Novartis drug Afinitor® significantly improves progression-free survival in advanced nonfunctional gastrointestinal and lung NET

- In pivotal study, everolimus reduced risk of disease progression by 52%; showed 11.0-month median progression-free survival vs 3.9 months for placebo
- Advanced, progressive, nonfunctional neuroendocrine tumors of GI or lung origin are rare forms of cancer with poor prognoses and limited treatment options
- RADIANT-4 results highlighted at key European cancer congress; worldwide regulatory filings are underway

Basel, September 27, 2015 – Novartis announced today results of a Phase III pivotal study showing Afinitor® (everolimus) tablets reduced the risk of progression by 52% (hazard ratio [HR] = 0.48; 95% confidence interval [CI], 0.35-0.67; p<0.00001) vs placebo in patients with advanced, progressive, nonfunctional neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin. The study, RADIANT-4, will be presented at the European Cancer Congress (ECC) 2015 in Vienna, Austria, and was highlighted in the ECC press conference on Saturday, September 26.

Additionally, the data show everolimus, a mammalian target of rapamycin (mTOR) inhibitor, extended median progression free survival (PFS) by 7.1 months: median PFS by central review was 11.0 months (95% CI, 9.23-13.3) in the everolimus arm and 3.9 months (95% CI, 3.58-7.43) in the placebo arm. Overall survival (OS) was a key secondary endpoint of the trial. While the OS data are not mature, the first interim analysis showed a trend favoring the everolimus arm. Additional OS analyses are planned. Another secondary endpoint was best overall response rate; the study found that 64% of patients receiving everolimus experienced at least some degree of tumor shrinkage compared to 26% of those on placebo.

Safety was also a secondary endpoint of the trial and adverse events (AEs) were consistent with the known safety profile of everolimus. The most common treatment-related grade 3/4 AEs (>5%) for everolimus and placebo, respectively, were stomatitis (9.0% vs 0.0%), diarrhea (7.0% vs 2.0%) and infections (7.0% vs 0.0%).

“Advanced, progressive, nonfunctional NET of GI or lung origin are rare and aggressive cancers, with limited treatment options,” said James Yao, MD, Professor of Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, and the study’s principal investigator. “These pivotal trial results demonstrate strong evidence for the efficacy of the mTOR inhibitor everolimus in this patient population.”

NET are a rare type of cancer that originate in neuroendocrine cells found throughout the body, and are most often found in the GI tract, lungs or pancreas. NET can be functional or nonfunctional: functional NET produce symptoms caused by the secretion of hormones and other substances; nonfunctional NET may produce symptoms caused by the tumor’s growth, such as intestinal blockage, pain and bleeding. At time of diagnosis, 5%-44% of patients with NET in the GI system and 28% of patients with lung...
NET have advanced disease, meaning the cancer has spread to other parts of the body and is more difficult to treat.

“These results show that everolimus has the potential to be a new, clinically meaningful therapy for patients with advanced, progressive, nonfunctional GI or lung NET, which typically have poor prognoses,” said Alessandro Riva, MD, Global Head, Novartis Oncology Development and Medical Affairs. “Our work with the RADIANT clinical program demonstrates our long-term commitment to NET and has yielded important data that have led to improved outcomes for patients with different types of NET.”

The results of the RADIANT-4 study—part of the largest clinical trial program in patients with advanced NET—will serve as the basis of worldwide regulatory submissions for Afinitor for the treatment of advanced, progressive, nonfunctional GI and lung NET. Afinitor is already approved in more than 95 countries worldwide for locally advanced, metastatic or unresectable progressive NET of pancreatic origin.

**About RADIANT-4**

RADIANT-4 (RAD001 In Advanced Neuroendocrine Tumors) is a Phase III prospective, double-blind, randomized, parallel group, placebo-controlled, multicenter study. The trial examined the efficacy and safety of everolimus plus best supportive care (BSC) vs placebo plus BSC in 302 patients with progressive, well-differentiated, nonfunctional, advanced NET of GI or lung origin. All patients received BSC during treatment, which excluded antitumor agents such as somatostatin analogues (SSAs). Patients were required to have ceased treatment with SSAs for 4 weeks before study entry. Everolimus demonstrated similar efficacy regardless of whether the patient had prior SSA therapy or not. Patients had no history or active symptoms of carcinoid syndrome, and had documented disease progression within the previous 6 months. Patients were randomized 2:1 to receive either daily everolimus 10 mg or daily placebo orally.

The primary endpoint of RADIANT-4 was PFS by central radiology review. Secondary endpoints included safety, OS, best overall response rate (defined as complete response plus partial response) and disease control rate.

The safety profile of everolimus was consistent with what has been observed in previous studies of this drug. The most common treatment-related AEs included stomatitis, diarrhea, peripheral edema, fatigue, and rash. At the time of the data analysis cutoff date, the primary reasons for treatment discontinuation were disease progression (37% in the everolimus arm vs 72% in the placebo arm) and adverse events (29% in the everolimus arm vs 7% in the placebo arm). A trend towards improved survival was observed at the time of interim OS analysis [HR=0.64; 95% CI, 0.40-1.05; p=0.037], with a total of 70 deaths recorded at the time of the data cutoff (42 [20.5%] in the everolimus arm and 28 [28.6%] in the placebo arm). The result was not statistically significant, since interim analysis significance threshold was p=0.000213.

**About Afinitor® (everolimus) tablets**

Afinitor® (everolimus) is approved in more than 95 countries, including the United States and throughout the European Union, for locally advanced, metastatic or unresectable progressive neuroendocrine tumors of pancreatic origin. It is also approved in 121 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.

Afinitor is also approved in more than 100 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®, 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 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 ≥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 ≥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.

**Disclaimer**

The foregoing release contains forward-looking statements that can be identified by words such as “underway,” “will,” “planned,” “potential,” “commitment,” “yet,” or similar terms, or by express or implied discussions regarding potential new indications or labeling for everolimus, or regarding potential future revenues from everolimus. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that everolimus will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that everolimus will be commercially successful in the future. In particular, management's expectations regarding everolimus could be affected by, among other things, the uncertainties inherent in research and development, including unexpected clinical trial results and additional analysis of existing clinical data; unexpected regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain proprietary intellectual property protection; general economic and industry conditions; global trends toward health care cost containment, including ongoing pricing pressures; unexpected safety issues; unexpected manufacturing or quality issues, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update
any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis
Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, eye care and cost-saving generic pharmaceuticals. Novartis is the only global company with leading positions in these areas. In 2014, the Group achieved net sales of USD 58.0 billion, while R&D throughout the Group amounted to approximately USD 9.9 billion (USD 9.6 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 120,000 full-time-equivalent associates. Novartis products are available in more than 180 countries around the world. For more information, please visit http://www.novartis.com.

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