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Overview: Phase III Pivotal Study of Afinitor® (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^{1,2}. NET can be defined as functional or nonfunctional. Functional NET are characterized by symptoms caused by the oversecretion of hormones and other substances³. 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^{3,4,5,6}. More than 70% of patients with NET have nonfunctional tumors⁷.

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 outcomes⁸.

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 unresectable, progressive, well-differentiated, nonfunctional, locally advanced or metastatic NET of GI (excluding pancreatic) or lung origin ⁹
Trial Design	<ul style="list-style-type: none">• Randomized, double-blind*, multicenter study of 302 patients (median age 63 years)• 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• 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 status⁹
Primary & Secondary Endpoints	<ul style="list-style-type: none">• 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 RECIST (Response Evaluation Criteria in Solid Tumors)<ul style="list-style-type: none">○ Supportive PFS analyses were based on an independent central radiology review



	<ul style="list-style-type: none"> Secondary endpoints included overall survival[‡] and best overall response rate (defined as complete response plus partial response)⁹
Trial Results	<ul style="list-style-type: none"> The primary endpoint of PFS was met: <ul style="list-style-type: none"> 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<0.001) 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 placebo⁹
Safety/Adverse Events	<ul style="list-style-type: none"> 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%) 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%) Afinitor was discontinued for adverse reactions in 29% of patients and dose reduction or delay was required in 70% of Afinitor-treated patients⁹

* = 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 is a prescription medicine used to treat adults with a type of cancer known as neuroendocrine tumor (NET) of the stomach and intestine (gastrointestinal) or lung that has progressed and cannot be treated with surgery. Afinitor is not for use in people with carcinoid tumors that actively produce hormones.

Important Safety Information

Patients should not take Afinitor if they are allergic to Afinitor or to any of its ingredients. Patients should tell their health care provider before taking Afinitor if they are allergic to sirolimus (Rapamune[®]) or temsirolimus (Torisel[®]).

Afinitor can cause serious side effects, including lung or breathing problems, infections, and kidney failure, which can even lead to death. If patients experience these side effects, they may need to stop taking Afinitor for a while or use a lower dose. Patients should follow their health care provider's instructions.

In some patients, lung or breathing problems may be severe and can even lead to death. Patients should tell their health care provider right away if they have any of these symptoms: new or worsening cough, shortness of breath, chest pain, difficulty breathing, or wheezing.



Afinitor may make patients more likely to develop an infection, such as pneumonia, or a bacterial, fungal, or viral infection. Viral infections may include reactivation of hepatitis B in people who have had hepatitis B in the past. In some people these infections may be severe and can even lead to death. Patients may need to be treated as soon as possible. Patients should tell their health care provider right away if they have a temperature of 100.5°F or above, chills, or do not feel well. Symptoms of hepatitis B or infection may include the following: fever, chills, skin rash, joint pain and inflammation, tiredness, loss of appetite, nausea, pale stools or dark urine, yellowing of the skin, or pain in the upper right side of the stomach.

Patients who take an angiotensin-converting enzyme (ACE) inhibitor medicine during treatment with Afinitor are at a possible increased risk for a type of allergic reaction called angioedema. Patients should get medical help right away if they have trouble breathing or develop swelling of the tongue, mouth, or throat during treatment with Afinitor.

Afinitor may cause kidney failure. In some people this may be severe and can even lead to death. Patients should have tests to check their kidney function before and during their treatment with Afinitor.

Afinitor can cause incisions to heal slowly or not heal well. Patients should tell their health care provider if their incision is red, warm, or painful; if they have blood, fluid, or pus in their incision; or if their incision opens up or is swollen.

Common side effects include mouth ulcers and sores. Other common side effects include infections, diarrhea, swelling of the arms, hands, feet, ankles, or other parts of the body, feeling weak or tired, rash, dry skin, itching, cough, shortness of breath, nausea, fever, weight loss, or loss of appetite.

Please see full Prescribing Information for Afinitor available at www.Afinitor.com.

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References

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