolaemia, epistaxis, cough and headache.

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

Tabulated summary of adverse drug reactions from clinical trials in oncology

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

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

Table 2 Adverse drug reactions from oncology trials

Infections and infestations	
Very common	Infections[a]
Blood and lymphatic system disorders	
Very common	Anaemia
Common	Thrombocytopenia, neutropenia, leukopenia, lymphopenia
Uncommon	Pancytopenia
Rare	Pure red cell aplasia
Immune system disorders	
Uncommon	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Decreased appetite, hyperglycaemia, hypercholesterolaemia
Common	Hypertriglyceridaemia, hypophosphataemia, diabetes mellitus, hyperlipidaemia, hypokalaemia, dehydration
Psychiatric disorders	
Common	Insomnia
Nervous system disorders	
Very common	Dysgeusia, headache
Uncommon	Ageusia
Cardiac disorders	
Uncommon	Congestive cardiac failure
Vascular disorders	
Common	Haemorrhage[b], hypertension, lymphoedema
Uncommon	Deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	
Very common	Pneumonitis[c], epistaxis, cough
Common	Dyspnoea
Uncommon	Haemoptysis, pulmonary embolism,
Rare	Acute respiratory distress syndrome
Gastrointestinal disorders	
Very common	Stomatitis[d], diarrhoea, nausea

Common	Vomiting, dry mouth, abdominal pain, oral pain, dyspepsia, dysphagia
Skin and subcutaneous tissue disorders	
Very common	Rash, pruritus
Common	Dry skin, nail disorder, acne, erythema, hand-foot syndrome[e]
Rare	Angioedema
Musculoskeletal and connective tissue disorders	
Common	Arthralgia
Renal and urinary disorders	
Common	Proteinuria, renal failure
Uncommon	Increased daytime urination, acute renal failure
Reproductive system and breast disorders	
Common	Menstruation irregular[f]
Uncommon	Amenorrhoea[f]
General disorders and administration site conditions	
Very common	Fatigue, asthenia, oedema peripheral
Common	Pyrexia, mucosal inflammation
Uncommon	Non-cardiac chest pain, impaired wound healing
Investigations	
Very common	Weight decreased
Common	Aspartate aminotransferase increased, alanine aminotransferase increased, blood creatinine increased

[a] Includes all reactions within the 'infections and infestations' system organ class including common: pneumonia, urinary tract infection; uncommon: bronchitis, herpes zoster, sepsis, abscess and isolated cases of opportunistic infections (e.g. aspergillosis, candidiasis and hepatitis B) and rare: viral myocarditis.

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

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

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

[e] reported as palmar-plantar erythrodysaesthesia syndrome

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

Clinically relevant laboratory abnormalities

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

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

Most of the observed abnormalities (≥1/100) were mild (grade 1) or moderate (grade 2).

Grade 3/4 haematology and chemistry abnormalities include:

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

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Afinitor via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 3 Adverse drug reactions from spontaneous reports and literature in Oncology and tuberous sclerosis complex (TSC) (frequency not known)

Injury, poisoning and procedural complications
Radiation recall syndrome

Description of selected adverse drug reactions

In clinical trials and post-marketing spontaneous reports, everolimus has been associated with serious cases of hepatitis B reactivation, including fatal outcome. Reactivation of infections is an expected event during periods of immunosuppression (see section WARNINGS AND PRECAUTIONS).

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

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

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

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

In a post-marketing single arm study in postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (N=92), topical treatment with dexamethasone 0.5 mg/5 mL alcohol-free oral solution (10 mL swished in the mouth for 2 minutes and then spat out, to be repeated 4 times daily for 8 weeks) was administered as a mouthwash to patients at the time of initiating treatment with Afinitor (10 mg/day) plus exemestane (25 mg/day) to reduce the incidence and severity of stomatitis. No food or drink was to be consumed for at least 1 hour after swishing and spitting the dexamethasone oral solution. The incidence of grade ≥2 stomatitis at 8 weeks was 2.4% (n=2/85 evaluable patients) which was lower than

historically reported at 27.4% (n=132/482) in the phase III study in this patient population (BOLERO-2). The incidence of grade 1 stomatitis was 18.8% (n=16/85) and no grade 3 or 4 stomatitis were reported. The overall safety profile in this study was consistent with that established for everolimus in the oncology and TSC settings, with the exception of oral candidiasis which was reported in 2.2% (n=2/92) of patients in this study compared to 0.2% (n=1/482) of patients in BOLERO-2.

Special populations

Geriatric patients (65 years of age or older)

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

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

INTERACTIONS

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of the multidrug efflux pump P-glycoprotein (PgP). Therefore, absorption and subsequent elimination of everolimus may be influenced by products that affect CYP3A4 and/or PgP.

In vitro, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

Agents that may increase everolimus blood concentrations

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

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

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

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

Concomitant treatment with moderate inhibitors of CYP3A4 (including but not limited to erythromycin, verapamil, ciclosporin, fluconazole, diltiazem, amprenavir, fosamprenavir, or aprepitant) and PgP inhibitors requires caution. Reduce the Afinitor dose if co-administered with moderate CYP3A4/PgP inhibitors (see sections DOSAGE REGIMEN AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

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

- erythromycin (a moderate CYP3A4 inhibitor and a PgP inhibitor; C_{max} and AUC increased by 2.0- and 4.4-fold, respectively).

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

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

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

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

Agents that may decrease everolimus blood concentrations

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

Concurrent treatment with strong CYP3A4/PgP inducers should be avoided. If Afinitor must be co-administered with a strong CYP3A4/PgP inducer (e.g. rifampicin and rifabutin), it may be necessary to adjust the Afinitor dose (see sections DOSAGE REGIMEN AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

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

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

Agents whose plasma concentration may be altered by everolimus

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

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

A study in healthy subjects demonstrated that co-administration of an oral dose of midazolam (CYP3A4 substrate) with everolimus resulted in a 25% increase in midazolam C_{max} and a 30% increase in midazolam $AUC_{(0\text{-}inf)}$, whereas the metabolic $AUC_{(0\text{-}inf)}$ ratio (1-hydroxy-midazolam/midazolam) and the terminal $t_{1/2}$ of midazolam were not affected. This suggests that increased exposure to midazolam is due to effects of everolimus in the gastrointestinal system when both drugs are taken at the same time. Therefore, everolimus may affect the

bioavailability of orally co-administered drugs which are CYP3A4 substrates. Everolimus is unlikely to affect the exposure of other CYP3A4 substrate drugs which are administered by non-oral routes such as intravenous, subcutaneous, and transdermal administration. (see section WARNINGS AND PRECAUTIONS).

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

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

Co-administration of everolimus and exemestane increased exemestane C_{min} and C2h by 45% and 71%, respectively. However, the corresponding estradiol levels at steady state (4 weeks) were not different between the two treatment arms. No increase in adverse events related to exemestane was observed in patients with hormone receptor-positive advanced breast cancer receiving the combination. The increase in exemestane levels is unlikely to have an impact on efficacy or safety.

Vaccinations

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

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk Summary

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

Animal Data

Oral doses of everolimus in female rats at ≥0.1 mg/kg (approximately 4% the AUC_{0-24h} in patients receiving the 10 mg daily dose) resulted in increased incidence of pre-implantation

loss. Everolimus crossed the placenta and was toxic to the conceptus. In rats, everolimus caused embryo/feto-toxicity at systemic exposure below the therapeutic level. This was manifested as mortality and reduced fetal weight. The incidence of skeletal variations and malformations (e.g. sternal cleft) was increased at 0.3 and 0.9 mg/kg. In rabbits, embryotoxicity was evident via an increase in late resorptions that occurred at an oral dose of 0.8 mg/kg (9.6 mg/m^2), approximately 1.6 times either the 10 mg daily dose in adults or the median dose administered to SEGA patients, and 1.3 times the median dose for patients with TSC and refractory seizures, on a body surface area basis. In rats, there was no evidence of adverse effects by treating males with everolimus on embryo-fetal parameters.

Human data

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

Lactation

Risk Summary

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

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

Females and males of reproductive potential

Contraception

Females of reproductive potential should be advised that animal studies have been performed showing Afinitor to be harmful to the developing fetus. Sexually-active females of reproductive potential should use effective contraception (one that results in an annual pregnancy rate <1% when used correctly) while receiving Afinitor, and for up to 8 weeks after ending treatment. Male patients taking Afinitor should not be prohibited from attempting to father children (see section NON-CLINICAL SAFETY DATA).

Infertility

Females and Males

Animal data

In animal reproductive studies, female fertility was not affected. However, pre-implantation losses were observed. In male rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count, and plasma testosterone levels were diminished at 5 mg/kg, which is within the range of therapeutic exposure (52 ng.hr/mL and 414 ng.hr/mL

respectively compared to 560 ng.hr/mL human exposure at 10 mg/day) and which caused a reduction in male fertility. There was evidence of reversibility.

Human data

Both male and female fertility may be compromised by treatment with everolimus (see section NON-CLINICAL SAFETY DATA). Menstrual irregularities, secondary amenorrhea and associated luteinizing hormone (LH)/follicle stimulating hormone (FSH) imbalance have been observed in female patients receiving everolimus. Blood levels of FSH and LH increased, blood levels of testosterone decreased, and azoospermia have been observed in male patients receiving everolimus.

OVERDOSAGE

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

Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been given with acceptable acute tolerability.

General supportive measures should be initiated in all cases of overdose.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

Everolimus is an inhibitor targeting mTOR (mammalian target of rapamycin), or more specifically, mTORC1 (mammalian 'target of rapamycin' complex 1). It exerts its activity through high affinity interaction with the intracellular receptor protein FKBP12. The FKBP12/everolimus complex binds to mTORC1, inhibiting its signaling capacity. mTOR is a key serine-threonine kinase playing a central role in the regulation of cell growth, proliferation and survival. The regulation of mTORC1 signaling 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.

mTORC1 signaling is effected through modulation of the phosphorylation of downstream effectors, the best characterized of which are the translational regulators S6 ribosomal protein kinase (S6K1) and eukaryotic initiation factor 4E-binding protein (4E-BP1). Disruption of S6K1 and 4E-BP1 function, as a consequence of mTORC1 inhibition, interferes with the translation of mRNAs encoding pivotal proteins involved in cell cycle regulation, glycolysis and adaptation to low oxygen conditions (hypoxia). This inhibits tumor 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 tumor angiogenic processes (e.g. the vascular endothelial growth factor VEGF) in multiple tumors such as RCC and angiomyolipoma). Two primary regulators of mTORC1 signaling are the oncogene suppressors tuberin-sclerosis complexes 1 & 2 (TSC1, TSC2). Loss or inactivation of either TSC1 or TSC2 leads to elevated rheb-GTP levels, a ras family GTPase, which interacts with the mTORC1 complex to cause its activation. mTORC1 activation leads to a downstream kinase signaling cascade, including activation of the S6K1. A substrate of mTOR complex 1 (mTORC1), S6K1

phosphorylates the estrogen receptor, which is responsible for ligand-independent receptor activation.

Everolimus is a potent inhibitor of the growth and proliferation of tumor cells, endothelial cells, fibroblasts and blood vessel-associated smooth muscle cells. Consistent with the central regulatory role of mTORC1, everolimus has been shown to reduce tumor cell proliferation, glycolysis and angiogenesis in solid tumors *in vivo*, and thus provides two independent mechanisms for inhibiting tumor growth: direct antitumor cell activity and inhibition of the tumor stromal compartment.

Activation of the mTOR pathway is a key adaptive change driving endocrine resistance in breast cancer. Various signal transduction pathways are activated to escape the effect of endocrine therapy. One pathway is the PI3K/Akt/mTOR pathway, which is constitutively activated in aromatase inhibitor (AI)-resistant and long-term estrogen-deprived breast cancer cells. *In vitro* studies show that estrogen-dependent and HER2+ breast cancer cells are sensitive to the inhibitory effects of everolimus, and that combination treatment with everolimus and aromatase inhibitors enhances the anti-tumor activity of everolimus in a synergistic manner. In breast cancer cells, resistance to AIs due to Akt activation can be reversed by co-administration with everolimus.

Pharmacodynamics (PD)

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

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

Pharmacokinetics (PK)

Absorption

After administration of Afinitor Tablets in patients with advanced solid tumors, 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. With single doses of 20 mg and higher, the increase in C_{max} is less than dose-proportional, however AUC shows dose-proportionality over the 5 to 70 mg dose range.

Food effect:

In healthy subjects, high fat meals reduced systemic exposure to 10 mg Afinitor Tablets (as measured by AUC) by 22% and the peak blood concentration C_{max} by 54%. Low-fat meals reduced AUC by 32% and C_{max} by 42%.

Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5,000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given Afinitor 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.

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

Biotransformation/metabolism

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

Elimination

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

Steady-state pharmacokinetics

After administration of Afinitor Tablets in patients with advanced solid tumors, 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 daily. 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. The mean elimination half-life of everolimus is approximately 30 hours.

Special populations

Hepatic impairment

The safety, tolerability and pharmacokinetics of Afinitor were evaluated in two single oral dose studies of Afinitor Tablets in subjects with impaired hepatic function relative to subjects with normal hepatic function. In one study the average AUC of everolimus in 8 subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in 8 subjects with normal hepatic function. In a second study of 34 subjects with different impaired hepatic function compared to normal subjects, there was a 1.6-fold, 3.3-fold, and 3.6-fold increase in exposure (i.e. $AUC_{(0\text{-inf})}$) for subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, respectively. Simulations of multiple dose pharmacokinetics support the dosing recommendations in hepatic impaired subjects based on their Child Pugh status.

Based on a meta-analysis of the two studies, dose adjustment is recommended for patients with hepatic impairment (see sections WARNINGS AND PRECAUTIONS and DOSAGE REGIMEN AND ADMINISTRATION).

Renal impairment

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

Pediatric patients (below 18 years)

There is no indication for use of Afinitor in the pediatric cancer population (see section DOSAGE REGIMEN AND ADMINISTRATION).

Geriatric patients (65 years of age or older)

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

Race/Ethnicity

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

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

CLINICAL STUDIES

Hormone receptor-positive advanced breast cancer

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

women with estrogen receptor-positive, HER 2-neu/non-amplified advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. Patients were randomized in a 2:1 ratio to receive either everolimus (10 mg daily) or matching placebo in addition to open-label exemestane (25 mg daily). Randomization was stratified by documented sensitivity to prior hormonal therapy (yes vs. no) and by the presence of visceral metastasis (yes vs. no). Sensitivity to prior hormonal therapy was defined as either (1) documented clinical benefit (complete response [CR], partial response [PR], stable disease ≥24 weeks) to at least one prior hormonal therapy in the advanced setting or (2) at least 24 months of adjuvant hormonal therapy prior to recurrence.

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

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

A total of 724 patients were randomized in 2:1 ratio to the combination everolimus (10 mg daily) + exemestane (25 mg daily) (n = 485) or placebo + exemestane arm (25 mg daily) (n = 239). The two treatment groups were generally balanced with respect to the baseline demographics of disease characteristics and history of prior anti-neoplastic usages. The median age of patients was 61 years (range 28 to 93) and 75% were Caucasian. The median duration of blinded treatment was 24 weeks for patients receiving Afinitor plus exemestane and 13.4 weeks for those receiving placebo plus exemestane.

The efficacy results were obtained from the final analysis of PFS after 510 local PFS events and 320 central PFS events were observed. Patients in the placebo + exemestane arm did not cross-over to everolimus at the time of progression.

The study demonstrated a statistically significant clinical benefit of everolimus + exemestane over placebo + exemestane by a 2.5-fold prolongation in median PFS (median: 7.82 months versus 3.19 months), resulting in a 55% risk reduction of progression or death (PFS HR 0.45; 95% CI: 0.38, 0.54; one-sided log-rank test p-value <0.0001 per local investigator assessment (see Table 4).

The analysis of PFS based on independent central radiological assessment was supportive and showed a 2.7-fold prolongation in median progression-free-survival (11.01 months versus 4.14 months), resulting in a 62% risk reduction of progression or death (PFS HR 0.38; 95% CI: 0.31, 0.48; one-sided log-rank test p-value<0.0001) (see Table 4).

Objective response as per investigator assessment based on RECIST was observed in 12.6% of patients (95% CI: 9.8, 15.9) in the everolimus + exemestane arm vs. 1.7% (95% CI: 0.5-4.2) in the placebo + exemestane arm (p<0.0001 for comparison between arms). Clinical benefit rate for everolimus + exemestane was 51.3% vs. 26.4% in the control arm; p<0.0001 (see Table 4).

Table 4 BOLERO-2 – Efficacy results

Analysis	Afinitor[a] N = 485	Placebo[a] N = 239	Hazard ratio	P-value
Median progression-free survival (months, 95% CI)				
Investigator radiological review	7.82 (6.93 to 8.48)	3.19 (2.76 to 4.14)	0.45 (0.38 to 0.54)	<0.0001
Independent radiological review	11.01 (9.66 to 15.01)	4.14 (2.89 to 5.55)	0.38 (0.31 to 0.48)	<0.0001
Best overall response (%, 95% CI)				
Objective response rate (ORR)[b]	12.6% (9.8 to 15.9)	1.7% (0.5 to 4.2)	n/a[d]	<0.0001[e]
Clinical benefit rate (CBR) [c]	51.3% (46.8 to 55.9)	26.4% (20.9 to 32.4)	n/a[d]	<0.0001[e]

[a] Plus exemestane

[b] Objective response rate = proportion of patients with CR or PR

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

[d] not applicable

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

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

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

The estimated PFS treatment effect was supported by planned subgroup analysis of PFS per investigator assessment. For all analyzed subgroups, (e.g. age group (<65 years and ≥65 years), region, race, # of organs involved, # of prior therapies, sensitivity to prior hormonal therapy, presence of visceral metastasis, prior chemotherapy, bone only lesions at baseline, baseline ECOG performance status, PgR status and prior use of hormonal therapy other than NSAI) a positive treatment effect was seen with everolimus + exemestane with an estimated hazard ratio vs. placebo + exemestane ranging from 0.25 to 0.62. 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.

Tumor reduction was also evident in 70.8% of patients in the everolimus + exemestane arm versus 29.7% for placebo + exemestane.

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

Effects on bone

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

Advanced neuroendocrine tumors of gastrointestinal, lung or pancreatic origin

RADIANT-3 (Study CRAD001C2324), a randomized, double-blind, multicenter phase III study of Afinitor plus best supportive care (BSC) versus placebo plus BSC in patients with advanced pancreatic neuroendocrine tumors (pNET), demonstrated a statistically significant clinical benefit of Afinitor over placebo by a 2.4-fold prolongation in median progression-free-survival PFS (11.04 months versus 4.6 months), resulting in a 65% risk reduction in PFS (HR 0.35; 95% CI: 0.27, 0.45; p<0.0001) (see Table 5).

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

The primary endpoint for the trial was PFS evaluated by RECIST (Response Evaluation Criteria in Solid Tumors, version 1.0) as per investigator radiology review. After documented radiological progression, patients could be unblinded by the investigator: those randomized 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 randomized 1:1 to receive either Afinitor 10 mg/day (n=207) or placebo (n=203). Demographics were well balanced (median age 58 years, 55% male, 78.5% Caucasian). Median duration of blinded study treatment was 37.8 weeks for patients receiving Afinitor and 16.1 weeks for those receiving placebo.

Table 5 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

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

The objective response rate per investigator assessment was 4.8% for the everolimus arm vs. 2.0% for the placebo arm. Tumor reduction was also evident in 64.4% of patients in the everolimus arm versus 20.6% for placebo.

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

RADIANT-4 (Study CRAD001T2302), a randomized, double-blind, multicenter phase III study of Afinitor plus best supportive care (BSC) versus placebo plus best supportive care was

conducted in patients with advanced non-functional neuroendocrine tumors (NET) of gastrointestinal or lung origin without a history of and no active symptoms related to carcinoid syndrome. Randomization was stratified by prior somatostatin analog (SSA) use, tumor origin and WHO performance status.

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

Secondary endpoints included overall survival (OS), Overall Response Rate (ORR), Disease Control Rate (DCR = proportion of patients with a best overall response of complete response, partial response or stable disease), Safety, change in Quality of Life (QoL) via FACT-G and time to WHO PS deterioration.

A total of 302 patients were randomized in a 2:1 ratio to receive either everolimus (10 mg daily) (n = 205) or placebo (n = 97). The two treatment groups were generally balanced with respect to the baseline demographics, disease characteristics and history of prior somatostatin analog (SSA) use. The median age of patients was 63 years (range 22 to 86) and 76% were Caucasian. The median duration of blinded treatment was 40.4 weeks for patients receiving Afinitor and 19.6 weeks for those receiving placebo. Patients in the placebo arm did not cross-over to everolimus at the time of progression.

The efficacy results were obtained from the final analysis of PFS after 178 PFS events were observed per independent radiological review.

The study demonstrated a statistically significant clinical benefit of everolimus over placebo by a 2.8-fold prolongation in median PFS (11.01 months versus 3.91 months), resulting in a 52% risk reduction of progression or death (HR 0.48; 95% CI: 0.35, 0.67; one-sided stratified log-rank test p-value <0.0001) per independent assessment (see Table 6).

The analysis of PFS based on local investigator assessment was supportive and showed a 2.5-fold prolongation in median progression-free-survival (13.96 months versus 5.45 months), resulting in a 61% risk reduction of progression or death (HR 0.39; 95% CI: 0.28, 0.54; one-sided stratified log-rank test p-value<0.0001) (see Table 6).

Table 6 RADIANT-4 – Progression Free Survival results

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

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

The overall PFS benefit favored Afinitor across predefined demographic and prognostic stratification subgroups (e.g., prior SSA treatment, tumor origin grouping and WHO performance status) and with a hazard ratio range of 0.43 to 0.63). A post-hoc subgroup analysis of PFS showed a positive PFS benefit for sites of tumor origin by gastrointestinal [HR=0.60 (95% CI:0.39 to 0.91)], lung [HR=0.50 (95% CI:0.28 to 0.88)] and carcinoma of unknown primary/other origin [HR=0.50 (95% CI:0.22 to 1.16)].

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

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

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

RADIANT-2 (Study CRAD001C2325), a randomized, double-blind, multicenter phase III study of Afinitor plus depot octreotide (Sandostatin LAR®) versus placebo plus depot octreotide in patients with advanced neuroendocrine tumors (carcinoid tumor) primarily of gastrointestinal or lung origin showed evidence of clinical benefit of Afinitor over placebo by a 5.1-month prolongation in median PFS (16.43 months versus 11.33 months; HR 0.77; 95% CI: 0.59 to 1.00; one-sided p=0.026), resulting in a 23% risk reduction in primary PFS (see Table 7). Although statistical significance was not reached for the primary analysis (boundary for statistical significance was p=0.0246), analyses which adjusted for informative censoring and imbalances in the two treatment arms showed a treatment effect in favor of everolimus.

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

The primary endpoint is PFS evaluated by RECIST as per independent radiological review. After documented radiological progression, patients could be unblinded by the investigator: those randomized 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 randomized 1:1 to receive either Afinitor 10 mg/day (n=216) or placebo (n=213), in addition to depot octreotide (Sandostatin LAR®, administered intramuscularly) 30 mg every 28 days. Median duration of blinded study treatment was 37.0 weeks for patients receiving Afinitor and 36.6 weeks for those receiving placebo. Notable imbalances were evident for several important baseline prognostic factors, mainly in favor of the placebo group.

Table 7 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

Analysis	N	Afinitor[a] N=216	Placebo[a] N=213	Hazard Ratio (95% CI)	p-value[c]

[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 a stratified log-rank test

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

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

The objective response rate per independent radiological review was 2.3% for the everolimus plus depot octreotide (Sandostatin LAR®) arm vs. 1.9% for the placebo plus depot octreotide (Sandostatin LAR®) arm. Tumor reduction was also evident in 75.0% of patients in the everolimus plus depot octreotide (Sandostatin LAR®) arm versus 44.8% in the placebo plus depot octreotide (Sandostatin LAR®) arm.

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

Advanced renal cell carcinoma

RECORD-1 (CRAD001C2240), a phase III, international, multicenter, randomized, double-blind study comparing Afinitor 10 mg/day and placebo, both in conjunction with best supportive care, was conducted in patients with metastatic renal cell carcinoma whose disease had progressed despite prior treatment with VEGFR-TKI (vascular endothelial growth factor receptor tyrosine kinase inhibitor) therapy (sunitinib, sorafenib, or both sunitinib and sorafenib). Prior therapy with bevacizumab and interferon-alpha was also permitted. Patients were stratified according to Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score (favourable- vs. intermediate- vs. poor-risk groups) and prior anticancer therapy (1 vs. 2 prior VEGFR-TKIs).

Progression-free survival, documented using RECIST (Response Evaluation Criteria in Solid Tumors) and assessed via a blinded, independent central review, was the primary endpoint. Secondary endpoints included safety, objective tumor response rate, overall survival, disease-related symptoms, and quality of life. After documented radiological progression, patients could be unblinded by the investigator: those randomized 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 randomized 2:1 to receive Afinitor (n=277) or placebo (n=139). Demographics were well balanced (pooled median age 61 years [range 27 to 85], 77% male, 88% Caucasian, 74% one prior VEGFR-TKI therapy). Median duration of blinded study treatment was 141 days for patients receiving Afinitor and 60 days for those receiving placebo.

Results from a planned interim analysis showed that Afinitor was superior to placebo for the primary endpoint of progression-free survival, with a statistically significant 67% reduction in the risk of progression or death (see Table 8).

Table 8 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

Six-month PFS rates were 36% for Afinitor therapy compared with 9% for placebo.

Confirmed objective tumor 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 stabilization (corresponding to 67% of the Afinitor treatment group).

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

patients receiving Afinitor as measured by disease-related symptoms (HR 0.75; 95% CI: 0.53 to 1.06; p=0.053).

NON-CLINICAL SAFETY DATA

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

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

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

Genotoxicity studies covering relevant genotoxicity endpoints showed no evidence of clastogenic or mutagenic activity. Administration of everolimus for up to 2 years did not indicate any oncogenic potential in mice and rats up to the highest doses, corresponding respectively to 3.9 and 0.2 times the estimated clinical exposure from a 10 mg daily dose.

Reproductive toxicity

For information on reproductive toxicity, see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Store in the original package in order to protect from light and moisture.

Afinitor should not be used after the date marked “EXP” on the pack.

Afinitor must be kept out of the sight and reach of children.

Do not store above 30ºC.

NATURE AND CONTENTS OF CONTAINER

PA/AL/PVC blister containing 10 tablets.

Packs containing 10 and 30 tablets

Manufacturer:

See folding box.

International Package Leaflet

Information issued: May 2021

Novartis Pharma AG, Basel, Switzerland