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Overview: Phase III Pivotal Study of Afinitor® (everolimus) Tablets in Patients with Progressive, Well-differentiated, Nonfunctional, Unresectable or Metastatic NET of 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 gastrointestinal (GI) tract, lungs or pancreas[1,2]. NET can be defined as functional or nonfunctional. The majority of patients with NET (72%) have nonfunctional NET, which are 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[3,4,5,6]. In contrast, functional NET are characterized by symptoms caused by the oversecretion of hormones and other substances[3].

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[1,2]. Progression, or the continued growth or spread of the tumor, is typically associated with poor prognoses[8].

Trial	**RAD001 In Advanced Neuroendocrine Tumors (RADIANT-4)**
Overview	Phase III study evaluating the safety and efficacy of Afinitor® (everolimus) tablets, a mammalian target of rapamycin (mTOR) inhibitor, plus best supportive care (BSC) vs placebo plus BSC in patients with advanced, well-differentiated (Grade 1 or Grade 2) nonfunctional NET of GI or lung origin[9]
Trial Design	• Randomized, double-blind*, parallel group, placebo-controlled, multicenter study of 302 patients (median age 63 years) • Patients had no history of and no active symptoms related to carcinoid syndrome and had history of prior somatostatin analogue (SSA) use • 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 performance status (WHO PS)[9]
Primary Endpoint	• The primary endpoint was progression-free survival (PFS†) based on independent radiological assessment (an imaging-based diagnostic process used to learn about the patient's condition) evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) ○ Supportive PFS analyses were based on an independent central radiology review
Trial Results	• The primary endpoint of PFS was met:

	○ 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<0.00001) • 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[9]
Safety/Adverse Events	• The most common treatment-related, all-grade adverse events (AEs) (incidence ≥20%) for Afinitor and placebo, respectively, were stomatitis (inflammation of the mouth or lips; 63% vs 19%), diarrhea (31% vs 16%), fatigue (31% vs 24%), infections (29% vs 4%), rash (27% vs 8%) and peripheral edema (accumulation of fluid causing swelling in lower limbs; 26% vs 4%) • The most common treatment-related grade 3/4 AEs (≥5%) for Afinitor and placebo, respectively, were stomatitis (9.0% vs 0.0%), diarrhea (7.0% vs 2.0%) and infections (7.0% vs 0.0%) • Afinitor was discontinued for AEs in 29% of patients and dose interruption was required in 70% of Afinitor-treated patients[9]

* = 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® (everolimus) tablets
Afinitor® (everolimus) tablets is approved in more than 110 countries, including the US and in the European Union, for locally advanced, metastatic or unresectable progressive NET of pancreatic origin. Afinitor is not indicated for the treatment of patients with functional carcinoid tumors in the US. Afinitor is now also approved in the US and EU for the treatment of adult patients with progressive, well-differentiated (Grade 1 or Grade 2), nonfunctional NET of gastrointestinal or lung origin that are unresectable, locally advanced or metastatic.

It is also approved in more than 120 countries including the US 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).

Additionally, Afinitor is approved in more than 110 countries including the United States 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® or Votubia®, Certican® and Zortress® 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 ffective 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 ≥10 percent) are infections (including sore throat and runny nose, upper respiratory tract infection, pneumonia, sinusitis, and urinary tract infection), mouth ulcers, skin rash, feeling tired, diarrhea, fever, vomiting, nausea, cough, decreased appetite, low level of red blood cells, headache, abnormal taste, absence of menstrual periods, acne, inflammation of lung tissue, irregular menstrual periods, swelling of extremities or other parts of the body, high level of blood sugar, feeling weak, itching, weight loss, high levels of cholesterol, and nose bleeds. The most common Grade 3-4 adverse drug reactions (incidence ≥2 percent) are mouth ulcers, infections (including pneumonia), low level of red blood cells, high level of blood sugar, feeling tired, absence of menstrual periods, diarrhea, low white blood cells, inflammation of lung tissue, feeling weak, fever, 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.

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