

## 1 INDICATIONS AND USAGE

AFINITOR tablets are indicated for the

- treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole.
- treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.
- treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease. AFINITOR is not indicated for the treatment of patients with functional carcinoid tumors.
- treatment of adult patients with progressive, well-differentiated (Grade 1 or Grade 2), non-functional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin with unresectable, locally advanced or metastatic disease. AFINITOR is not indicated for the treatment of patients with functional carcinoid tumors.
- treatment of adult and pediatric patients, 1 years of age and older, with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not candidates for curative surgical resection. The effectiveness of AFINITOR is based on an analysis of change in SEGA volume (see section CLINICAL STUDIES). Clinical benefit such as improvement in disease-related symptoms or increase in overall survival has not been demonstrated.
- treatment of adult patients with renal angiomyolipoma (AML) and tuberous sclerosis complex (TSC), not requiring immediate surgery. The effectiveness of AFINITOR in the treatment of renal angiomyolipoma is based on an analysis of durable objective responses in patients treated for a median of 8.3 months. Further follow-up of patients is required to determine long-term outcomes.

## 2 DOSAGE AND ADMINISTRATION

- Select the recommended dosage form based on the indication [*see Indications and Usage*].
- Modify the dosage for patients with hepatic impairment or for patients taking drugs that inhibit or induce P-glycoprotein (P-gp) and CYP3A4 [*see Dosage and Administration*].

### 2.1 Recommended Dosage for Hormone Receptor-Positive, HER2-Negative Breast Cancer, Neuroendocrine tumor (NET), Renal Cell Carcinoma (RCC) and Tuberous Sclerosis Complex (TSC)-Associated Renal Angiomyolipoma

The recommended dose of AFINITOR is 10 mg orally once daily until disease progression or unacceptable toxicity.

### 2.2 Recommended Dosage for Tuberous Sclerosis Complex (TSC)-Associated Subependymal Giant Cell Astrocytoma (SEGA)

The recommended starting dosage of AFINITOR is 4.5 mg/m<sup>2</sup> orally once daily until disease progression or unacceptable toxicity [see *Dosage and Administration*].

### 2.3 Therapeutic Drug Monitoring (TDM) and Dose Titration for Tuberous Sclerosis Complex (TSC)-Associated Subependymal Giant Cell Astrocytoma (SEGA)

- Monitor everolimus whole blood trough concentrations at time points recommended in Table 1.
- Titrate the dose to attain trough concentrations of 5ng/mL to 15 ng/mL.
- Adjust the dose using the following equation:

New dose\* = current dose x (target concentration divided by current concentration)

\*The maximum dose increment at any titration must not exceed 5mg. Multiple dose titrations may be required to attain the target trough concentration.

- When possible, use the same assay and laboratory for TDM throughout treatment.

**Table 1: Recommended Timing of Therapeutic Drug Monitoring**

| Event                                                               | When to Assess Trough Concentrations After Event |
|---------------------------------------------------------------------|--------------------------------------------------|
| Initiation of AFINITOR                                              | 1 to 2 weeks                                     |
| Modification of AFINITOR dose                                       | 1 to 2 weeks                                     |
| Switch between AFINITOR                                             | 1 to 2 weeks                                     |
| Initiation or discontinuation of P-gp and moderate CYP3A4 inhibitor | 2 weeks                                          |
| Initiation or discontinuation of P-gp and strong CYP3A4 inducer     | 2 weeks                                          |
| Change in hepatic function                                          | 2 weeks                                          |
| Stable dose with changing body surface area (BSA)                   | Every 3 to 6 months                              |
| Stable dose with stable BSA                                         | Every 6 to 12 months                             |
| Abbreviation: P-gp, P-glycoprotein.                                 |                                                  |

### 2.4 Dosage Modifications for Adverse Reactions

Table 2 summarizes recommendations for dosage modifications of AFINITOR for the management of adverse reactions.

**Table 2: Recommended Dosage Modifications for AFINITOR for Adverse Reactions**

| Adverse Reaction                                                     | Severity | Dosage Modification                                                                                                                                                                                                                                                      |
|----------------------------------------------------------------------|----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Non-infectious pneumonitis<br>[see <i>Warnings and Precautions</i> ] | Grade 2  | Withhold until improvement to Grade 0 or 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength. Permanently discontinue if toxicity does not resolve or improve to Grade 1 within 4 weeks. |

|                                                                                               |                    |                                                                                                                                                                                                                                                                                                                   |
|-----------------------------------------------------------------------------------------------|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                               | Grade 3            | Withhold until improvement to Grade 0 or 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength. If toxicity recurs at Grade 3, permanently discontinue.                                                                             |
|                                                                                               | Grade 4            | Permanently discontinue.                                                                                                                                                                                                                                                                                          |
| Stomatitis<br><i>[see Warnings and Precautions]</i>                                           | Grade 2            | Withhold until improvement to Grade 0 or 1. Resume at same dose.<br>If recurs at Grade 2, withhold until improvement to Grade 0 or 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.                                           |
|                                                                                               | Grade 3            | Withhold until improvement to Grade 0 or 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.                                                                                                                                     |
|                                                                                               | Grade 4            | Permanently discontinue.                                                                                                                                                                                                                                                                                          |
| Metabolic events (e.g., hyperglycemia, dyslipidemia)<br><i>[see Warnings and Precautions]</i> | Grade 3            | Withhold until improvement to Grade 0, 1, or 2. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.                                                                                                                                 |
|                                                                                               | Grade 4            | Permanently discontinue.                                                                                                                                                                                                                                                                                          |
| Other non-hematologic toxicities                                                              | Grade 2            | If toxicity becomes intolerable, withhold until improvement to Grade 0 or 1. Resume at same dose.<br>If toxicity recurs at Grade 2, withhold until improvement to Grade 0 or 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength. |
|                                                                                               | Grade 3            | Withhold until improvement to Grade 0 or 1. Consider resuming at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.<br>If recurs at Grade 3, permanently discontinue.                                                                        |
|                                                                                               | Grade 4            | Permanently discontinue.                                                                                                                                                                                                                                                                                          |
| Thrombocytopenia<br><i>[see Warnings and Precautions]</i>                                     | Grade 2            | Withhold until improvement to Grade 0 or 1. Resume at same dose.                                                                                                                                                                                                                                                  |
|                                                                                               | Grade 3 OR Grade 4 | Withhold until improvement to Grade 0 or 1. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.                                                                                                                                     |
| Neutropenia<br><i>[see Warnings and Precautions]</i>                                          | Grade 3            | Withhold until improvement to Grade 0, 1 or 2. Resume at same dose.                                                                                                                                                                                                                                               |
|                                                                                               | Grade 4            | Withhold until improvement to Grade 0, 1 or 2. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.                                                                                                                                  |
| Febrile neutropenia<br><i>[see Warnings and Precautions]</i>                                  | Grade 3            | Withhold until improvement to Grade 0, 1 or 2 and no fever. Resume at 50% of previous dose; change to every other day dosing if the reduced dose is lower than the lowest available strength.                                                                                                                     |
|                                                                                               | Grade 4            | Permanently discontinue.                                                                                                                                                                                                                                                                                          |

## 2.5 Dosage Modifications for Hepatic Impairment

The recommended dosages of AFINITOR for patients with hepatic impairment are described in Table 3 [see *Use in Specific Populations*]:

**Table 3: Recommended Dosage Modifications for Patients with Hepatic Impairment**

| Indication                                                                                                                                        | Dose Modification for AFINITOR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|---------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Breast Cancer, NET, RCC, and TSC-Associated Renal Angiomyolipoma                                                                                  | <ul style="list-style-type: none"> <li>Mild hepatic impairment (Child-Pugh class A) – 7.5 mg orally once daily; decrease the dose to 5 mg orally once daily if a dose of 7.5 mg once daily is not tolerated.</li> <li>Moderate hepatic impairment (Child-Pugh class B) – 5 mg orally once daily; decrease the dose to 2.5 mg orally once daily if a dose of 5 mg once daily is not tolerated.</li> <li>Severe hepatic impairment (Child-Pugh class C) – 2.5 mg orally once daily if the desired benefit outweighs the risk; do not exceed a dose of 2.5 mg once daily.</li> </ul> |
| TSC-Associated SEGA                                                                                                                               | <ul style="list-style-type: none"> <li>Severe hepatic impairment (Child-Pugh class C) – 2.5 mg/m<sup>2</sup> orally once daily.</li> <li>Adjust dose based on everolimus trough concentrations as recommended [see <i>Dosage and Administration</i>].</li> </ul>                                                                                                                                                                                                                                                                                                                  |
| Abbreviations: NET, Neuroendocrine Tumors; RCC, Renal Cell Carcinoma; SEGA, Subependymal Giant Cell Astrocytoma; TSC, Tuberous Sclerosis Complex. |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

## 2.6 Dosage Modifications for P-gp and CYP3A4 Inhibitors

- Avoid the concomitant use of P-gp and strong CYP3A4 inhibitors [see *Drug Interactions*].
- Avoid ingesting grapefruit and grapefruit juice.
- Reduce the dose for patients taking AFINITOR with a P-gp and moderate CYP3A4 inhibitor as recommended in Table 4 [see *Drug Interactions, Clinical Pharmacology*].

**Table 4: Recommended Dosage Modifications for Concurrent Use of AFINITOR with a P-gp and Moderate CYP3A4 Inhibitor**

| Indication                                                       | Dose Modification for AFINITOR                                                                                                                                                                                                                                                                                                                                                                                                           |
|------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Breast Cancer, NET, RCC, and TSC-Associated Renal Angiomyolipoma | <ul style="list-style-type: none"> <li>Reduce dose to 2.5 mg once daily.</li> <li>May increase dose to 5 mg once daily if tolerated.</li> <li>Resume dose administered prior to inhibitor initiation, once the inhibitor is discontinued for 3 days.</li> </ul>                                                                                                                                                                          |
| TSC-Associated SEGA                                              | <ul style="list-style-type: none"> <li>Reduce the daily dose by 50%.</li> <li>Change to every other day dosing if the reduced dose is lower than the lowest available strength.</li> <li>Resume dose administered prior to inhibitor initiation, once the inhibitor is discontinued for 3 days.</li> <li>Assess trough concentrations when initiating and discontinuing the inhibitor [see <i>Dosage and Administration</i>].</li> </ul> |

## 2.7 Dosage Modifications for P-gp and CYP3A4 Inducers

- Avoid concomitant use of St. John's Wort (*Hypericum perforatum*).
- Increase the dose for patients taking AFINITOR with a P-gp and strong CYP3A4 inducer as recommended in Table 5 [see *Drug Interactions, Clinical Pharmacology*].

**Table 5: Recommended Dosage Modifications for Concurrent Use of AFINITOR with P-gp and Strong CYP3A4 Inducers**

| Indication                                                       | Dose Modification for AFINITOR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Breast Cancer, NET, RCC, and TSC-Associated Renal Angiomyolipoma | <ul style="list-style-type: none"> <li>• Avoid coadministration where alternatives exist.</li> <li>• If coadministration cannot be avoided, double the daily dose using increments of 5 mg or less. Multiple increments may be required.</li> <li>• Resume the dose administered prior to inducer initiation, once an inducer is discontinued for 5 days.</li> </ul>                                                                                                                                                                                                          |
| TSC-Associated SEGA                                              | <ul style="list-style-type: none"> <li>• Double the daily dose using increments of 5 mg or less. Multiple increments may be required.</li> <li>• Addition of another strong CYP3A4 inducer in a patient already receiving treatment with a strong CYP3A4 inducer may not require additional dosage modification.</li> <li>• Assess trough concentrations when initiating and discontinuing the inducer [see <i>Dosage and Administration</i>].</li> <li>• Resume the dose administered before starting any inducer, once all inducers are discontinued for 5 days.</li> </ul> |

## 2.8 Administration and Preparation

- Administer AFINITOR at the same time each day.
- Administer AFINITOR consistently either with or without food [see *Clinical Pharmacology*].
- If a dose of AFINITOR is missed, it can be administered up to 6 hours after the time it is normally administered. After more than 6 hours, the dose should be skipped for that day. The next day, AFINITOR should be administered at its usual time. Double doses should not be administered to make up for the dose that was missed.

AFINITOR should be swallowed whole with a glass of water. Do not break or crush tablets.

## 3 DOSAGE FORMS AND STRENGTHS

Tablets, white to slightly yellow and elongated with a bevelled edge:

- 2.5 mg: engraved with "LCL" on one side and "NVR" on the other.

- 5 mg: engraved with “5” on one side and “NVR” on the other.
- 10 mg: engraved with “UHE” on one side and “NVR” on the other.

## 4 CONTRAINDICATIONS

AFINITOR is contraindicated in patients with clinically significant hypersensitivity to everolimus or to other rapamycin derivatives [see *Warnings and Precautions*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Non-infectious Pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Non-infectious pneumonitis was reported in up to 19% of patients treated with AFINITOR in clinical trials, some cases were reported with pulmonary hypertension (including pulmonary arterial hypertension) as a secondary event. The incidence of Grade 3 and 4 non-infectious pneumonitis was up to 4% and up to 0.2%, respectively [see *Adverse Reactions*]. Fatal outcomes have been observed.

Consider a diagnosis of non-infectious pneumonitis in patients presenting with non-specific respiratory signs and symptoms. Consider opportunistic infections, such as pneumocystis jiroveci pneumonia (PJP) in the differential diagnosis. Advise patients to report promptly any new or worsening respiratory symptoms.

Continue AFINITOR without dose alteration in patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms. Imaging appears to overestimate the incidence of clinical pneumonitis.

For Grade 2 to 4 non-infectious pneumonitis, withhold or permanently discontinue AFINITOR based on severity [see *Dosage and Administration*]. Corticosteroids may be indicated until clinical symptoms resolve. Administer prophylaxis for PJP when concomitant use of corticosteroids or other immunosuppressive agents are required. The development of pneumonitis has been reported even at a reduced dose.

### 5.2 Infections

AFINITOR has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoal infections, including infections with opportunistic pathogens [see *Adverse Reactions*]. Localized and systemic infections, including pneumonia, mycobacterial infections, other bacterial infections, invasive fungal infections (e.g., aspergillosis, candidiasis, or PJP), and viral infections (e.g., reactivation of hepatitis B virus) have occurred. Some of these infections have been severe (e.g., sepsis, septic shock, or resulting in multisystem organ failure) or fatal. The incidence of Grade 3 and 4 infections was up to 10% and up to 3%, respectively. The incidence of serious infections was reported at a higher frequency in patients < 6 years of age [see *Use in Specific Populations*].

Complete treatment of preexisting invasive fungal infections prior to starting treatment. Monitor for signs and symptoms of infection. Withhold or permanently discontinue AFINITOR based on severity of infection [see *Dosage and Administration*].

Administer prophylaxis for PJP when concomitant use of corticosteroids or other immunosuppressive agents are required.

### **5.3 Severe Hypersensitivity Reactions**

Hypersensitivity reactions to AFINITOR have been observed and include anaphylaxis, dyspnea, flushing, chest pain, and angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment) [see *Contraindications*].

The incidence of Grade 3 hypersensitivity reactions was up to 1%. Permanently discontinue AFINITOR for the development of clinically significant hypersensitivity.

### **5.4 Angioedema with Concomitant Use of Angiotensin-Converting Enzyme (ACE) Inhibitors**

Patients taking concomitant ACE inhibitors with AFINITOR may be at increased risk for angioedema (e.g., swelling of the airways or tongue, with or without respiratory impairment). In a pooled analysis of randomized double-blind oncology clinical trials, the incidence of angioedema in patients taking AFINITOR with an ACE inhibitor was 6.8% compared to 1.3% in the control arm with an ACE inhibitor. Permanently discontinue AFINITOR for angioedema.

### **5.5 Stomatitis**

Stomatitis, including mouth ulcers and oral mucositis, has occurred in patients treated with AFINITOR at an incidence ranging from 44% to 78% across clinical trials. Grades 3-4 stomatitis was reported in 4% to 9% of patients [see *Adverse Reactions*]. Stomatitis most often occurs within the first 8 weeks of treatment. When starting AFINITOR, initiating dexamethasone alcohol-free oral solution as a swish and spit mouthwash reduces the incidence and severity of stomatitis [see *Adverse Reactions*]. If stomatitis does occur, mouthwashes and/or other topical treatments are recommended. Avoid alcohol-, hydrogen peroxide-, iodine-, or thyme- containing products, as they may exacerbate the condition. Do not administer antifungal agents, unless fungal infection has been diagnosed.

### **5.6 Renal Failure**

Cases of renal failure (including acute renal failure), some with a fatal outcome, have occurred in patients taking AFINITOR. Elevations of serum creatinine and proteinuria have been reported in patients taking AFINITOR [see *Adverse Reactions*]. The incidence of Grade 3 and 4 elevations of serum creatinine was up to 2% and up to 1%, respectively. The incidence of Grade 3 and 4 proteinuria was up to 1% and up to 0.5%, respectively. Monitor renal function prior to starting AFINITOR and annually thereafter. Monitor renal function at least every 6 months in patients who have additional risk factors for renal failure.

### **5.7 Risk of Impaired Wound Healing**

Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF signaling pathway. Therefore, AFINITOR has the potential to adversely affect wound healing.

Withhold AFINITOR for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of treatment upon resolution of wound healing complications has not been established.

### **5.8 Geriatric Patients**

In the randomized hormone receptor-positive, HER2-negative breast cancer study (BOLERO-2), the incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients  $\geq 65$  years of age compared to 2% in patients  $< 65$  years of age. Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients  $\geq 65$  years of age compared to 17% in patients  $< 65$  years of age. Careful monitoring and appropriate dose adjustments for adverse reactions are recommended [*see Dosage and Administration, Use in Specific Populations*].

### **5.9 Metabolic Disorders**

Hyperglycemia, hypercholesterolemia, and hypertriglyceridemia have been reported in patients taking AFINITOR at an incidence up to 75%, 86%, and 73%, respectively. The incidence of these Grade 3 and 4 laboratory abnormalities was up to 15% and up to 0.4%, respectively [*see Adverse Reactions*]. In non-diabetic patients, monitor fasting serum glucose prior to starting AFINITOR and annually thereafter. In diabetic patients, monitor fasting serum glucose more frequently as clinically indicated. Monitor lipid profile prior to starting AFINITOR and annually thereafter. When possible, achieve optimal glucose and lipid control prior to starting AFINITOR. For Grade 3 to 4 metabolic events, withhold or permanently discontinue AFINITOR based on severity [*see Dosage and Administration*].

### **5.10 Myelosuppression**

Anemia, lymphopenia, neutropenia, and thrombocytopenia have been reported in patients taking AFINITOR. The incidence of these Grade 3 and 4 laboratory abnormalities was up to 16% and up to 2%, respectively [*see Adverse Reactions*]. Monitor complete blood count (CBC) prior to starting AFINITOR every 6 months for the first year of treatment and annually thereafter. Withhold or permanently discontinue AFINITOR based on severity [*see Dosage and Administration*].

### **5.11 Risk of Infection or Reduced Immune Response with Vaccination**

The safety of immunization with live vaccines during AFINITOR therapy has not been studied. Due to the potential increased risk of infection, avoid the use of live vaccines and close contact with individuals who have received live vaccines during treatment with AFINITOR.

Due to the potential increased risk of infection or reduced immune response with vaccination, complete the recommended childhood series of vaccinations according to American Council on Immunization Practices (ACIP) guidelines prior to the start of therapy. An accelerated vaccination schedule may be appropriate.

### **5.12 Radiation Sensitization and Radiation Recall**

Radiation sensitization and recall, in some cases severe, involving cutaneous and visceral organs (including radiation esophagitis and pneumonitis) have been reported in patients treated with radiation prior to, during, or subsequent to AFINITOR treatment [*see Adverse Reactions*].

Monitor patients closely when AFINITOR is administered during or sequentially with radiation treatment.

### 5.13 Embryo-Fetal Toxicity

Based on animal studies and the mechanism of action, AFINITOR can cause fetal harm when administered to a pregnant woman. In animal studies, everolimus caused embryo-fetal toxicities in rats when administered during the period of organogenesis at maternal exposures that were lower than human exposures at the clinical dose of 10 mg once daily. Advise pregnant women of the potential risk to a fetus.

Advise female patients of reproductive potential to avoid becoming pregnant and to use effective contraception during treatment with AFINITOR and for 8 weeks after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with AFINITOR and for 4 weeks after the last dose [see *Use in Specific Populations*].

## 6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Non-infectious pneumonitis [see *Warnings and Precautions*].
- Infections [see *Warnings and Precautions*].
- Severe Hypersensitivity Reactions [see *Warnings and Precautions*].
- Angioedema with concomitant use of ACE inhibitors [see *Warnings and Precautions*].
- Stomatitis [see *Warnings and Precautions*].
- Renal failure [see *Warnings and Precautions*].
- Impaired wound healing [see *Warnings and Precautions*].
- Metabolic Disorders [see *Warnings and Precautions*].
- Myelosuppression [see *Warnings and Precautions*].
- Radiation Sensitization and Radiation Recall [see *Warnings and Precautions*].

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

#### Hormone Receptor-Positive, HER2-Negative Breast Cancer

The safety of AFINITOR (10 mg orally once daily) in combination with exemestane (25 mg orally once daily) (n = 485) vs. placebo in combination with exemestane (n = 239) was evaluated in a randomized, controlled trial (BOLERO-2) in patients with advanced or metastatic hormone receptor-positive, HER2-negative breast cancer. The median age of patients was 61 years (28 to 93 years), and 75% were White. The median follow-up was approximately 13 months.

The most common adverse reactions (incidence  $\geq 30\%$ ) were stomatitis, infections, rash, fatigue, diarrhea, and decreased appetite. The most common Grade 3-4 adverse reactions (incidence  $\geq 2\%$ ) were stomatitis, infections, hyperglycemia, fatigue, dyspnea, pneumonitis, and diarrhea. The most common laboratory abnormalities (incidence  $\geq 50\%$ ) were hypercholesterolemia, hyperglycemia, increased aspartate transaminase (AST), anemia, leukopenia, thrombocytopenia, lymphopenia, increased alanine transaminase (ALT), and hypertriglyceridemia. The most common Grade 3-4 laboratory abnormalities (incidence  $\geq 3\%$ ) were lymphopenia, hyperglycemia, anemia, hypokalemia, increased AST, increased ALT, and thrombocytopenia.

Fatal adverse reactions occurred in 2% of patients who received AFINITOR. The rate of adverse reactions resulting in permanent discontinuation was 24% for the AFINITOR arm. Dose adjustments (interruptions or reductions) occurred in 63% of patients in the AFINITOR arm.

Adverse reactions reported with an incidence of  $\geq 10\%$  for patients receiving AFINITOR vs. placebo are presented in Table 6. Laboratory abnormalities are presented in Table 7. The median duration of treatment with AFINITOR was 23.9 weeks; 33% were exposed to AFINITOR for a period of  $\geq 32$  weeks.

**Table 6: Adverse Reactions Reported in  $\geq 10\%$  of Patients with Hormone Receptor-Positive Breast Cancer in BOLERO-2**

|                                              | AFINITOR with Exemestane<br>N = 482 |                  | Placebo with Exemestane<br>N = 238 |                  |
|----------------------------------------------|-------------------------------------|------------------|------------------------------------|------------------|
|                                              | All Grades<br>%                     | Grade 3-4<br>%   | All Grades<br>%                    | Grade 3-4<br>%   |
| <b>Gastrointestinal</b>                      |                                     |                  |                                    |                  |
| Stomatitis <sup>a</sup>                      | 67                                  | 8 <sup>d</sup>   | 11                                 | 0.8              |
| Diarrhea                                     | 33                                  | 2                | 18                                 | 0.8              |
| Nausea                                       | 29                                  | 0.4              | 28                                 | 1                |
| Vomiting                                     | 17                                  | 1                | 12                                 | 0.8              |
| Constipation                                 | 14                                  | 0.4 <sup>d</sup> | 13                                 | 0.4              |
| Dry mouth                                    | 11                                  | 0                | 7                                  | 0                |
| <b>General</b>                               |                                     |                  |                                    |                  |
| Fatigue                                      | 36                                  | 4                | 27                                 | 1 <sup>d</sup>   |
| Edema peripheral                             | 19                                  | 1 <sup>d</sup>   | 6                                  | 0.4 <sup>d</sup> |
| Pyrexia                                      | 15                                  | 0.2 <sup>d</sup> | 7                                  | 0.4 <sup>d</sup> |
| Asthenia                                     | 13                                  | 2                | 4                                  | 0                |
| <b>Infections</b>                            |                                     |                  |                                    |                  |
| Infections <sup>b</sup>                      | 50                                  | 6                | 25                                 | 2 <sup>d</sup>   |
| <b>Investigations</b>                        |                                     |                  |                                    |                  |
| Weight loss                                  | 25                                  | 1 <sup>d</sup>   | 6                                  | 0                |
| <b>Metabolism and nutrition</b>              |                                     |                  |                                    |                  |
| Decreased appetite                           | 30                                  | 1 <sup>d</sup>   | 12                                 | 0.4 <sup>d</sup> |
| Hyperglycemia                                | 14                                  | 5                | 2                                  | 0.4 <sup>d</sup> |
| <b>Musculoskeletal and connective tissue</b> |                                     |                  |                                    |                  |
| Arthralgia                                   | 20                                  | 0.8 <sup>d</sup> | 17                                 | 0                |
| Back pain                                    | 14                                  | 0.2 <sup>d</sup> | 10                                 | 0.8 <sup>d</sup> |
| Pain in extremity                            | 9                                   | 0.4 <sup>d</sup> | 11                                 | 2 <sup>d</sup>   |
| <b>Nervous system</b>                        |                                     |                  |                                    |                  |
| Dysgeusia                                    | 22                                  | 0.2 <sup>d</sup> | 6                                  | 0                |
| Headache                                     | 21                                  | 0.4 <sup>d</sup> | 14                                 | 0                |

|                                              |    |                  |     |   |
|----------------------------------------------|----|------------------|-----|---|
| <b>Psychiatric</b>                           |    |                  |     |   |
| Insomnia                                     | 13 | 0.2 <sup>d</sup> | 8   | 0 |
| <b>Respiratory, thoracic and mediastinal</b> |    |                  |     |   |
| Cough                                        | 24 | 0.6 <sup>d</sup> | 12  | 0 |
| Dyspnea                                      | 21 | 4                | 11  | 1 |
| Epistaxis                                    | 17 | 0                | 1   | 0 |
| Pneumonitis <sup>c</sup>                     | 19 | 4                | 0.4 | 0 |
| <b>Skin and subcutaneous tissue</b>          |    |                  |     |   |
| Rash                                         | 39 | 1 <sup>d</sup>   | 6   | 0 |
| Pruritus                                     | 13 | 0.2 <sup>d</sup> | 5   | 0 |
| Alopecia                                     | 10 | 0                | 5   | 0 |
| <b>Vascular</b>                              |    |                  |     |   |
| Hot flush                                    | 6  | 0                | 14  | 0 |

Grading according to NCI CTCAE Version 3.0.

<sup>a</sup>Includes stomatitis, mouth ulceration, aphthous stomatitis, glossodynia, gingival pain, glossitis, and lip ulceration.

<sup>b</sup>Includes all reported infections, including but not limited to, urinary tract infections, respiratory tract (upper and lower) infections, skin infections, and gastrointestinal tract infections.

<sup>c</sup>Includes pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis.

<sup>d</sup>No Grade 4 adverse reactions were reported.

**Table 7: Selected Laboratory Abnormalities Reported in ≥ 10% of Patients with Hormone Receptor-Positive Breast Cancer in BOLERO-2**

| Laboratory Parameter          | AFINITOR with<br>Exemestane<br>N = 482 |                  | Placebo with Exemestane<br>N = 238 |                  |
|-------------------------------|----------------------------------------|------------------|------------------------------------|------------------|
|                               | All Grades                             | Grade 3-4        | All Grades                         | Grade 3-4        |
|                               | %                                      | %                | %                                  | %                |
| <b>Hematology<sup>a</sup></b> |                                        |                  |                                    |                  |
| Anemia                        | 68                                     | 6                | 40                                 | 1                |
| Leukopenia                    | 58                                     | 2 <sup>b</sup>   | 28                                 | 6                |
| Thrombocytopenia              | 54                                     | 3                | 5                                  | 0.4              |
| Lymphopenia                   | 54                                     | 12               | 37                                 | 6                |
| Neutropenia                   | 31                                     | 2 <sup>b</sup>   | 11                                 | 2                |
| <b>Chemistry</b>              |                                        |                  |                                    |                  |
| Hypercholesterolemia          | 70                                     | 1                | 38                                 | 2                |
| Hyperglycemia                 | 69                                     | 9                | 44                                 | 1                |
| Increased AST                 | 69                                     | 4                | 45                                 | 3                |
| Increased ALT                 | 51                                     | 4                | 29                                 | 5 <sup>b</sup>   |
| Hypertriglyceridemia          | 50                                     | 0.8 <sup>b</sup> | 26                                 | 0                |
| Hypoalbuminemia               | 33                                     | 0.8 <sup>b</sup> | 16                                 | 0.8 <sup>b</sup> |
| Hypokalemia                   | 29                                     | 4                | 7                                  | 1 <sup>b</sup>   |
| Increased creatinine          | 24                                     | 2                | 13                                 | 0                |

Grading according to NCI CTCAE Version 3.0.

<sup>a</sup>Reflects corresponding adverse drug reaction reports of anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia (collectively as pancytopenia), which occurred at lower frequency.

<sup>b</sup>No Grade 4 laboratory abnormalities were reported.

### Topical Prophylaxis for Stomatitis

In a single arm study (SWISH; N = 92) in postmenopausal women with hormone receptor-positive, HER2-negative breast cancer beginning AFINITOR (10 mg orally once daily) in combination with exemestane (25 mg orally once daily), patients started dexamethasone 0.5 mg/5 mL alcohol-free mouthwash (10 mL swished for 2 minutes and spat, 4 times daily for 8 weeks) concurrently with AFINITOR and exemestane. No food or drink was to be consumed for at least 1 hour after swishing and spitting the dexamethasone mouthwash. The primary objective of this study was to assess the incidence of Grade 2 to 4 stomatitis within 8 weeks. The incidence of Grade 2 to 4 stomatitis within 8 weeks was 2%, which was lower than the 33% reported in the BOLERO-2 trial. The incidence of Grade 1 stomatitis was 19%. No cases of Grade 3 or 4 stomatitis were reported. Oral candidiasis was reported in 2% of patients in this study compared to 0.2% in the BOLERO-2 trial.

Coadministration of AFINITOR and dexamethasone alcohol-free oral solution has not been studied in pediatric patients.

### Pancreatic Neuroendocrine Tumors (PNET)

In a randomized, controlled trial (RADIANT-3) of AFINITOR (n = 204) vs. placebo (n = 203) in patients with advanced PNET the median age of patients was 58 years (20 to 87 years), 79% were White, and 55% were male. Patients on the placebo arm could cross over to open-label AFINITOR upon disease progression.

The most common adverse reactions (incidence  $\geq 30\%$ ) were stomatitis, rash, diarrhea, fatigue, edema, abdominal pain, nausea, fever, and headache. The most common Grade 3-4 adverse reactions (incidence  $\geq 5\%$ ) were stomatitis and diarrhea. The most common laboratory abnormalities (incidence  $\geq 50\%$ ) were anemia, hyperglycemia, increased alkaline phosphatase, hypercholesterolemia, decreased bicarbonate, and increased AST. The most common Grade 3-4 laboratory abnormalities (incidence  $\geq 3\%$ ) were hyperglycemia, lymphopenia, anemia, hypophosphatemia, increased alkaline phosphatase, neutropenia, increased AST, hypokalemia, and thrombocytopenia.

Deaths during double-blind treatment where an adverse reaction was the primary cause occurred in seven patients on AFINITOR. Causes of death on the AFINITOR arm included one case of each of the following: acute renal failure, acute respiratory distress, cardiac arrest, death (cause unknown), hepatic failure, pneumonia, and sepsis. After cross-over to open-label AFINITOR, there were three additional deaths, one due to hypoglycemia and cardiac arrest in a patient with insulinoma, one due to myocardial infarction with congestive heart failure, and the other due to sudden death. The rate of adverse reactions resulting in permanent discontinuation was 20% for the AFINITOR group. Dose delay or reduction was necessary in 61% of AFINITOR patients. Grade 3-4 renal failure occurred in six patients in the AFINITOR arm. Thrombotic events included five patients with pulmonary embolus in the AFINITOR arm as well as three patients with thrombosis in the AFINITOR arm.

Table 8 compares the incidence of adverse reactions reported with an incidence of  $\geq 10\%$  for patients receiving AFINITOR vs. placebo. Laboratory abnormalities are summarized in Table 9. The median duration of treatment in patients who received AFINITOR was 37 weeks.

In female patients aged 18 to 55 years, irregular menstruation occurred in 5 of 46 (11%) AFINITOR-treated females.

**Table 8: Adverse Reactions Reported in  $\geq 10\%$  of Patients with PNET in RADIANT-3**

|                                              | AFINITOR<br>N = 204 |                  | Placebo<br>N = 203 |                  |
|----------------------------------------------|---------------------|------------------|--------------------|------------------|
|                                              | All Grades<br>%     | Grade 3-4<br>%   | All Grades<br>%    | Grade 3-4<br>%   |
| <b>Gastrointestinal</b>                      |                     |                  |                    |                  |
| Stomatitis <sup>a</sup>                      | 70                  | 7 <sup>d</sup>   | 20                 | 0                |
| Diarrhea <sup>b</sup>                        | 50                  | 6                | 25                 | 3 <sup>d</sup>   |
| Abdominal pain                               | 36                  | 4 <sup>d</sup>   | 32                 | 7                |
| Nausea                                       | 32                  | 2 <sup>d</sup>   | 33                 | 2 <sup>d</sup>   |
| Vomiting                                     | 29                  | 1 <sup>d</sup>   | 21                 | 2 <sup>d</sup>   |
| Constipation                                 | 14                  | 0                | 13                 | 0.5 <sup>d</sup> |
| Dry mouth                                    | 11                  | 0                | 4                  | 0                |
| <b>General</b>                               |                     |                  |                    |                  |
| Fatigue/malaise                              | 45                  | 4                | 27                 | 3                |
| Edema (general and peripheral)               | 39                  | 2                | 12                 | 1 <sup>d</sup>   |
| Fever                                        | 31                  | 1                | 13                 | 0.5 <sup>d</sup> |
| Asthenia                                     | 19                  | 3 <sup>d</sup>   | 20                 | 3 <sup>d</sup>   |
| <b>Infections</b>                            |                     |                  |                    |                  |
| Nasopharyngitis/rhinitis/URI                 | 25                  | 0                | 13                 | 0                |
| Urinary tract infection                      | 16                  | 0                | 6                  | 0.5 <sup>d</sup> |
| <b>Investigations</b>                        |                     |                  |                    |                  |
| Weight loss                                  | 28                  | 0.5 <sup>d</sup> | 11                 | 0                |
| <b>Metabolism and nutrition</b>              |                     |                  |                    |                  |
| Decreased appetite                           | 30                  | 1 <sup>d</sup>   | 18                 | 1 <sup>d</sup>   |
| Diabetes mellitus                            | 10                  | 2 <sup>d</sup>   | 0.5                | 0                |
| <b>Musculoskeletal and connective tissue</b> |                     |                  |                    |                  |
| Arthralgia                                   | 15                  | 1                | 7                  | 0.5 <sup>d</sup> |
| Back pain                                    | 15                  | 1 <sup>d</sup>   | 11                 | 1 <sup>d</sup>   |
| Pain in extremity                            | 14                  | 0.5 <sup>d</sup> | 6                  | 1 <sup>d</sup>   |
| Muscle spasms                                | 10                  | 0                | 4                  | 0                |
| <b>Nervous system</b>                        |                     |                  |                    |                  |
| Headache/migraine                            | 30                  | 0.5 <sup>d</sup> | 15                 | 1 <sup>d</sup>   |
| Dysgeusia                                    | 19                  | 0                | 5                  | 0                |
| Dizziness                                    | 12                  | 0.5 <sup>d</sup> | 7                  | 0                |
| <b>Psychiatric</b>                           |                     |                  |                    |                  |
| Insomnia                                     | 14                  | 0                | 8                  | 0                |
| <b>Respiratory, thoracic and mediastinal</b> |                     |                  |                    |                  |
| Cough/productive cough                       | 25                  | 0.5 <sup>d</sup> | 13                 | 0                |
| Epistaxis                                    | 22                  | 0                | 1                  | 0                |
| Dyspnea/dyspnea exertional                   | 20                  | 3                | 7                  | 0.5 <sup>d</sup> |
| Pneumonitis                                  | 17                  | 4                | 0                  | 0                |
| Oropharyngeal pain                           | 11                  | 0                | 6                  | 0                |
| <b>Skin and subcutaneous</b>                 |                     |                  |                    |                  |
| Rash                                         | 59                  | 0.5              | 19                 | 0                |
| Nail disorders                               | 22                  | 0.5              | 2                  | 0                |
| Pruritus/pruritus generalized                | 21                  | 0                | 13                 | 0                |

|                    |    |   |   |                |
|--------------------|----|---|---|----------------|
| Dry skin/xeroderma | 13 | 0 | 6 | 0              |
| <b>Vascular</b>    |    |   |   |                |
| Hypertension       | 13 | 1 | 6 | 1 <sup>d</sup> |

Grading according to NCI CTCAE Version 3.0.

<sup>a</sup>Includes stomatitis, aphthous stomatitis, gingival pain/swelling/ulceration, glossitis, glossodynia, lip ulceration, mouth ulceration, tongue ulceration, and mucosal inflammation.

<sup>b</sup>Includes diarrhea, enteritis, enterocolitis, colitis, defecation urgency, and steatorrhea.

<sup>c</sup>Includes pneumonitis, interstitial lung disease, pulmonary fibrosis, and restrictive pulmonary disease.

<sup>d</sup>No Grade 4 adverse reactions were reported.

**Table 9: Selected Laboratory Abnormalities Reported in  $\geq 10\%$  of Patients with PNET in RADIANT-3**

| Laboratory parameter           | AFINITOR<br>N=204 |           | Placebo<br>N=203 |           |
|--------------------------------|-------------------|-----------|------------------|-----------|
|                                | All Grades        | Grade 3-4 | All Grades       | Grade 3-4 |
|                                | %                 | %         | %                | %         |
| <b>Hematology</b>              |                   |           |                  |           |
| Anemia                         | 86                | 15        | 63               | 1         |
| Lymphopenia                    | 45                | 16        | 22               | 4         |
| Thrombocytopenia               | 45                | 3         | 11               | 0         |
| Leukopenia                     | 43                | 2         | 13               | 0         |
| Neutropenia                    | 30                | 4         | 17               | 2         |
| <b>Chemistry</b>               |                   |           |                  |           |
| Hyperglycemia (fasting)        | 75                | 17        | 53               | 6         |
| Increased alkaline phosphatase | 74                | 8         | 66               | 8         |
| Hypercholesterolemia           | 66                | 0.5       | 22               | 0         |
| Bicarbonate decreased          | 56                | 0         | 40               | 0         |
| Increased AST                  | 56                | 4         | 41               | 4         |
| Increased ALT                  | 48                | 2         | 35               | 2         |
| Hypophosphatemia               | 40                | 10        | 14               | 3         |
| Hypertriglyceridemia           | 39                | 0         | 10               | 0         |
| Hypocalcemia                   | 37                | 0.5       | 12               | 0         |
| Hypokalemia                    | 23                | 4         | 5                | 0         |
| Increased creatinine           | 19                | 2         | 14               | 0         |
| Hyponatremia                   | 16                | 1         | 16               | 1         |
| Hypoalbuminemia                | 13                | 1         | 8                | 0         |
| Hyperbilirubinemia             | 10                | 1         | 14               | 2         |
| Hyperkalemia                   | 7                 | 0         | 10               | 0.5       |

Grading according to NCI CTCAE Version 3.0.

#### Neuroendocrine Tumors (NET) of Gastrointestinal (GI) or Lung Origin

In a randomized, controlled trial (RADIANT-4) of AFINITOR (n = 202 treated) vs. placebo (n = 98 treated) in patients with advanced non-functional NET of GI or lung origin, the median age of patients was 63 years (22-86 years), 76% were White, and 53% were female. The median duration of exposure to AFINITOR was 9.3 months; 64% of patients were treated for  $\geq 6$  months and 39% were treated for  $\geq 12$  months. AFINITOR was discontinued for adverse reactions in 29% of patients, dose reduction or delay was required in 70% of AFINITOR-treated patients.

Serious adverse reactions occurred in 42% of AFINITOR-treated patients and included 3 fatal events (cardiac failure, respiratory failure, and septic shock). Adverse reactions occurring at an incidence of  $\geq 10\%$  and at  $\geq 5\%$  absolute incidence over placebo (all Grades) or  $\geq 2\%$  higher incidence over placebo (Grade 3 and 4) are presented in Table 10. Laboratory abnormalities are presented in Table 11.

**Table 10: Adverse Reactions in  $\geq 10\%$  of AFINITOR-Treated Patients with Non-Functional NET of GI or Lung Origin in RADIANT-4**

|                                              | AFINITOR<br>N = 202 |                | Placebo<br>N = 98 |                |
|----------------------------------------------|---------------------|----------------|-------------------|----------------|
|                                              | All Grades<br>%     | Grade 3-4<br>% | All Grades<br>%   | Grade 3-4<br>% |
| <b>Gastrointestinal</b>                      |                     |                |                   |                |
| Stomatitis <sup>a</sup>                      | 63                  | 9 <sup>d</sup> | 22                | 0              |
| Diarrhea                                     | 41                  | 9              | 31                | 2 <sup>d</sup> |
| Nausea                                       | 26                  | 3              | 17                | 1 <sup>d</sup> |
| Vomiting                                     | 15                  | 4 <sup>d</sup> | 12                | 2 <sup>d</sup> |
| <b>General</b>                               |                     |                |                   |                |
| Peripheral edema                             | 39                  | 3 <sup>d</sup> | 6                 | 1 <sup>d</sup> |
| Fatigue                                      | 37                  | 5              | 36                | 1 <sup>d</sup> |
| Asthenia                                     | 23                  | 3              | 8                 | 0              |
| Pyrexia                                      | 23                  | 2              | 8                 | 0              |
| <b>Infections</b>                            |                     |                |                   |                |
| Infections <sup>b</sup>                      | 58                  | 11             | 29                | 2              |
| <b>Investigations</b>                        |                     |                |                   |                |
| Weight loss                                  | 22                  | 2 <sup>d</sup> | 11                | 1 <sup>d</sup> |
| <b>Metabolism and nutrition</b>              |                     |                |                   |                |
| Decreased appetite                           | 22                  | 1 <sup>d</sup> | 17                | 1 <sup>d</sup> |
| <b>Nervous system</b>                        |                     |                |                   |                |
| Dysgeusia                                    | 18                  | 1 <sup>d</sup> | 4                 | 0              |
| <b>Respiratory, thoracic and mediastinal</b> |                     |                |                   |                |
| Cough                                        | 27                  | 0              | 20                | 0              |
| Dyspnea                                      | 20                  | 3 <sup>d</sup> | 11                | 2              |
| Pneumonitis <sup>c</sup>                     | 16                  | 2 <sup>d</sup> | 2                 | 0              |
| Epistaxis                                    | 13                  | 1 <sup>d</sup> | 3                 | 0              |
| <b>Skin and subcutaneous</b>                 |                     |                |                   |                |
| Rash                                         | 30                  | 1 <sup>d</sup> | 9                 | 0              |
| Pruritus                                     | 17                  | 1 <sup>d</sup> | 9                 | 0              |

Grading according to NCI CTCAE Version 4.03.

<sup>a</sup>Includes stomatitis, mouth ulceration, aphthous stomatitis, gingival pain, glossitis, tongue ulceration, and mucosal inflammation.

<sup>b</sup>Urinary tract infection, nasopharyngitis, upper respiratory tract infection, lower respiratory tract infection (pneumonia, bronchitis), abscess, pyelonephritis, septic shock and viral myocarditis.

<sup>c</sup>Includes pneumonitis and interstitial lung disease.

<sup>d</sup>No Grade 4 adverse reactions were reported.

**Table 11: Selected Laboratory Abnormalities in  $\geq 10\%$  of AFINITOR-Treated Patients with Non-Functional NET of GI or Lung Origin in RADIANT-4**

|                         | AFINITOR<br>N=202 |                | Placebo<br>N=98 |                |
|-------------------------|-------------------|----------------|-----------------|----------------|
|                         | All Grades<br>%   | Grade 3-4<br>% | All Grades<br>% | Grade 3-4<br>% |
| <b>Hematology</b>       |                   |                |                 |                |
| Anemia                  | 81                | 5 <sup>a</sup> | 41              | 2 <sup>a</sup> |
| Lymphopenia             | 66                | 16             | 32              | 2 <sup>a</sup> |
| Leukopenia              | 49                | 2 <sup>a</sup> | 17              | 0              |
| Thrombocytopenia        | 33                | 2              | 11              | 0              |
| Neutropenia             | 32                | 2 <sup>a</sup> | 15              | 3 <sup>a</sup> |
| <b>Chemistry</b>        |                   |                |                 |                |
| Hypercholesterolemia    | 71                | 0              | 37              | 0              |
| Increased AST           | 57                | 2              | 34              | 2 <sup>a</sup> |
| Hyperglycemia (fasting) | 55                | 6 <sup>a</sup> | 36              | 1 <sup>a</sup> |
| Increased ALT           | 46                | 5              | 39              | 1 <sup>a</sup> |
| Hypophosphatemia        | 43                | 4 <sup>a</sup> | 15              | 2 <sup>a</sup> |
| Hypertriglyceridemia    | 30                | 3              | 8               | 1 <sup>a</sup> |
| Hypokalemia             | 27                | 6              | 12              | 3 <sup>a</sup> |
| Hypoalbuminemia         | 18                | 0              | 8               | 0              |

Grading according to NCI CTCAE Version 4.03.

<sup>a</sup>No Grade 4 laboratory abnormalities were reported.

### Renal Cell Carcinoma (RCC)

The data described below reflect exposure to AFINITOR (n = 274) and placebo (n = 137) in a randomized, controlled trial (RECORD-1) in patients with metastatic RCC who received prior treatment with sunitinib and/or sorafenib. The median age of patients was 61 years (27 to 85 years), 88% were White, and 78% were male. The median duration of blinded study treatment was 141 days (19 to 451 days) for patients receiving AFINITOR.

The most common adverse reactions (incidence  $\geq 30\%$ ) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common Grade 3-4 adverse reactions (incidence  $\geq 3\%$ ) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities (incidence  $\geq 50\%$ ) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common Grade 3-4 laboratory abnormalities (incidence  $\geq 3\%$ ) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia.

Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the AFINITOR arm. The rate of adverse reactions resulting in permanent discontinuation was 14% for the AFINITOR group. The most common adverse reactions leading to treatment discontinuation were pneumonitis and dyspnea. Infections, stomatitis, and pneumonitis were the most common reasons for treatment delay or dose reduction. The most common medical interventions required during AFINITOR treatment were for infections, anemia, and stomatitis.

Adverse reactions reported with an incidence of  $\geq 10\%$  for patients receiving AFINITOR vs. placebo are presented in Table 12. Laboratory abnormalities are presented in Table 13.

**Table 12: Adverse Reactions Reported in  $\geq 10\%$  of Patients with RCC and at a Higher Rate in the AFINITOR Arm than in the Placebo Arm in RECORD-1**

|                                              | AFINITOR<br>N = 274 |                  | Placebo<br>N = 137 |                  |
|----------------------------------------------|---------------------|------------------|--------------------|------------------|
|                                              | All Grades<br>%     | Grade 3-4<br>%   | All Grades<br>%    | Grade 3-4<br>%   |
| <b>Gastrointestinal</b>                      |                     |                  |                    |                  |
| Stomatitis <sup>a</sup>                      | 44                  | 4                | 8                  | 0                |
| Diarrhea                                     | 30                  | 2 <sup>d</sup>   | 7                  | 0                |
| Nausea                                       | 26                  | 2 <sup>d</sup>   | 19                 | 0                |
| Vomiting                                     | 20                  | 2 <sup>d</sup>   | 12                 | 0                |
| <b>Infections<sup>b</sup></b>                | 37                  | 10               | 18                 | 2                |
| <b>General</b>                               |                     |                  |                    |                  |
| Asthenia                                     | 33                  | 4                | 23                 | 4                |
| Fatigue                                      | 31                  | 6 <sup>d</sup>   | 27                 | 4                |
| Edema peripheral                             | 25                  | < 1 <sup>d</sup> | 8                  | < 1 <sup>d</sup> |
| Pyrexia                                      | 20                  | < 1 <sup>d</sup> | 9                  | 0                |
| Mucosal inflammation                         | 19                  | 2 <sup>d</sup>   | 1                  | 0                |
| <b>Respiratory, thoracic and mediastinal</b> |                     |                  |                    |                  |
| Cough                                        | 30                  | < 1 <sup>d</sup> | 16                 | 0                |
| Dyspnea                                      | 24                  | 8                | 15                 | 3 <sup>d</sup>   |
| Epistaxis                                    | 18                  | 0                | 0                  | 0                |
| Pneumonitis <sup>c</sup>                     | 14                  | 4 <sup>d</sup>   | 0                  | 0                |
| <b>Skin and subcutaneous tissue</b>          |                     |                  |                    |                  |
| Rash                                         | 29                  | 1 <sup>d</sup>   | 7                  | 0                |
| Pruritus                                     | 14                  | < 1 <sup>d</sup> | 7                  | 0                |
| Dry skin                                     | 13                  | < 1 <sup>d</sup> | 5                  | 0                |
| <b>Metabolism and nutrition</b>              |                     |                  |                    |                  |
| Anorexia                                     | 25                  | 2 <sup>d</sup>   | 14                 | < 1 <sup>d</sup> |
| <b>Nervous system</b>                        |                     |                  |                    |                  |
| Headache                                     | 19                  | 1                | 9                  | < 1 <sup>d</sup> |

|                                              |    |                |   |   |
|----------------------------------------------|----|----------------|---|---|
| Dysgeusia                                    | 10 | 0              | 2 | 0 |
| <b>Musculoskeletal and connective tissue</b> |    |                |   |   |
| Pain in extremity                            | 10 | 1 <sup>d</sup> | 7 | 0 |

Grading according to NCI CTCAE Version 3.0.

<sup>a</sup>Stomatitis (including aphthous stomatitis), and mouth and tongue ulceration.<sup>b</sup>Includes all reported infections, including but not limited to, respiratory tract (upper and lower) infections, urinary tract infections, and skin infections.<sup>c</sup>Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, and alveolitis.

<sup>d</sup>No Grade 4 adverse reactions were reported.

Other notable adverse reactions occurring more frequently with AFINITOR than with placebo, but with an incidence of < 10% include:

*Gastrointestinal:* Abdominal pain (9%), dry mouth (8%), hemorrhoids (5%), dysphagia (4%)

*General:* Weight loss (9%), chest pain (5%), chills (4%), impaired wound healing (< 1%)

*Respiratory, thoracic and mediastinal:* Pleural effusion (7%), pharyngolaryngeal pain (4%), rhinorrhea (3%)

*Skin and subcutaneous tissue:* Hand-foot syndrome (reported as palmar-plantar erythrodysesthesia syndrome) (5%), nail disorder (5%), erythema (4%), onychoclasia (4%), skin lesion (4%), acneiform dermatitis (3%), angioedema (< 1%)

*Metabolism and nutrition:* Exacerbation of pre-existing diabetes mellitus (2%), new onset of diabetes mellitus (< 1%)

*Psychiatric:* Insomnia (9%)

*Nervous system:* Dizziness (7%), paresthesia (5%)

*Ocular:* Eyelid edema (4%), conjunctivitis (2%)

*Vascular:* Hypertension (4%), deep vein thrombosis (< 1%)

*Renal and urinary:* Renal failure (3%)

*Cardiac:* Tachycardia (3%), congestive cardiac failure (1%)

*Musculoskeletal and connective tissue:* Jaw pain (3%)

*Hematologic:* Hemorrhage (3%)

**Table 13: Selected Laboratory Abnormalities Reported in Patients with RCC at a Higher Rate in the AFINITOR Arm than the Placebo Arm in RECORD-1**

| Laboratory parameter          | AFINITOR N = 274 |                  | Placebo N = 137 |                |
|-------------------------------|------------------|------------------|-----------------|----------------|
|                               | All Grades<br>%  | Grade 3-4<br>%   | All Grades<br>% | Grade 3-4<br>% |
| <b>Hematology<sup>a</sup></b> |                  |                  |                 |                |
| Anemia                        | 92               | 13               | 79              | 6              |
| Lymphopenia                   | 51               | 18               | 28              | 5 <sup>b</sup> |
| Thrombocytopenia              | 23               | 1 <sup>b</sup>   | 2               | < 1            |
| Neutropenia                   | 14               | < 1              | 4               | 0              |
| <b>Chemistry</b>              |                  |                  |                 |                |
| Hypercholesterolemia          | 77               | 4 <sup>b</sup>   | 35              | 0              |
| Hypertriglyceridemia          | 73               | < 1 <sup>b</sup> | 34              | 0              |
| Hyperglycemia                 | 57               | 16               | 25              | 2 <sup>b</sup> |
| Increased creatinine          | 50               | 2 <sup>b</sup>   | 34              | 0              |
| Hypophosphatemia              | 37               | 6 <sup>b</sup>   | 8               | 0              |
| Increased AST                 | 25               | 1                | 7               | 0              |
| Increased ALT                 | 21               | 1 <sup>b</sup>   | 4               | 0              |
| Hyperbilirubinemia            | 3                | 1                | 2               | 0              |

Grading according to NCI CTCAE Version 3.0.

<sup>a</sup>Reflects corresponding adverse drug reaction reports of anemia, leukopenia, lymphopenia, neutropenia, and thrombocytopenia (collectively pancytopenia), which occurred at lower frequency.

<sup>b</sup>No Grade 4 laboratory abnormalities were reported.

### Tuberous Sclerosis Complex (TSC)-Associated Renal Angiomyolipoma

The data described below are based on a randomized (2:1), double-blind, placebo-controlled trial (EXIST-2) of AFINITOR in 118 patients with renal angiomyolipoma as a feature of TSC (n = 113) or sporadic lymphangiomyomatosis (n = 5). The median age of patients was 31 years (18 to 61 years), 89% were White, and 34% were male. The median duration of blinded study treatment was 48 weeks (2 to 115 weeks) for patients receiving AFINITOR.

The most common adverse reaction reported for AFINITOR (incidence  $\geq 30\%$ ) was stomatitis. The most common Grade 3-4 adverse reactions (incidence  $\geq 2\%$ ) were stomatitis and amenorrhea. The most common laboratory abnormalities (incidence  $\geq 50\%$ ) were hypercholesterolemia, hypertriglyceridemia, and anemia. The most common Grade 3-4 laboratory abnormality (incidence  $\geq 3\%$ ) was hypophosphatemia.

The rate of adverse reactions resulting in permanent discontinuation was 3.8% in the AFINITOR-treated patients. Adverse reactions leading to permanent discontinuation in the AFINITOR arm were hypersensitivity/angioedema/bronchospasm, convulsion, and hypophosphatemia. Dose adjustments (interruptions or reductions) due to adverse reactions occurred in 52% of AFINITOR-treated patients. The most common adverse reaction leading to AFINITOR dose adjustment was stomatitis.

Adverse reactions reported with an incidence of  $\geq 10\%$  for patients receiving AFINITOR and occurring more frequently with AFINITOR than with placebo are presented in Table 14. Laboratory abnormalities are presented in Table 15.

**Table 14: Adverse Reactions Reported in  $\geq 10\%$  of AFINITOR-Treated Patients with TSC-Associated Renal Angiomyolipoma in EXIST-2**

|                                              | AFINITOR<br>N = 79 |                | Placebo<br>N = 39 |                |
|----------------------------------------------|--------------------|----------------|-------------------|----------------|
|                                              | All Grades<br>%    | Grade 3-4<br>% | All Grades<br>%   | Grade 3-4<br>% |
| <b>Gastrointestinal</b>                      |                    |                |                   |                |
| Stomatitis <sup>a</sup>                      | 78                 | 6 <sup>b</sup> | 23                | 0              |
| Vomiting                                     | 15                 | 0              | 5                 | 0              |
| Diarrhea                                     | 14                 | 0              | 5                 | 0              |
| <b>General</b>                               |                    |                |                   |                |
| Peripheral edema                             | 13                 | 0              | 8                 | 0              |
| <b>Infections</b>                            |                    |                |                   |                |
| Upper respiratory tract infection            | 11                 | 0              | 5                 | 0              |
| <b>Musculoskeletal and connective tissue</b> |                    |                |                   |                |
| Arthralgia                                   | 13                 | 0              | 5                 | 0              |
| <b>Respiratory, thoracic and mediastinal</b> |                    |                |                   |                |
| Cough                                        | 20                 | 0              | 13                | 0              |
| <b>Skin and subcutaneous tissue</b>          |                    |                |                   |                |
| Acne                                         | 22                 | 0              | 5                 | 0              |

Grading according to NCI CTCAE Version 3.0

<sup>a</sup>Includes stomatitis, aphthous stomatitis, mouth ulceration, gingival pain, glossitis, and glossodynia.

<sup>b</sup>No Grade 4 adverse reactions were reported.

Amenorrhea occurred in 15% of AFINITOR-treated females (8 of 52). Other adverse reactions involving the female reproductive system were menorrhagia (10%), menstrual irregularities (10%), and vaginal hemorrhage (8%).

The following additional adverse reactions occurred in less than 10% of AFINITOR-treated patients: epistaxis (9%), decreased appetite (6%), otitis media (6%), depression (5%), abnormal taste (5%), increased blood luteinizing hormone (LH) levels (4%), increased blood follicle stimulating hormone (FSH) levels (3%), hypersensitivity (3%), ovarian cyst (3%), pneumonitis (1%), and angioedema (1%).

**Table 15: Selected Laboratory Abnormalities Reported in AFINITOR-Treated Patients with TSC-Associated Renal Angiomyolipoma in EXIST-2**

|                                | AFINITOR<br>N=79 |                | Placebo<br>N=39 |           |
|--------------------------------|------------------|----------------|-----------------|-----------|
|                                | All Grades       | Grade 3-4      | All Grades      | Grade 3-4 |
|                                | %                | %              | %               | %         |
| <b>Hematology</b>              |                  |                |                 |           |
| Anemia                         | 61               | 0              | 49              | 0         |
| Leukopenia                     | 37               | 0              | 21              | 0         |
| Neutropenia                    | 25               | 1              | 26              | 0         |
| Lymphopenia                    | 20               | 1 <sup>a</sup> | 8               | 0         |
| Thrombocytopenia               | 19               | 0              | 3               | 0         |
| <b>Chemistry</b>               |                  |                |                 |           |
| Hypercholesterolemia           | 85               | 1 <sup>a</sup> | 46              | 0         |
| Hypertriglyceridemia           | 52               | 0              | 10              | 0         |
| Hypophosphatemia               | 49               | 5 <sup>a</sup> | 15              | 0         |
| Increased alkaline phosphatase | 32               | 1 <sup>a</sup> | 10              | 0         |
| Increased AST                  | 23               | 1 <sup>a</sup> | 8               | 0         |
| Increased ALT                  | 20               | 1 <sup>a</sup> | 15              | 0         |
| Hyperglycemia (fasting)        | 14               | 0              | 8               | 0         |

Grading according to NCI CTCAE Version 3.0.

<sup>a</sup>No Grade 4 laboratory abnormalities were reported.

Updated safety information from 112 patients treated with AFINITOR for a median duration of 3.9 years identified the following additional adverse reactions and selected laboratory abnormalities: increased partial thromboplastin time (63%), increased prothrombin time (40%), decreased fibrinogen (38%), urinary tract infection (31%), proteinuria (18%), abdominal pain (16%), pruritus (12%), gastroenteritis (12%), myalgia (11%), and pneumonia (10%).

#### TSC-Associated Subependymal Giant Cell Astrocytoma (SEGA)

The data described below are based on a randomized (2:1), double-blind, placebo-controlled trial (EXIST-1) of AFINITOR in 117 patients with SEGA and TSC. The median age of patients was 9.5 years (0.8 to 26 years), 93% were White, and 57% were male. The median duration of blinded study treatment was 52 weeks (24 to 89 weeks) for patients receiving AFINITOR.

The most common adverse reactions reported for AFINITOR (incidence  $\geq 30\%$ ) were stomatitis and respiratory tract infection. The most common Grade 3-4 adverse reactions (incidence  $\geq 2\%$ ) were stomatitis, pyrexia, pneumonia, gastroenteritis, aggression, agitation, and amenorrhea. The most common laboratory abnormalities (incidence  $\geq 50\%$ ) were hypercholesterolemia and elevated partial thromboplastin time. The most common Grade 3-4 laboratory abnormality (incidence  $\geq 3\%$ ) was neutropenia.

There were no adverse reactions resulting in permanent discontinuation. Dose adjustments (interruptions or reductions) due to adverse reactions occurred in 55% of AFINITOR-treated patients. The most common adverse reaction leading to AFINITOR dose adjustment was stomatitis.

Adverse reactions reported with an incidence of  $\geq 10\%$  for patients receiving AFINITOR and occurring more frequently with AFINITOR than with placebo are reported in Table 16. Laboratory abnormalities are presented in Table 17.

**Table 16: Adverse Reactions Reported in  $\geq 10\%$  of AFINITOR-Treated Patients with TSC-Associated SEGA in EXIST-1**

|                                                                  | AFINITOR<br>N = 78 |                | Placebo<br>N = 39 |                |
|------------------------------------------------------------------|--------------------|----------------|-------------------|----------------|
|                                                                  | All Grades<br>%    | Grade 3-4<br>% | All Grades<br>%   | Grade 3-4<br>% |
| <b>Gastrointestinal</b>                                          |                    |                |                   |                |
| Stomatitis <sup>a</sup>                                          | 62                 | 9 <sup>f</sup> | 26                | 3 <sup>f</sup> |
| Vomiting                                                         | 22                 | 1 <sup>f</sup> | 13                | 0              |
| Diarrhea                                                         | 17                 | 0              | 5                 | 0              |
| Constipation                                                     | 10                 | 0              | 3                 | 0              |
| <b>Infections</b>                                                |                    |                |                   |                |
| Respiratory tract infection <sup>b</sup>                         | 31                 | 3              | 23                | 0              |
| Gastroenteritis <sup>c</sup>                                     | 10                 | 5              | 3                 | 0              |
| Pharyngitis streptococcal                                        | 10                 | 0              | 3                 | 0              |
| <b>General</b>                                                   |                    |                |                   |                |
| Pyrexia                                                          | 23                 | 6 <sup>f</sup> | 18                | 3 <sup>f</sup> |
| Fatigue                                                          | 14                 | 0              | 3                 | 0              |
| <b>Psychiatric</b>                                               |                    |                |                   |                |
| Anxiety, aggression or other behavioral disturbance <sup>d</sup> | 21                 | 5 <sup>f</sup> | 3                 | 0              |
| <b>Skin and subcutaneous tissue</b>                              |                    |                |                   |                |
| Rash <sup>e</sup>                                                | 21                 | 0              | 8                 | 0              |
| Acne                                                             | 10                 | 0              | 5                 | 0              |

Grading according to NCI CTCAE Version 3.0.

<sup>a</sup>Includes mouth ulceration, stomatitis, and lip ulceration.

<sup>b</sup>Includes respiratory tract infection, upper respiratory tract infection, and respiratory tract infection viral.

<sup>c</sup>Includes gastroenteritis, gastroenteritis viral, and gastrointestinal infection.

<sup>d</sup>Includes agitation, anxiety, panic attack, aggression, abnormal behavior, and obsessive compulsive disorder.

<sup>e</sup>Includes rash, rash generalized, rash macular, rash maculo-papular, rash papular, dermatitis allergic, and urticaria.

<sup>f</sup>No Grade 4 adverse reactions were reported.

Amenorrhea occurred in 17% of AFINITOR-treated females aged 10 to 55 years (3 of 18). For this same group of AFINITOR-treated females, the following menstrual abnormalities were reported: dysmenorrhea (6%), menorrhagia (6%), metrorrhagia (6%), and unspecified menstrual irregularity (6%).

The following additional adverse reactions occurred in less than 10% of AFINITOR-treated patients: nausea (8%), pain in extremity (8%), insomnia (6%), pneumonia (6%), epistaxis (5%), hypersensitivity (3%), increased blood luteinizing hormone (LH) levels (1%), and pneumonitis (1%).

**Table 17: Selected Laboratory Abnormalities Reported in AFINITOR-Treated Patients with TSC-Associated SEGA in EXIST-1**

|                                      | AFINITOR<br>N=78 |                | Placebo<br>N=39 |                |
|--------------------------------------|------------------|----------------|-----------------|----------------|
|                                      | All Grades<br>%  | Grade 3-4<br>% | All Grades<br>% | Grade 3-4<br>% |
| <b>Hematology</b>                    |                  |                |                 |                |
| Elevated partial thromboplastin time | 72               | 3 <sup>a</sup> | 44              | 5 <sup>a</sup> |
| Neutropenia                          | 46               | 9 <sup>a</sup> | 41              | 3 <sup>a</sup> |
| Anemia                               | 41               | 0              | 21              | 0              |
| <b>Chemistry</b>                     |                  |                |                 |                |
| Hypercholesterolemia                 | 81               | 0              | 39              | 0              |
| Elevated AST                         | 33               | 0              | 0               | 0              |
| Hypertriglyceridemia                 | 27               | 0              | 15              | 0              |
| Elevated ALT                         | 18               | 0              | 3               | 0              |
| Hypophosphatemia                     | 9                | 1 <sup>a</sup> | 3               | 0              |

Grading according to NCI CTCAE Version 3.0.

<sup>a</sup>No Grade 4 laboratory abnormalities were reported.

Updated safety information from 111 patients treated with AFINITOR for a median duration of 47 months identified the following additional notable adverse reactions and selected laboratory abnormalities: decreased appetite (14%), hyperglycemia (13%), hypertension (11%), urinary tract infection (9%), decreased fibrinogen (8%), cellulitis (6%), abdominal pain (5%), decreased weight (5%), elevated creatinine (5%), and azoospermia (1%).

## 6.2 Postmarketing Experience

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

- *Blood and lymphatic disorders:* Thrombotic microangiopathy
- *Cardiac:* Cardiac failure with some cases reported with pulmonary hypertension (including pulmonary arterial hypertension) as a secondary event
- *Gastrointestinal:* Acute pancreatitis
- *Hepatobiliary:* Cholecystitis and cholelithiasis
- *Infections:* Sepsis and septic shock
- *Nervous system:* Reflex sympathetic dystrophy
- *Vascular:* Arterial thrombotic events, lymphedema
- *Injury, poisoning and procedural complications:* Radiation sensitization and radiation recall

## 7 DRUG INTERACTIONS

### 7.1 Effect of Other Drugs on AFINITOR

#### Inhibitors

Avoid the concomitant use of P-gp and strong CYP3A4 inhibitors [see *Dosage and Administration, Clinical Pharmacology*].

Reduce the dose for patients taking AFINITOR with a P-gp and moderate CYP3A4 inhibitor as recommended [see *Dosage and Administration, Clinical Pharmacology*].

#### Inducers

Increase the dose for patients taking AFINITOR with a P-gp and strong CYP3A4 inducer as recommended [see *Dosage and Administration, Clinical Pharmacology*].

### **7.2 Effects of Combination Use of Angiotensin Converting Enzyme (ACE) Inhibitors**

Patients taking concomitant ACE inhibitors with AFINITOR may be at increased risk for angioedema. Avoid the concomitant use of ACE inhibitors with AFINITOR [see *Warnings and Precautions*].

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

Based on animal studies and the mechanism of action [see *Clinical Pharmacology*], AFINITOR can cause fetal harm when administered to a pregnant woman. There are limited case reports of AFINITOR use in pregnant women; however, these reports are not sufficient to inform about risks of birth defects or miscarriage. In animal studies, everolimus caused embryo-fetal toxicities in rats when administered during the period of organogenesis at maternal exposures that were lower than human exposures at the recommended dose of AFINITOR 10 mg orally once daily (see Data). Advise pregnant women of the potential risk to the fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage is 2% to 4% and 15% to 20% of clinically recognized pregnancies, respectively.

#### Data

##### *Animal Data*

In animal reproductive studies, oral administration of everolimus to female rats before mating and through organogenesis induced embryo-fetal toxicities, including increased resorption, pre-implantation and post-implantation loss, decreased numbers of live fetuses, malformation (e.g., sternal cleft), and retarded skeletal development. These effects occurred in the absence of maternal toxicities.

Embryo-fetal toxicities in rats occurred at doses  $\geq 0.1$  mg/kg ( $0.6$  mg/m<sup>2</sup>) with resulting exposures of approximately 4% of the human exposure at the recommended dose of AFINITOR 10 mg orally once daily based on area under the curve (AUC). In rabbits, embryo-toxicity evident as an increase in resorptions occurred at an oral dose of  $0.8$  mg/kg ( $9.6$  mg/m<sup>2</sup>), approximately 1.6 times the recommended dose of AFINITOR 10 mg orally once daily or the median dose administered to patients with tuberous sclerosis complex (TSC)-associated subependymal giant cell astrocytoma (SEGA) based on body surface area. The effect in rabbits occurred in the presence of maternal toxicities.

In a pre- and post-natal development study in rats, animals were dosed from implantation through lactation. At the dose of 0.1 mg/kg (0.6 mg/m<sup>2</sup>), there were no adverse effects on delivery and lactation or signs of maternal toxicity; however, there were reductions in body weight (up to 9% reduction from the control) and in survival of offspring (~5% died or missing). There were no drug-related effects on the developmental parameters (morphological development, motor activity, learning, or fertility assessment) in the offspring.

## 8.2 Lactation

### Risk Summary

There are no data on the presence of everolimus or its metabolites in human milk, the effects of everolimus on the breastfed infant or on milk production. Everolimus and its metabolites passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Because of the potential for serious adverse reactions in breastfed infants from everolimus, advise women not to breastfeed during treatment with AFINITOR and for 2 weeks after the last dose.

## 8.3 Females and Males of Reproductive Potential

### Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to starting AFINITOR [*see Use in Specific Population*].

### Contraception

AFINITOR can cause fetal harm when administered to pregnant women [*see Use in Specific Populations*].

*Females:* Advise female patients of reproductive potential to use effective contraception during treatment with AFINITOR and for 8 weeks after the last dose.

*Males:* Advise male patients with female partners of reproductive potential to use effective contraception during treatment with AFINITOR and for 4 weeks after the last dose.

### Infertility

*Females:* Menstrual irregularities, secondary amenorrhea, and increases in luteinizing hormone (LH) and follicle stimulating hormone (FSH) occurred in female patients taking AFINITOR. Based on these findings, AFINITOR may impair fertility in female patients [*see Adverse Reactions, Nonclinical Toxicology*].

*Males:* Cases of reversible azoospermia have been reported in male patients taking AFINITOR. In male rats, sperm motility, sperm count, plasma testosterone levels and fertility were diminished at AUC similar to those of the clinical dose of AFINITOR 10 mg orally once daily. Based on these findings, AFINITOR may impair fertility in male patients [*see Nonclinical Toxicology*].

## 8.4 Pediatric Use

### TSC-Associated SEGA

The safety and effectiveness of AFINITOR have been established in pediatric patients age 1 year and older with TSC-associated SEGA that requires therapeutic intervention but cannot be curatively resected. Use of AFINITOR for this indication is supported by evidence from a randomized, double-blind, placebo-controlled trial in adult and pediatric patients (EXIST-1); an open-label, single-arm trial in adult and pediatric patients (Study 2485); and additional pharmacokinetic data in pediatric patients [see *Adverse Reactions*, *Clinical Pharmacology*, *Clinical Studies*]. The safety and effectiveness of AFINITOR have not been established in pediatric patients less than 1 year of age with TSC-associated SEGA.

In EXIST-1, the incidence of infections and serious infections were reported at a higher frequency in patients < 6 years of age. Ninety- six percent of 23 AFINITOR-treated patients < 6 years had at least one infection compared to 67% of 55 AFINITOR-treated patients  $\geq$  6 years. Thirty-five percent of 23 AFINITOR-treated patients < 6 years of age had at least 1 serious infection compared to 7% of 55 AFINITOR-treated patients  $\geq$  6 years.

Although a conclusive determination cannot be made due to the limited number of patients and lack of a comparator arm in the open label follow-up periods of EXIST-1 and Study 2485, AFINITOR did not appear to adversely impact growth and pubertal development in the 115 pediatric patients treated with AFINITOR for a median duration of 4.1 years.

#### Other Indications

The safety and effectiveness of AFINITOR in pediatric patients have not been established in:

- Hormone receptor-positive, HER2-negative breast cancer
- Neuroendocrine tumors (NET)
- Renal cell carcinoma (RCC)
- TSC-associated renal angiomyolipoma

### **8.5 Geriatric Use**

In BOLERO-2, 40% of patients with breast cancer treated with AFINITOR were  $\geq$  65 years of age, while 15% were  $\geq$  75 years of age. No overall differences in effectiveness were observed between elderly and younger patients. The incidence of deaths due to any cause within 28 days of the last AFINITOR dose was 6% in patients  $\geq$  65 years of age compared to 2% in patients < 65 years of age.

Adverse reactions leading to permanent treatment discontinuation occurred in 33% of patients  $\geq$  65 years of age compared to 17% in patients < 65 years of age.

In RECORD-1, 41% of patients with renal cell carcinoma treated with AFINITOR were  $\geq$  65 years of age, while 7% were  $\geq$  75 years of age. In RADIANT-3, 30% of patients with PNET treated with AFINITOR were  $\geq$  65 years of age, while 7% were  $\geq$  75 years of age. No overall differences in safety or effectiveness were observed between elderly and younger patients.

### **8.6 Hepatic Impairment**

AFINITOR exposure may increase in patients with hepatic impairment [see *Clinical Pharmacology*].

For patients with breast cancer, NET, RCC, and TSC-associated renal angiomyolipoma who have hepatic impairment, reduce the AFINITOR dose as recommended [*see Dosage and Administration*].

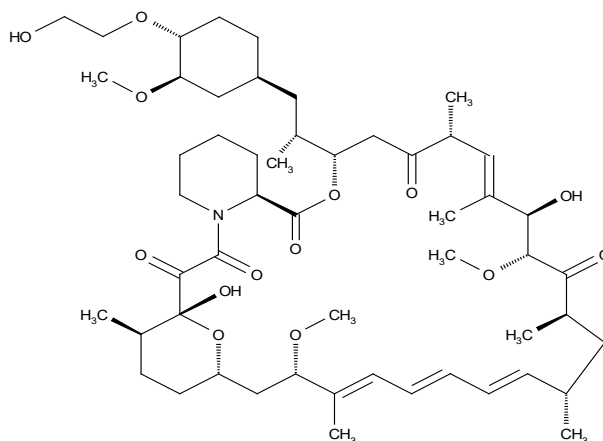
For patients with TSC-associated SEGA who have severe hepatic impairment (Child-Pugh class C), reduce the starting dose of AFINITOR as recommended and adjust the dose based on everolimus trough concentrations [*see Dosage and Administration*].

## 9 DESCRIPTION

AFINITOR (everolimus) are kinase inhibitors.

The chemical name of everolimus is (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-[(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxo-4-aza-tricyclo[30.3.1.0<sup>4,9</sup>]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone.

The molecular formula is C<sub>53</sub>H<sub>83</sub>NO<sub>14</sub> and the molecular weight is 958.2 g/mol. The structural formula is:



AFINITOR for oral administration contains 5 mg or 10 mg of everolimus and the following inactive ingredients: anhydrous lactose, butylated hydroxytoluene, crospovidone, hypromellose, lactose monohydrate, and magnesium stearate.

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

Everolimus is an inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase, downstream of the PI3K/AKT pathway. The mTOR pathway is dysregulated in several human cancers and in tuberous sclerosis complex (TSC). Everolimus binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation with mTOR complex 1 (mTORC1) and thus inhibition of mTOR kinase activity. Everolimus reduced the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic initiation factor 4E-binding protein (4E-BP1), downstream effectors of mTOR, involved in protein synthesis. S6K1 is a substrate of mTORC1 and phosphorylates the activation domain 1 of the estrogen receptor which results in ligand-independent activation of the receptor. In addition, everolimus inhibited the expression of hypoxia-inducible factor (e.g., HIF-1)

and reduced the expression of vascular endothelial growth factor (VEGF). Inhibition of mTOR by everolimus has been shown to reduce cell proliferation, angiogenesis, and glucose uptake in *in vitro* and/or *in vivo* studies.

Constitutive activation of the PI3K/Akt/mTOR pathway can contribute to endocrine resistance in breast cancer. *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 Akt, HER2, or aromatase inhibitors enhances the anti-tumor activity of everolimus in a synergistic manner.

Two regulators of mTORC1 signaling are the oncogene suppressors tuberin-sclerosis complexes 1 and 2 (*TSC1*, *TSC2*). Loss or inactivation of either *TSC1* or *TSC2* leads to activation of downstream signaling. In TSC, a genetic disorder, inactivating mutations in either the *TSC1* or the *TSC2* gene lead to hamartoma formation throughout the body as well as seizures and epileptogenesis.

Overactivation of mTOR results in neuronal dysplasia, aberrant axonogenesis and dendrite formation, increased excitatory synaptic currents, reduced myelination, and disruption of the cortical laminar structure causing abnormalities in neuronal development and function. Treatment with an mTOR inhibitor in animal models of mTOR dysregulation in the brain resulted in seizure suppression, prevention of the development of new-onset seizures, and prevention of premature death.

## 10.2 Pharmacodynamics

### Exposure-Response Relationship

In patients with TSC-associated subependymal giant cell astrocytoma (SEGA), the magnitude of the reduction in SEGA volume was correlated with the everolimus trough concentration.

### Cardiac Electrophysiology

In a randomized, placebo-controlled, cross-over study, 59 healthy subjects were administered a single oral dose of AFINITOR (20 mg and 50 mg) and placebo. AFINITOR at single doses up to 50 mg did not prolong the QT/QTc interval.

## 10.3 Pharmacokinetics

### Absorption

After administration of AFINITOR in patients with advanced solid tumors, peak everolimus concentrations are reached 1 to 2 hours after administration of oral doses ranging from 5 mg to 70 mg. Following single doses,  $C_{max}$  is dose-proportional with daily dosing between 5 mg 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 mg to 70 mg dose range. Steady-state was achieved within 2 weeks following once-daily dosing.

In patients with TSC-associated SEGA, everolimus  $C_{min}$  was approximately dose-proportional within the dose range from 1.35 mg/m<sup>2</sup> to 14.4 mg/m<sup>2</sup>.

**Effect of Food:** In healthy subjects, a high-fat meal (containing approximately 1000 calories and 55 grams of fat) reduced systemic exposure **to** AFINITOR 10 mg (as measured by AUC) by 22% and the peak blood concentration  $C_{\max}$  by 54%. Light-fat meals (containing approximately 500 calories and 20 grams of fat) 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 5000 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 orally once daily. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.

### Elimination

The mean elimination half-life of everolimus is approximately 30 hours.

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

**Excretion:** No specific elimination studies have been undertaken in cancer patients. Following the administration of a 3 mg single dose of radiolabeled everolimus in patients who were receiving cyclosporine, 80% of the radioactivity was recovered from the feces, while 5% was excreted in the urine. The parent substance was not detected in urine or feces.

### Specific Populations

No relationship was apparent between oral clearance and age or sex in patients with cancer.

**Patients with Renal Impairment:** No significant influence of creatinine clearance (25 to 178 mL/min) was detected on oral clearance (CL/F) of everolimus.

**Patients with Hepatic Impairment:** Compared to normal subjects, there was a 1.8-fold, 3.2-fold, and 3.6-fold increase in AUC for subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment, respectively. In another study, the average AUC of everolimus in subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in subjects with normal hepatic function [see *Dosage and Administration, Use in Specific Populations*].

**Pediatric Patients:** In patients with TSC-associated SEGA, the mean  $C_{\min}$  values normalized to mg/m<sup>2</sup> dose in pediatric patients (< 18 years of age) were lower than those observed in adults,

suggesting that everolimus clearance adjusted to body surface area was higher in pediatric patients as compared to adults.

*Race or Ethnicity:* Based on a cross-study comparison, Japanese patients had on average exposures that were higher than non- Japanese patients receiving the same dose. Oral clearance (CL/F) is on average 20% higher in Black patients than in White patients.

### Drug Interaction Studies

*Effect of CYP3A4 and P-glycoprotein (P-gp) Inhibitors on Everolimus:* Everolimus exposure increased when AFINITOR was coadministered with:

- ketoconazole (a P-gp and strong CYP3A4 inhibitor) - C<sub>max</sub> and AUC increased by 3.9- and 15-fold, respectively.
- erythromycin (a P-gp and moderate CYP3A4 inhibitor) - C<sub>max</sub> and AUC increased by 2- and 4.4-fold, respectively.
- verapamil (a P-gp and moderate CYP3A4 inhibitor) - C<sub>max</sub> and AUC increased by 2.3- and 3.5-fold, respectively.

*Effect of CYP3A4 and P-gp Inducers on Everolimus:* The coadministration of AFINITOR with rifampin, a P-gp and strong inducer of CYP3A4, decreased everolimus AUC by 63% and C<sub>max</sub> by 58% compared to AFINITOR alone [see *Dosage and Administration*].

*Effect of Everolimus on CYP3A4 Substrates:* No clinically significant pharmacokinetic interactions were observed between AFINITOR and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate), pravastatin (a non-CYP3A4 substrate), and simvastatin (a CYP3A4 substrate).

The coadministration of an oral dose of midazolam (sensitive CYP3A4 substrate) with AFINITOR resulted in a 25% increase in midazolam C<sub>max</sub> and a 30% increase in midazolam AUC<sub>0-inf</sub>.

The coadministration of AFINITOR with exemestane increased exemestane C<sub>min</sub> by 45% and C<sub>2h</sub> by 64%; however, the corresponding estradiol levels at steady state (4 weeks) were not different between the 2 treatment arms. No increase in adverse reactions related to exemestane was observed in patients with hormone receptor-positive, HER2-negative advanced breast cancer receiving the combination.

The coadministration of AFINITOR with long acting octreotide increased octreotide C<sub>min</sub> by approximately 50%.

*Effect of Everolimus on Antiepileptic drugs (AEDs):* Everolimus increased pre-dose concentrations of the carbamazepine, clobazam, oxcarbazepine, and clobazam's metabolite N-desmethyloclobazam by about 10%. Everolimus had no impact on pre-dose concentrations of AEDs that are substrates of CYP3A4 (e.g., clonazepam and zonisamide) or other AEDs, including valproic acid, topiramate, phenobarbital, and phenytoin.

## 11 NONCLINICAL TOXICOLOGY

### 11.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Administration of everolimus for up to 2 years did not indicate oncogenic potential in mice and rats up to the highest doses tested (0.9 mg/kg) corresponding, respectively to 3.9 and 0.2 times the estimated human exposure based on AUC at the recommended dose of AFINITOR 10 mg orally once daily.

Everolimus was not genotoxic in a battery of in vitro assays (Ames mutation test in Salmonella, mutation test in L5178Y mouse lymphoma cells, and chromosome aberration assay in V79 Chinese hamster cells). Everolimus was not genotoxic in an in vivo mouse bone marrow micronucleus test at doses up to 500 mg/kg/day (1500 mg/m<sup>2</sup>/day, approximately 255-fold the recommended dose of AFINITOR 10 mg orally once daily, and approximately 200-fold the median dose administered to patients with TSC-associated SEGA, based on the body surface area), administered as 2 doses, 24 hours apart.

Based on non-clinical findings, AFINITOR may impair male fertility. In a 13-week male fertility study in rats, testicular morphology was affected at doses of 0.5 mg/kg and above. Sperm motility, sperm count, and plasma testosterone levels were diminished in rats treated with 5 mg/kg. The exposures at these doses (52 ng•hr/mL and 414 ng•hr/mL, respectively) were within the range of human exposure at the recommended dose of AFINITOR 10 mg orally once daily (560 ng•hr/mL) and resulted in infertility in the rats at 5 mg/kg. Effects on male fertility occurred at AUC<sub>0-24h</sub> values 10% to 81% lower than human exposure at the recommended dose of AFINITOR 10 mg orally once daily. After a 10-13 week non-treatment period, the fertility index increased from zero (infertility) to 60%.

Oral doses of everolimus in female rats at doses  $\geq 0.1$  mg/kg (approximately 4% the human exposure based on AUC at the recommended dose of AFINITOR 10 mg orally once daily) resulted in increased incidence of pre-implantation loss, suggesting that the drug may reduce female fertility.

### 11.2 Animal Toxicology and/or Pharmacology

In juvenile rat toxicity studies, dose-related delayed attainment of developmental landmarks including delayed eye-opening, delayed reproductive development in males and females and increased latency time during the learning and memory phases were observed at doses as low as 0.15 mg/kg/day.

## 12 CLINICAL STUDIES

### 12.1 Hormone Receptor-Positive, HER2-Negative Breast Cancer

A randomized, double-blind, multicenter study (BOLERO-2, NCT00863655) of AFINITOR in combination with exemestane vs. placebo in combination with exemestane was conducted in 724 postmenopausal women with estrogen receptor-positive, HER2- negative advanced breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole. Randomization was stratified by documented sensitivity to prior hormonal therapy (yes vs. no) and by the presence of visceral metastasis (yes versus no). Sensitivity to prior hormonal therapy was defined as either (1) documented clinical benefit (complete response [CR], partial response [PR], stable disease  $\geq 24$  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. Patients were permitted to have received 0-1 prior lines of chemotherapy for advanced disease. The major efficacy outcome measure was progression-free survival (PFS) evaluated by RECIST (Response Evaluation Criteria in Solid Tumors), based on investigator (local radiology) assessment. Other outcome measures included overall survival (OS) and objective response rate (ORR).

Patients were randomized 2:1 to AFINITOR 10 mg orally once daily in combination with exemestane 25 mg once daily (n = 485) or to placebo in combination with exemestane 25 mg orally once daily (n = 239). The two treatment groups were generally balanced with respect to baseline demographics and disease characteristics. Patients were not permitted to cross over to AFINITOR at the time of disease progression.

The trial demonstrated a statistically significant improvement in PFS by investigator assessment (Table 18 and Figure 1). The results of the PFS analysis based on independent central radiological assessment were consistent with the investigator assessment. PFS results were also consistent across the subgroups of age, race, presence and extent of visceral metastases, and sensitivity to prior hormonal therapy.

ORR was higher in the AFINITOR in combination with exemestane arm vs. the placebo in combination with exemestane arm (Table 18). There were 3 complete responses (0.6%) and 58 partial responses (12%) in the AFINITOR arm. There were no complete responses and 4 partial responses (1.7%) in the placebo in combination with exemestane arm.

After a median follow-up of 39.3 months, there was no statistically significant difference in OS between the AFINITOR in combination with exemestane arm and the placebo in combination with exemestane arm [HR 0.89 (95% CI: 0.73, 1.10)].

**Table 18: Efficacy Results in Hormone-Receptor Positive, HER-2 Negative Breast Cancer in BOLERO-2**

| Analysis                                                 | AFINITOR<br>with exemestane<br>N=485 | Placebo<br>with exemestane<br>N=239 | Hazard Ratio                      | p-value               |
|----------------------------------------------------------|--------------------------------------|-------------------------------------|-----------------------------------|-----------------------|
| <b>Median progression-free survival (months, 95% CI)</b> |                                      |                                     |                                   |                       |
| Investigator radiological review                         | 7.8<br>(6.9, 8.5)                    | 3.2<br>(2.8, 4.1)                   | 0.45 <sup>a</sup><br>(0.38, 0.54) | < 0.0001 <sup>b</sup> |
| Independent radiological review                          | 11.0<br>(9.7, 15.0)                  | 4.1<br>(2.9, 5.6)                   | 0.38 <sup>a</sup><br>(0.3, 0.5)   | < 0.0001 <sup>b</sup> |
| <b>Best overall response (% , 95% CI)</b>                |                                      |                                     |                                   |                       |
| Objective response rate (ORR) <sup>c</sup>               | 12.6%<br>(9.8, 15.9)                 | 1.7%<br>(0.5, 4.2)                  | n/a <sup>d</sup>                  |                       |

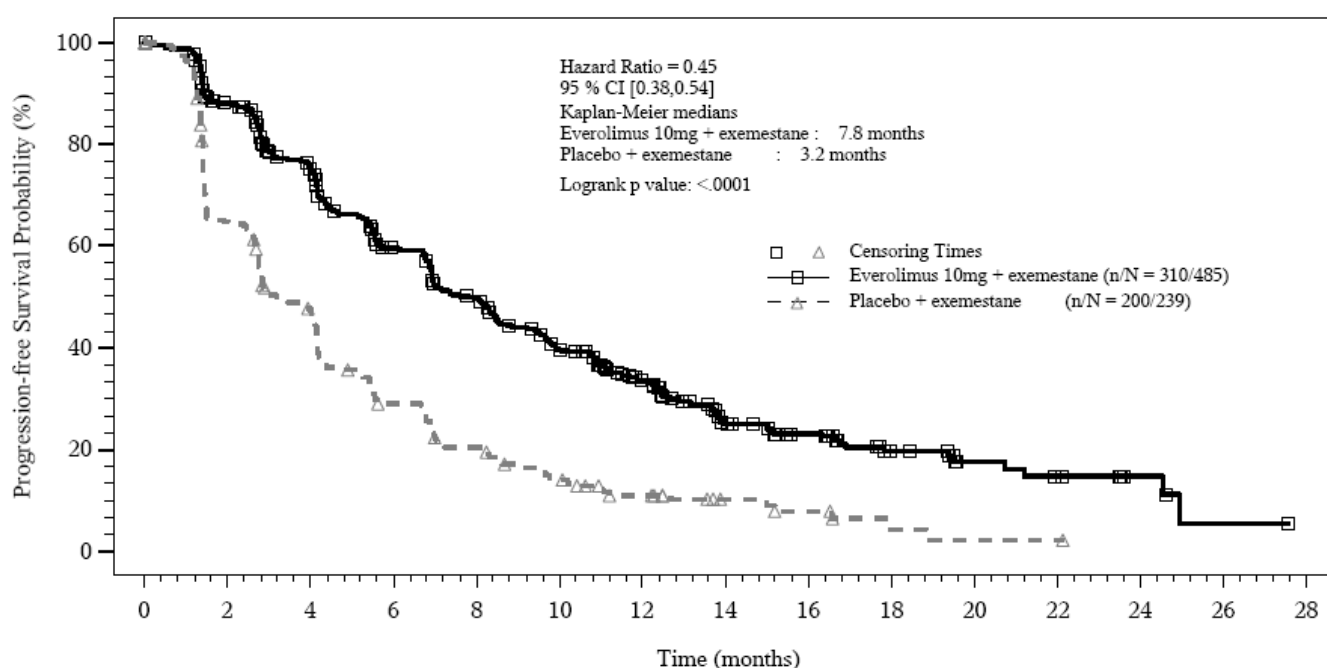
<sup>a</sup>Hazard ratio is obtained from the stratified Cox proportional-hazards model by sensitivity to prior hormonal therapy and presence of visceral metastasis.

<sup>b</sup>p-value is obtained from the one-sided log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis.

<sup>c</sup>Objective response rate = proportion of patients with CR or PR.

<sup>d</sup>Not applicable.

**Figure 1: Kaplan-Meier Curves for Progression-Free Survival by Investigator Radiological Review in Hormone Receptor-Positive, HER-2 Negative Breast Cancer in BOLERO-2**



## 12.2 Neuroendocrine Tumors (NET)

### Pancreatic Neuroendocrine Tumors (PNET)

A randomized, double-blind, multi-center trial (RADIANT-3, NCT00510068) of AFINITOR in combination with best supportive care (BSC) compared to placebo in combination with BSC was conducted in patients with locally advanced or metastatic advanced PNET and disease progression within the prior 12 months. Patients were stratified by prior cytotoxic chemotherapy (yes vs. no) and WHO performance status (0 vs. 1 and 2). Treatment with somatostatin analogs was allowed as part of BSC. The major efficacy outcome was PFS evaluated by RECIST. After documented radiological progression, patients randomized to placebo could receive open-label AFINITOR. Other outcome measures included ORR, response duration, and OS.

Patients were randomized 1:1 to receive either AFINITOR 10 mg once daily (n = 207) or placebo (n = 203). Demographics were well balanced (median age 58 years, 55% male, 79% White). Of the 203 patients randomized to BSC, 172 patients (85%) received AFINITOR following documented radiologic progression.

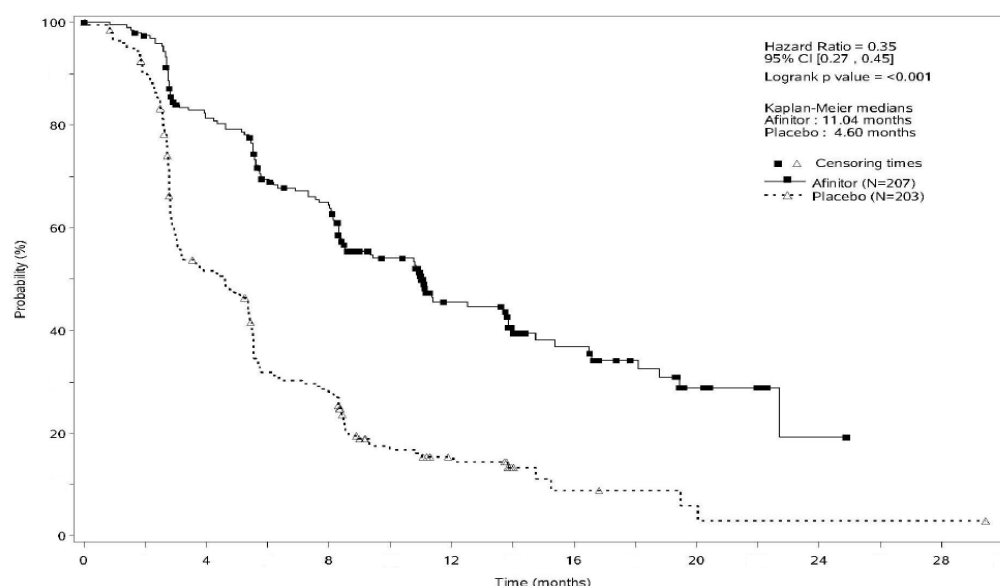
The trial demonstrated a statistically significant improvement in PFS (Table 19 and Figure 2). PFS improvement was observed across all patient subgroups, irrespective of prior somatostatin analog use. The PFS results by investigator radiological review, central radiological review and adjudicated radiological review are shown below in Table 19.

**Table 19: Progression-Free Survival Results in PNET in RADIANT-3**

| Analysis                                        | N   | AFINITOR<br>N=207<br>Median progression-free<br>survival (months) (95% CI) | Placebo<br>N=203<br>Median progression-free<br>survival (months) (95% CI) | Hazard Ratio<br>(95%CI) | p-value |
|-------------------------------------------------|-----|----------------------------------------------------------------------------|---------------------------------------------------------------------------|-------------------------|---------|
|                                                 | 410 |                                                                            |                                                                           |                         |         |
| Investigator radiological<br>review             |     | 11.0<br>(8.4, 13.9)                                                        | 4.6<br>(3.1, 5.4)                                                         | 0.35<br>(0.27, 0.45)    | <0.001  |
| Central radiological<br>review                  |     | 13.7<br>(11.2, 18.8)                                                       | 5.7<br>(5.4, 8.3)                                                         | 0.38<br>(0.28, 0.51)    | <0.001  |
| Adjudicated radiological<br>review <sup>a</sup> |     | 11.4<br>(10.8, 14.8)                                                       | 5.4<br>(4.3, 5.6)                                                         | 0.34<br>(0.26, 0.44)    | <0.001  |

<sup>a</sup> includes adjudication for discrepant assessments between investigator radiological review and central radiological review.

**Figure 2: Kaplan-Meier Curves for Progression-Free Survival by Investigator Radiological Review in PNET in RADIANT-3**



Investigator-determined response rate was 4.8% in the AFINITOR arm and there were no complete responses. OS was not statistically significantly different between arms [HR = 0.94 (95% CI 0.73, 1.20); p = 0.30].

### **NET of Gastrointestinal (GI) or Lung Origin**

A randomized, double-blind, multicenter study (RADIANT-4, NCT01524783) of AFINITOR in combination with BSC compared to placebo in combination with BSC was conducted in patients with unresectable, locally advanced or metastatic, well differentiated, non-functional NET of GI (excluding pancreatic) or lung origin. The study required that patients had well-differentiated (low or intermediate grade) histology, no prior or current history of carcinoid symptoms, and evidence of disease progression within 6 months prior to randomization. Patients were randomized 2:1 to receive either AFINITOR 10 mg once daily or placebo, and stratified by prior somatostatin analog use (yes vs. no), tumor origin and WHO performance status (0 vs. 1). The major efficacy outcome measure was PFS based on independent radiological assessment evaluated by RECIST. Additional efficacy outcome measures were OS and ORR.

A total of 302 patients were randomized, 205 to the AFINITOR arm and 97 to the placebo arm. The median age was 63 years (22 to 86 years); 47% were male; 76% were White; 74% had WHO performance status of 0 and 26% had WHO performance status of 1. The most common primary sites of tumor were lung (30%), ileum (24%), and rectum (13%).

The study demonstrated a statistically significant improvement in PFS per independent radiological review (Table 20 and Figure 3). The final OS analysis did not show a statistically significant difference between those patients who received AFINITOR or placebo (HR = 0.90 [95% CI: 0.66, 1.24]).

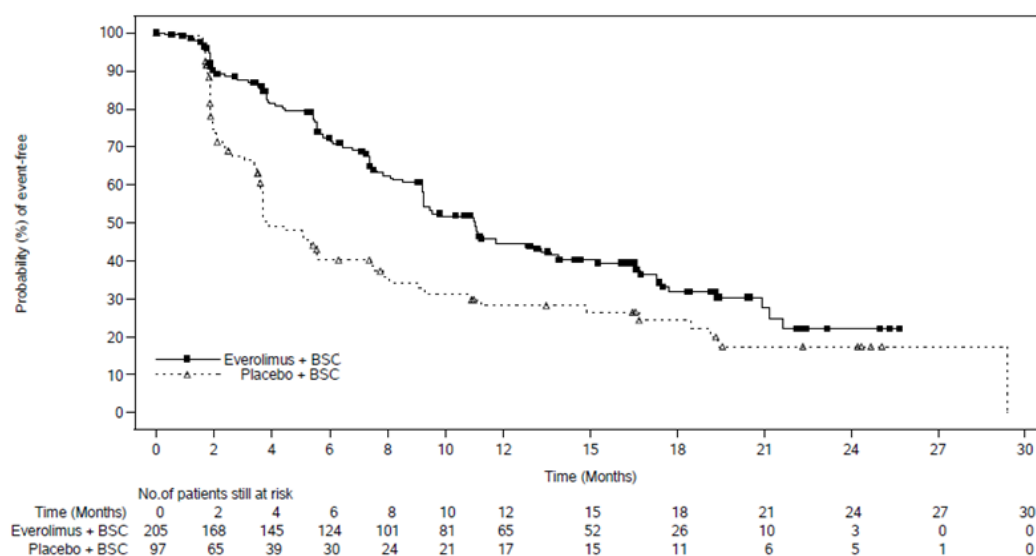
**Table 20: Progression-Free Survival in Neuroendocrine Tumors of Gastrointestinal or Lung Origin in RADIANT-4**

|                                    | <b>Afinitor<br/>N=205</b> | <b>Placebo<br/>N=97</b> |
|------------------------------------|---------------------------|-------------------------|
| <b>Progression-Free Survival</b>   |                           |                         |
| Number of Events                   | 113 (55%)                 | 65 (67%)                |
| Progressive Disease                | 104 (51%)                 | 60 (62%)                |
| Death                              | 9 (4%)                    | 5 (5%)                  |
| Median PFS in months (95% CI)      | 11.0 (9.2, 13.3)          | 3.9 (3.6, 7.4)          |
| Hazard Ratio (95% CI) <sup>a</sup> | 0.48 (0.35, 0.67)         |                         |
| p-value <sup>b</sup>               | < 0.001                   |                         |
| <b>Overall Response Rate</b>       | 2%                        | 1%                      |

<sup>a</sup>Hazard ratio is obtained from the stratified Cox model.

<sup>b</sup>p-value is obtained from the stratified log-rank test.

**Figure 3: Kaplan-Meier Curves for Progression-Free Survival in NET of GI or Lung Origin in RADIANT-4**



### **Lack of Efficacy in Locally Advanced or Metastatic Carcinoid Tumors**

The safety and effectiveness of AFINITOR in patients with locally advanced or metastatic functional carcinoid tumors have not been demonstrated. In a randomized (1:1), double-blind, multi-center trial (RADIANT-2, NCT00412061) in 429 patients with carcinoid tumors, AFINITOR in combination with long-acting octreotide (Sandostatin LAR®) was compared to placebo in combination with long-acting octreotide. After documented radiological progression, patients on the placebo arm could receive AFINITOR; of those randomized to placebo, 67% received open-label AFINITOR in combination with long-acting octreotide. The study did not meet its major efficacy outcome measure of a statistically significant improvement in PFS and the final analysis of OS favored the placebo in combination with long-acting octreotide arm.

### **12.3 Renal Cell Carcinoma (RCC)**

An international, multi-center, randomized, double-blind trial (RECORD-1, NCT00410124) comparing AFINITOR 10 mg once daily and placebo, both in conjunction with BSC, was conducted in patients with metastatic RCC whose disease had progressed despite prior treatment with sunitinib, sorafenib, or both sequentially. Prior therapy with bevacizumab, interleukin 2, or interferon- $\alpha$  was also permitted. Randomization was stratified according to prognostic score and prior anticancer therapy. The major efficacy outcome measure for the trial was PFS evaluated by RECIST, based on a blinded, independent, central radiologic review. After documented radiological progression, patients randomized to placebo could receive open-label AFINITOR. Other outcome measures included OS.

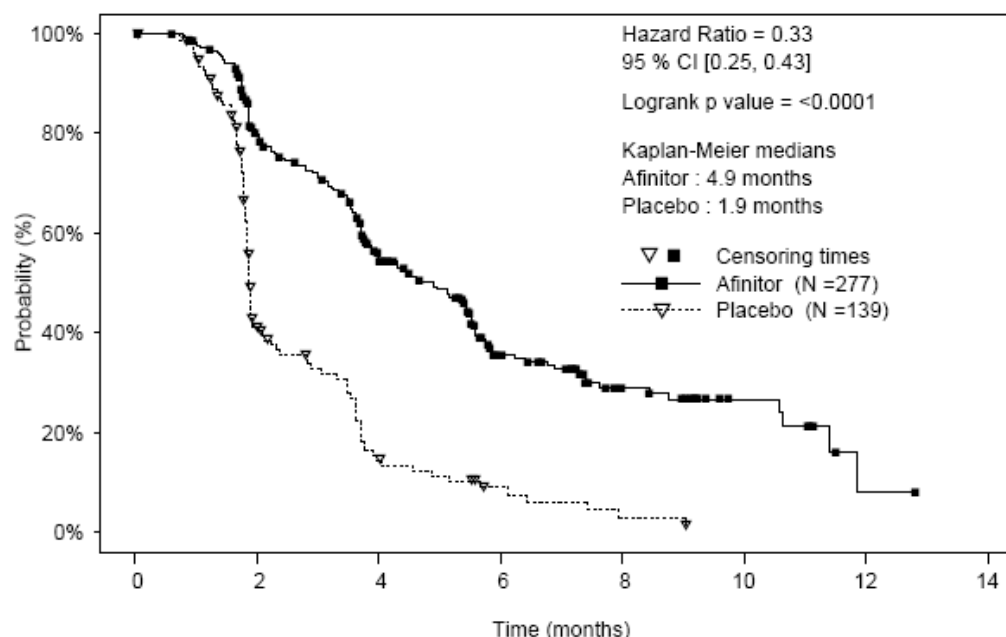
In total, 416 patients were randomized 2:1 to receive AFINITOR (n = 277) or placebo (n = 139). Demographics were well balanced between the arms (median age 61 years; 77% male, 88% White, 74% received prior sunitinib or sorafenib, and 26% received both sequentially).

AFINITOR was superior to placebo for PFS (Table 21 and Figure 4). The treatment effect was similar across prognostic scores and prior sorafenib and/or sunitinib. Final OS results yield a hazard ratio of 0.90 (95% CI: 0.71, 1.14), with no statistically significant difference between the arms. Planned cross-over from placebo due to disease progression to open-label AFINITOR occurred in 80% of the 139 patients and may have confounded the OS benefit.

**Table 21: Progression-Free Survival and Objective Response Rate by Central Radiologic Review in RCC in RECORD-1**

|                                                            | <b>AFINITOR<br/>N=277</b> | <b>Placebo<br/>N=139</b> | <b>Hazard Ratio<br/>(95% CI)</b> | <b>p-value<sup>a</sup></b> |
|------------------------------------------------------------|---------------------------|--------------------------|----------------------------------|----------------------------|
| <b>Median Progression-free Survival</b>                    | 4.9 months                | 1.9 months               | 0.33                             | <0.0001                    |
| <b>(95% CI)</b>                                            | (4.0, 5.5)                | (1.8, 1.9)               | (0.25, 0.43)                     |                            |
| <b>Objective Response Rate</b>                             | 2%                        | 0%                       | n/a <sup>b</sup>                 | n/a <sup>b</sup>           |
| <sup>a</sup> Log-rank test stratified by prognostic score. |                           |                          |                                  |                            |
| <sup>b</sup> Not applicable.                               |                           |                          |                                  |                            |

**Figure 4: Kaplan-Meier Curves for Progression-Free Survival in RCC in RECORD-1**



## 12.4 Tuberous Sclerosis Complex (TSC)-Associated Renal Angiomyolipoma

A randomized (2:1), double-blind, placebo-controlled trial (EXIST-2, NCT00790400) of AFINITOR was conducted in 118 patients with renal angiomyolipoma as a feature of TSC (n = 113) or sporadic lymphangiomyomatosis (n = 5). The key eligibility requirements for this trial were at least one

angiomyolipoma of  $\geq 3$  cm in longest diameter on CT/MRI based on local radiology assessment, no immediate indication for surgery, and age  $\geq 18$  years. Patients received AFINITOR 10 mg or matching placebo orally once daily until disease progression or unacceptable toxicity. CT or MRI scans for disease assessment were obtained at baseline, 12, 24, and 48 weeks and annually thereafter. Clinical and photographic assessment of skin lesions were conducted at baseline and every 12 weeks thereafter until treatment discontinuation. The major efficacy outcome measure was angiomyolipoma response rate based on independent central radiology review, which was defined as a  $\geq 50\%$  reduction in angiomyolipoma volume, absence of new angiomyolipoma lesion  $\geq 1$  cm, absence of kidney volume increase  $\geq 20\%$ , and no angiomyolipoma related bleeding of  $\geq$  Grade 2. Key supportive efficacy outcome measures were time to angiomyolipoma progression and skin lesion response rate. The primary analyses of efficacy outcome measures were limited to the blinded treatment period and conducted 6 months after the last patient was randomized. The comparative angiomyolipoma response rate analysis was stratified by use of enzyme-inducing antiepileptic drugs (EIAEDs) at randomization (yes vs. no).

Of the 118 patients enrolled, 79 were randomized to AFINITOR and 39 to placebo. The median age was 31 years (18 to 61 years), 34% were male, and 89% were White. At baseline, 17% of patients were receiving EIAEDs. On central radiology review at baseline, 92% of patients had at least 1 angiomyolipoma of  $\geq 3$  cm in longest diameter, 29% had angiomyolipomas  $\geq 8$  cm, 78% had bilateral angiomyolipomas, and 97% had skin lesions. The median values for the sum of all target renal angiomyolipoma lesions at baseline were 85 cm<sup>3</sup> (9 to 1612 cm<sup>3</sup>) and 120 cm<sup>3</sup> (3 to 4520 cm<sup>3</sup>) in the AFINITOR and placebo arms, respectively. Forty-six (39%) patients had prior renal embolization or nephrectomy. The median duration of follow-up was 8.3 months (0.7 to 24.8 months) at the time of the primary analysis.

The renal angiomyolipoma response rate was statistically significantly higher in AFINITOR-treated patients (Table 22). The median response duration was 5.3+ months (2.3+ to 19.6+ months).

There were 3 patients in the AFINITOR arm and 8 patients in the placebo arm with documented angiomyolipoma progression by central radiologic review (defined as a  $\geq 25\%$  increase from nadir in the sum of angiomyolipoma target lesion volumes to a value greater than baseline, appearance of a new angiomyolipoma  $\geq 1$  cm in longest diameter, an increase in renal volume  $\geq 20\%$  from nadir for either kidney and to a value greater than baseline, or Grade  $\geq 2$  angiomyolipoma-related bleeding). The time to angiomyolipoma progression was statistically significantly longer in the AFINITOR arm (HR 0.08 [95% CI: 0.02, 0.37];  $p < 0.0001$ ).

**Table 22: Angiomyolipoma Response Rate in TSC-Associated Renal Angiomyolipoma in EXIST-2**

|                                                     | <b>AFINITOR<br/>N=79</b> | <b>Placebo<br/>N=39</b> | <b>p-value</b>    |
|-----------------------------------------------------|--------------------------|-------------------------|-------------------|
| <b>Primary analysis</b>                             |                          |                         |                   |
| <b>Angiomyolipoma response rate<sup>a</sup> - %</b> | <b>41.8</b>              | <b>0</b>                | <b>&lt;0.0001</b> |
| 95% CI                                              | (30.8, 53.4)             | (0.0, 9.0)              |                   |

<sup>a</sup> Per independent central radiology review.

Skin lesion response rates were assessed by local investigators for 77 patients in the AFINITOR arm and 37 patients in the placebo arm who presented with skin lesions at study entry. The skin lesion response rate was statistically significantly higher in the AFINITOR arm (26% vs. 0,  $p = 0.0011$ ); all

skin lesion responses were partial responses, defined as visual improvement in 50% to 99% of all skin lesions durable for at least 8 weeks (Physician's Global Assessment of Clinical Condition).

Patients randomized to placebo were permitted to receive AFINITOR at the time of angiomyolipoma progression or after the time of the primary analysis. After the primary analysis, patients treated with AFINITOR underwent additional follow-up CT or MRI scans to assess tumor status until discontinuation of treatment or completion of 4 years of follow-up after the last patient was randomized. A total of 112 patients (79 randomized to AFINITOR and 33 randomized to placebo) received at least one dose of AFINITOR. The median duration of AFINITOR treatment was 3.9 years (0.5 months to 5.3 years) and the median duration of follow-up was 3.9 years (0.9 months to 5.4 years). During the follow-up period after the primary analysis, 32 patients (in addition to the 33 patients identified at the time of the primary analysis) had an angiomyolipoma response based upon independent central radiology review. Among the 65 responders out of 112 patients, the median time to angiomyolipoma response was 2.9 months (2.6 to 33.8 months). Fourteen percent of the 112 patients treated with AFINITOR had angiomyolipoma progression by the end of the follow-up period. No patient underwent a nephrectomy for angiomyolipoma progression and one patient underwent renal embolization while treated with AFINITOR.

## **12.5 Tuberous Sclerosis Complex (TSC)-Associated Subependymal Giant Cell Astrocytoma (SEGA)**

### **EXIST-1**

A randomized (2:1), double-blind, placebo-controlled trial (EXIST-1, NCT00789828) of AFINITOR was conducted in 117 pediatric and adult patients with SEGA and TSC. Eligible patients had at least one SEGA lesion  $\geq 1$  cm in longest diameter on MRI based on local radiology assessment and one or more of the following: serial radiological evidence of SEGA growth, a new SEGA lesion  $\geq 1$  cm in longest diameter, or new or worsening hydrocephalus. Patients randomized to the treatment arm received AFINITOR at a starting dose of 4.5 mg/m<sup>2</sup> daily, with subsequent dose adjustments as needed to achieve and maintain everolimus trough concentrations of 5 to 15 ng/mL as tolerated. AFINITOR or matched placebo continued until disease progression or unacceptable toxicity. MRI scans for disease assessment were obtained at baseline, 12, 24, and 48 weeks, and annually thereafter. The main efficacy outcome measure was SEGA response rate based on independent central radiology review. SEGA response was defined as a  $\geq 50\%$  reduction in the sum of SEGA volume relative to baseline, in the absence of unequivocal worsening of non-target SEGA lesions, a new SEGA lesion  $\geq 1$  cm, and new or worsening hydrocephalus. The primary analysis of SEGA response rate was limited to the blinded treatment period and conducted 6 months after the last patient was randomized. The analysis of SEGA response rate was stratified by use of enzyme-inducing antiepileptic drugs (EIAEDs) at randomization (yes vs. no).

Of the 117 patients enrolled, 78 were randomized to AFINITOR and 39 to placebo. The median age was 9.5 years (0.8 to 26 years); a total of 20 patients were  $< 3$  years, 54 patients were 3 to  $< 12$  years, 27 patients were 12 to  $< 18$  years, and 16 patients were  $\geq 18$  years; 57% were male, and 93% were White. At baseline, 18% of patients were receiving EIAEDs. Based on central radiology review at baseline, 98% of patients had at least one SEGA lesion  $\geq 1.0$  cm in longest diameter, 79% had bilateral

SEGAs, 43% had  $\geq 2$  target SEGA lesions, 26% had growth in or into the inferior surface of the ventricle, 9% had evidence of growth beyond the subependymal tissue adjacent to the ventricle, and 7% had radiographic evidence of hydrocephalus. The median values for the sum of all target SEGA lesions at baseline were 1.63 cm<sup>3</sup> (0.18 to 25.15 cm<sup>3</sup>) and 1.30 cm<sup>3</sup> (0.32 to 9.75 cm<sup>3</sup>) in the AFINITOR and placebo arms, respectively. Eight (7%) patients had prior SEGA-related surgery. The median duration of follow-up was 8.4 months (4.6 to 17.2 months) at the time of primary analysis.

The SEGA response rate was statistically significantly higher in AFINITOR-treated patients (Table 23). At the time of the primary analysis, all SEGA responses were ongoing and the median duration of response was 5.3 months (2.1 to 8.4 months).

With a median follow-up of 8.4 months, SEGA progression was detected in 15.4% of the 39 patients randomized to receive placebo and none of the 78 patients randomized to receive AFINITOR. No patient in either treatment arm required surgical intervention.

**Table 23: Subependymal Giant Cell Astrocytoma Response Rate in TSC-Associated SEGA in EXIST-1**

|                                             | <b>AFINITOR</b><br><b>N=78</b> | <b>Placebo</b><br><b>N=39</b> | <b>p-value</b>    |
|---------------------------------------------|--------------------------------|-------------------------------|-------------------|
| <b>Primary analysis</b>                     |                                |                               |                   |
| <b>SEGA response rate<sup>a</sup> - (%)</b> | <b>35</b>                      | <b>0</b>                      | <b>&lt;0.0001</b> |
| <b>95% CI</b>                               | <b>24, 46</b>                  | <b>0, 9</b>                   |                   |

<sup>a</sup> Per independent central radiology review

Patients randomized to placebo were permitted to receive AFINITOR at the time of SEGA progression or after the primary analysis, whichever occurred first. After the primary analysis, patients treated with AFINITOR underwent additional follow-up MRI scans to assess tumor status until discontinuation of treatment or completion of 4 years of follow-up after the last patient was randomized. A total of 111 patients (78 patients randomized to AFINITOR and 33 patients randomized to placebo) received at least one dose of AFINITOR. Median duration of AFINITOR treatment and follow-up was 3.9 years (0.2 to 4.9 years).

By four years after the last patient was enrolled, 58% of the 111 patients treated with AFINITOR had a  $\geq 50\%$  reduction in SEGA volume relative to baseline, including 27 patients identified at the time of the primary analysis and 37 patients with a SEGA response after the primary analysis. The median time to SEGA response was 5.3 months (2.5 to 33.1 months). Twelve percent of the 111 patients treated with AFINITOR had documented disease progression by the end of the follow-up period and no patient required surgical intervention for SEGA during the study.

### **Study 2485**

Study 2485 (NCT00411619) was an open-label, single-arm trial conducted to evaluate the antitumor activity of AFINITOR 3 mg/m<sup>2</sup>/orally once daily in patients with SEGA and TSC. Serial radiological evidence of SEGA growth was required for entry. Tumor assessments were performed every 6 months for 60 months after the last patient was enrolled or disease progression, whichever occurred earlier. The major efficacy outcome measure was the reduction in volume of the largest SEGA lesion with 6 months of treatment, as assessed via independent central radiology review. Progression was defined as an increase in volume of the largest SEGA lesion over baseline that was  $\geq 25\%$  over the nadir observed on study.

A total of 28 patients received AFINITOR for a median duration of 5.7 years (5 months to 6.9 years); 82% of the 28 patients remained on AFINITOR for at least 5 years. The median age was 11 years (3 to 34 years), 61% male, 86% White.

At the primary analysis, 32% of the 28 patients (95% CI: 16%, 52%) had an objective response at 6 months, defined as at least a 50% decrease in volume of the largest SEGA lesion. At the completion of the study, the median duration of durable response was 12 months (3 months to 6.3 years).

By 60 months after the last patient was enrolled, 11% of the 28 patients had documented disease progression. No patient developed a new SEGA lesion while on AFINITOR. Nine additional patients were identified as having a  $\geq 50\%$  volumetric reduction in their largest SEGA lesion between 1 to 4 years after initiating AFINITOR, including 3 patients who had surgical resection with subsequent regrowth prior to receiving AFINITOR.

### **13 INCOMPATIBILITIES**

Not applicable.

### **14 STORAGE**

Do not store above 30°C.

Protect from light.

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

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

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

### **15 PACK SIZE**

Available in Alu-Alu blister packs of 1x10 / 3x10 / 6x10 / 9x10 tablets.

Not all pack size may be marketed.

#### **Product Registration Holder:**

Novartis Corporation (Malaysia) Sdn. Bhd.

Level 18, Imazium,

No. 8, Jalan SS21/37,

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47400 Petaling Jaya, Selangor

**Malaysian Package Leaflet**

Information issued: 31 May 2021 and USPI Feb 2022

Date of revision: 19 May 2026

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**Novartis Pharma AG, Basel, Switzerland**