Novartis announces results of trial evaluating the use of Afinitor® in first-line treatment in HER2+ advanced breast cancer at SABCS

- **BOLERO-1 trial explored everolimus in women with HER2+ advanced breast cancer and did not meet criteria for statistical significance in first primary objective**

- **The second primary objective in the HER2+ pre-defined HR- subgroup of the trial showed an improvement in progression-free survival, though not statistically significant, supporting continued research of the PI3K/AKT/mTOR pathway**

- **Afinitor is approved for use in more than 90 countries in combination with exemestane for the treatment of HR+/HER2- advanced breast cancer, which globally represents 70% of all invasive breast cancers**

**Basel, December 12, 2014** – Novartis today announced results of the BOLERO-1 (Breast cancer trials of Oral Everolimus-1) trial of Afinitor® (everolimus) tablets in combination with trastuzumab (Herceptin®) and paclitaxel as a first-line treatment in women with human epidermal growth factor receptor-2 positive (HER2+) advanced breast cancer at the 2014 San Antonio Breast Cancer Symposium (SABCS).

The trial was conducted in HER2+ advanced breast cancer patients, a population that represents approximately 20% of advanced breast cancers and differs from the hormone receptor-positive, human epidermal growth factor receptor-2 negative (HR+/HER2-) advanced breast cancer patients for whom Afinitor in combination with exemestane following a non-steroidal aromatase inhibitor is approved worldwide. The study did not meet the threshold of statistical significance for the primary objectives of progression-free survival (PFS) among women with HER2+ advanced breast cancer or the pre-defined hormone-receptor negative, human epidermal growth factor receptor-2 positive (HR-/HER2+) subgroup.

“For more than two years, Afinitor has positively impacted the HR positive treatment landscape as an important therapy for women living with advanced breast cancer,” said Alessandro Riva, Global Head, Oncology Development and Medical Affairs, Novartis Oncology. “The results of this trial in HER2 positive support our research approach of investigating various treatment combinations targeting the PI3K/AKT/mTOR pathway in advanced breast cancer and we thank all of the researchers and patients who participated in the BOLERO-1 study.”

The results of BOLERO-1, a Phase III, randomized, double-blind, placebo-controlled multicenter trial of 719 patients with HER2+ locally advanced or metastatic breast cancer, showed that the median PFS with everolimus plus trastuzumab and paclitaxel was 15.0 months versus 14.5 months with placebo plus trastuzumab and paclitaxel, a difference of 0.5 months (hazard ratio=0.89 [95% CI: 0.73 to 1.08]; p=0.1166).
In the HR- subgroup of women with HER2+ advanced breast cancer, a second primary objective, everolimus plus trastuzumab and paclitaxel treatment demonstrated benefit over the placebo arm prolonging median PFS by 7.2 months. The median PFS was 20.3 months with everolimus plus trastuzumab and paclitaxel and 13.1 months with placebo plus trastuzumab and paclitaxel. While this difference was clinically relevant, the results did not demonstrate statistical significance.

The combination of everolimus, trastuzumab and paclitaxel was generally well-tolerated. Adverse events were consistent with the known safety profile of everolimus with the most common all-grade adverse reactions (incidence >= 35%) being stomatitis, diarrhea, alopecia, rash, cough, pyrexia, neutropenia and fatigue. The most common Grade 3-4 adverse reactions (incidence >= 2%) were neutropenia, stomatitis, diarrhea, anemia, hypokalaemia, leukopenia, hyperglycemia, fatigue, pyrexia and dyspnoea.

Afinitor is currently approved in more than 90 countries across the globe, including the countries of the European Union and the United States, to treat postmenopausal women with HR+/HER2- advanced breast cancer in combination with exemestane after recurrence or progression following a non-steroidal aromatase inhibitor. The specific indications vary by country. HR+/HER2- advanced breast cancer is the most common form of the disease. Approximately 70% of all invasive breast cancers are positive for HR expression at the time of diagnosis.

About PI3K/AKT/mTOR pathway
In advanced breast cancer, there are several different pathways that, when activated, can be responsible for tumor growth and progression. One of these pathways is known as the PI3K/AKT/mTOR pathway. Everolimus targets mTOR, a protein that acts as an important regulator of tumor cell division and blood vessel growth. Additional preclinical research shows that activation of the PI3K/AKT/mTOR pathway is frequently a characteristic of worsening prognosis through increased aggressiveness of the tumor, resistance to treatment and tumor progression. Overactivation of this pathway has also been associated with potential resistance to trastuzumab treatment and disease progression in women with HER2+ advanced breast cancer.

About advanced breast cancer
Advanced breast cancer comprises metastatic breast cancer (stage IV) and locally advanced breast cancer (stage III). Metastatic breast cancer is the most serious form of the disease and occurs when the cancer has spread to other parts of the body, such as the brain, bones or liver. Locally advanced breast cancer occurs when the cancer has spread to lymph nodes and/or other tissue in the area of the breast but not to distant sites in the body.

Eighty percent of advanced breast cancer is either HR+ and/or HER2+. HR+ advanced breast cancer is the most common type of advanced breast cancer, with an estimated 220,000 women diagnosed globally each year. HR+ advanced breast cancer is characterized by hormone receptor-positive tumors, a group of cancers that express receptors for certain hormones such as estrogen and progesterone. Cancer cell growth can be driven by these hormones.

In HER2+ advanced breast cancer, overexpression of the HER2 gene activates signaling pathways, such as the mTOR pathway, leading to the uncontrolled growth and division of cancer cells. Globally, an estimated 140,000 women are living with HER2+ advanced breast cancer. HER2+ advanced breast cancer represents approximately 20% of advanced breast cancer diagnoses.
About Afinitor® (everolimus)

Everolimus is approved as Afinitor® in the European Union for the treatment of hormone receptor-positive, human epidermal growth factor receptor-2 negative (HR+/HER2-) advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor (NSAI). In the United States, Afinitor is approved for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2 negative (advanced HR+/HER2-) breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole.

Afinitor (everolimus) tablets is approved in more than 110 countries, including the United States and throughout the European Union, in the oncology settings of advanced renal cell carcinoma following progression on or after vascular endothelial growth factor (VEGF)-targeted therapy and for locally advanced, metastatic or unresectable progressive neuroendocrine tumors of pancreatic origin.

Everolimus is also available from Novartis for use in certain non-oncology patient populations in tuberous sclerosis complex related disease and transplantation 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 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, absence of menstrual periods, infections (including upper respiratory tract infection, sore throat and runny nose, sinusitis, and pneumonia), nausea, decreased appetite, low level of red blood cells, high levels of cholesterol, abnormal taste, acne, irregular menstrual periods, inflammation of lung tissue, high level of blood sugar, weight loss, itching, swelling of extremities or other parts of the body, nose bleeds, and headache. The most common Grade 3-4 adverse drug reactions (incidence ≥2 percent) are mouth ulcers, absence of menstrual periods, low level of red blood cells, infections (including pneumonia), high level of blood sugar, feeling tired or weak, low white blood cells, inflammation of lung tissue, diarrhea, 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 “supporting,” “support,” “can,” “has not yet,” “will,” or similar terms, or by express or
implied discussions regarding potential new marketing approvals, 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 manufacturing 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, cost-saving generic pharmaceuticals, preventive vaccines, over-the-counter and animal health products. Novartis is the only global company with leading positions in these areas. In 2013, the Group achieved net sales of USD 57.9 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 133,000 full-time-equivalent associates and sell products in more than 150 countries around the world. For more information, please visit http://www.novartis.com.

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References

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