

## FOR EX-US MEDIA USE ONLY

### Overview: Phase III Pivotal Study of Afinitor<sup>®</sup> (everolimus) Tablets in Patients with Advanced, Progressive, Well-differentiated, Nonfunctional Neuroendocrine Tumors (NET) of Gastrointestinal (GI) or Lung Origin

Neuroendocrine tumors (NET) are a rare type of cancer that originate in neuroendocrine cells throughout the body, and are most often found in the GI tract, lungs or pancreas<sup>1,2</sup>. NET can be defined as functional or nonfunctional. Functional NET are characterized by symptoms caused by the oversecretion of hormones and other substances<sup>3</sup>. Nonfunctional NET may be characterized by symptoms caused by tumor growth, such as intestinal obstruction, pain and bleeding for GI NET, and asthma, chronic obstructive pulmonary disease and pneumonia for lung NET<sup>3,4,5,6</sup>. More than 70% of patients with NET have nonfunctional tumors<sup>7</sup>.

At time of diagnosis, 5% to 44% (depending on site of tumor origin) of patients with NET in the GI tract and 28% of patients with lung NET have advanced disease, meaning the cancer has spread to other areas of the body, making it difficult to treat<sup>1,2</sup>. Progression, or the continued growth or spread of the tumor, is typically associated with poor outcomes<sup>8</sup>.

Trial <b>RAD001 In Advanced Neuroendocrine Tumors (RADIANT-4)</b>	
<b>Overview</b>	Phase III study evaluating the safety and efficacy of Afinitor <sup>®</sup> (everolimus) tablets, a mammalian target of rapamycin (mTOR) inhibitor, plus best supportive care (BSC) vs placebo plus BSC in patients with unresectable, progressive, well-differentiated, nonfunctional, locally advanced or metastatic NET of GI (excluding pancreatic) or lung origin <sup>9</sup>
<b>Trial Design</b>	<ul style="list-style-type: none"><li>• Randomized, double-blind*, multicenter study of 302 patients (median age 63 years)</li><li>• Patients had low or intermediate grade histology, no history or active symptoms of carcinoid syndrome, had documented disease progression within the previous 6 months and were required to have ceased treatment with somatostatin analogues (SSA) for 4 weeks before study entry</li><li>• Patients were randomized 2:1 to receive either Afinitor 10 mg daily plus BSC (n=205) or placebo plus BSC (n=97) and were grouped by prior SSA use, tumor origin and World Health Organization (WHO) performance status<sup>9</sup></li></ul>
<b>Primary &amp; Secondary Endpoints</b>	<ul style="list-style-type: none"><li>• The primary endpoint was progression-free survival (PFS<sup>†</sup>) based on independent radiological assessment (an imaging-based diagnostic process used to learn about the patient's condition) evaluated by RECIST (Response Evaluation Criteria in Solid Tumors)<ul style="list-style-type: none"><li>○ Supportive PFS analyses were based on an independent central radiology review</li></ul></li></ul>



	<ul style="list-style-type: none"> <li>Secondary endpoints included overall survival<sup>†</sup> and best overall response rate (defined as complete response plus partial response)<sup>9</sup></li> </ul>
<b>Trial Results</b>	<ul style="list-style-type: none"> <li>The primary endpoint of PFS was met:           <ul style="list-style-type: none"> <li>Afinitor significantly improved PFS, reducing the risk of progression by 52% (hazard ratio [HR] = 0.48; 95% confidence interval [CI], 0.35-0.67; p&lt;0.001)</li> </ul> </li> <li>Data also showed Afinitor increased median PFS by 7.1 months: median PFS by central review was 11.0 months (95% CI, 9.2-13.3) with Afinitor compared to 3.9 months (95% CI, 3.6-7.4) with placebo<sup>9</sup></li> </ul>
<b>Safety/Adverse Events</b>	<ul style="list-style-type: none"> <li>The most common treatment-related, all-grade adverse events (AEs) (incidence ≥30%) were stomatitis (63%), infections (58%), diarrhea (41%), peripheral edema (accumulation of fluid causing swelling in lower limbs) 39%, fatigue (37%) and rash (30%)</li> <li>The most common grade 3/4 AEs (≥5%) for Afinitor and placebo, respectively, were infections (11.0% vs 2.0%), diarrhea (9.0% vs 2.0%), stomatitis (inflammation of the mouth or lips; 9.0% vs 0.0%), fatigue (5.0% vs 1.0%) and hyperglycemia (5.0% vs 0.0%)</li> <li>Afinitor was discontinued for adverse reactions in 29% of patients and dose reduction or delay was required in 70% of Afinitor-treated patients<sup>9</sup></li> </ul>

\* = A clinical trial in which the medical staff, patients and research analysts do not know the specific type of treatment patients receive until after the clinical trial concludes

† = Length of time that patients live with a disease without it becoming worse during and after treatment

‡ = Length of time that patients are alive from either the date of diagnosis or the start of treatment

### About Afinitor<sup>®</sup> (everolimus) tablets

Afinitor<sup>®</sup> (everolimus) tablets is now approved by the United States (US) Food and Drug Administration (FDA) for the treatment of adult patients with progressive, well-differentiated, nonfunctional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin that are unresectable, locally advanced or metastatic. Additionally, Afinitor is approved in 99 countries, including the US and throughout the European Union, for locally advanced, metastatic or unresectable progressive NET of pancreatic origin. It is also approved in >120 countries including the United States and European Union for advanced renal cell carcinoma following progression on or after vascular endothelial growth factor (VEGF)-targeted therapy (in the US, specifically following sunitinib and sorafenib.)

Afinitor is also approved in 102 countries including the US and European Union for advanced HR+/HER2- breast cancer in combination with exemestane, after prior endocrine therapy.

Everolimus is also available from Novartis for use in certain non-oncology patient populations under the brand names Afinitor<sup>®</sup> or Votubia<sup>®</sup>, Certican<sup>®</sup> and Zortress<sup>®</sup> and is exclusively licensed to Abbott and sublicensed to Boston Scientific for use in drug-eluting stents.



Indications vary by country and not all indications are available in every country. The safety and efficacy profile of everolimus has not yet been established outside the approved indications. Because of the uncertainty of clinical trials, there is no guarantee that everolimus will become commercially available for additional indications anywhere else in the world.

### **Important Safety Information about Afinitor® (everolimus) tablets**

Afinitor/Votubia can cause serious side effects including lung or breathing problems, infections (including sepsis), and kidney failure, which can lead to death. Patients taking concomitant angiotensin-converting enzyme (ACE) inhibitors may be at an increased risk for angioedema. Mouth ulcers and mouth sores are common side effects. Afinitor/Votubia can affect blood cell counts, kidney and liver function, and blood sugar, cholesterol, and triglyceride levels. Afinitor/Votubia may cause fetal harm in pregnant women. Highly effective contraception is recommended for women of child-bearing potential while receiving Afinitor/Votubia and for up to eight weeks after ending treatment. Women taking Afinitor/Votubia should not breast feed. Fertility in women and men may be affected by treatment with Afinitor/Votubia.

The most common adverse drug reactions (incidence  $\geq 10$  percent) are mouth ulcers, skin rash, feeling tired or weak, diarrhea, infections (including upper respiratory tract infection, sore throat and runny nose, sinusitis, middle ear infection and pneumonia), absence of menstrual periods, high levels of cholesterol, nausea, decreased appetite, low level of red blood cells, acne, abnormal taste, irregular menstrual periods, inflammation of lung tissue, swelling of extremities or other parts of the body, high level of blood sugar, itching, weight loss, nose bleeds, cough and headache. The most common grade 3-4 adverse drug reactions (incidence  $\geq 2$  percent) are mouth ulcers, infections (including pneumonia), low level of red blood cells, absence of menstrual periods, high level of blood sugar, feeling tired or weak, diarrhea, low white blood cells, inflammation of lung tissue and spontaneous bleeding or bruising. Cases of hepatitis B reactivation, blood clots in the lung or legs, and pneumocystis jirovecii pneumonia (PJP) have been reported. Abnormalities were observed in hematology and clinical chemistry laboratory tests.

### **References**

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