

# Early Data Presented at ASCO Show Potential of RAD001 to Enhance Efficacy of, and Overcome Resistance to, Breast Cancer Treatments

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- - Randomized Phase II data show RAD001 significantly increased efficacy of letrozole tablets in women with newly diagnosed hormone-positive breast cancer
- - Phase I studies suggest RAD001 may help overcome a major pathway of resistance to trastuzumab
- - Novartis to further explore potential of RAD001 in breast cancer by initiating new trial in early 2009

EAST HANOVER, N.J., June 2 /PRNewswire/ -- Early proof-of-concept studies presented today show RAD001 (everolimus) may offer a novel treatment strategy for breast cancer by enhancing the efficacy of, and overcoming resistance to, several commonly used breast cancer treatments.

Findings from a Phase II study show that RAD001 enhances tumor shrinkage when given in combination with letrozole tablets (Femara®) to postmenopausal women with newly diagnosed estrogen receptor-positive (ER+) breast cancer. Further, initial results from two Phase I trials in which RAD001 was combined with trastuzumab (Herceptin®) and chemotherapy agents suggest that the addition of RAD001 overcame resistance to trastuzumab. The combination appears highly active, achieving complete responses in a few patients and partial responses or stable disease in a majority of patients.

These results were among several studies of RAD001 presented at the 44th annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago, Illinois, US. RAD001 is an investigational once-daily oral therapy that may offer a new approach to cancer treatment by continuously inhibiting the mTOR protein, a central regulator of tumor cell division and blood vessel growth in cancer cells.

"The mTOR pathway is a major route to resistance in targeted cancer therapies, and the early data in combination with Herceptin and chemotherapy demonstrate proof of concept that by inhibiting mTOR we may be able to overcome resistance to these medicines," said David Epstein, CEO and President of Novartis Oncology. "These remarkable early findings support exploring the potential of RAD001 in addressing unmet medical needs in women with HER2+ breast cancer in a larger randomized clinical trial."

For breast cancer patients whose disease becomes resistant to available drugs, identifying the mechanism of resistance is important for restoring activity to treatment. Preclinical studies have shown that RAD001, an inhibitor of mTOR, acts on the pathway that mediates trastuzumab resistance and has the potential to help restore response in patients who are refractory to therapy. RAD001 works through direct antitumor activity as well as through its influence on two of the most important pathways for breast cancer, the estrogen receptor and the HER2/neu pathways.

Based on these data, Novartis will initiate a new trial to evaluate the potential of RAD001 in breast cancer in early 2009. Plans for this trial are ongoing and will be announced at a later date.

"In patients with hormone-sensitive breast cancer, the results from the randomized Phase II study are exciting because they show that adding RAD001 to initial treatment with letrozole tablets may improve outcomes for

early-stage breast cancer patients," said Professor Jose Baselga, MD, Hospital Vall D'Hebron, Barcelona, Spain. "Taken together, the results of the three trials announced today indicate that RAD001 has a promising potential across various subsets of breast cancer."

#### Study results

ABSTRACT #530 - "Improved clinical and cell cycle response with an mTOR inhibitor, daily oral RAD001 (everolimus) plus letrozole versus placebo plus letrozole in a randomized phase II neoadjuvant trial in ER+ breast cancer"

Jose Baselga, MD, Hospital Vall D'Hebron, Barcelona, Spain

This randomized, double-blind, Phase II placebo-controlled trial of 270 postmenopausal women found that RAD001 10 mg increased both the clinical and the cell cycle efficacy of letrozole tablets 2.5 mg in the treatment of newly diagnosed ER+ breast cancer. The overall clinical response rate with RAD001 in combination with letrozole tablets was clinically important as compared to letrozole tablets alone (68% versus 59%, one-sided  $P=0.062$ , respectively). The results were also confirmed by ultrasound (58% versus 47%, one-sided  $P=0.035$ , respectively). In addition, cell cycle response in the RAD001/letrozole treatment arm, as measured by major reduction in Ki67, an indication of tumor cell proliferation, was twice that as measured in the placebo/letrozole treatment arm.

Adverse events in the RAD001/letrozole treatment arm were manageable. The most frequent grade 3/4 adverse events in the RAD001/letrozole treatment arm were high blood sugar (5%), mouth sores (2%), pneumonitis (2%) and infections (2%). The rate of grade 3/4 adverse events was 23% in the RAD001/letrozole treatment arm versus 4% in the placebo/letrozole treatment arm. All three cases of grade 3 pneumonitis completely resolved after discontinuation of RAD001.

ABSTRACT #1003 - "Multicenter phase I clinical trial of daily and weekly RAD001 (everolimus) in combination with weekly paclitaxel and trastuzumab in patients with HER2-overexpressing metastatic breast cancer with prior resistance to trastuzumab"

Fabrice Andre, MD, PhD, Institut Gustave Roussy, Villejuif, France

This multicenter Phase I-II trial evaluated daily RAD001 (5 mg, 10 mg) and weekly RAD001 (30 mg, 50 mg and 70 mg) regimens in combination with paclitaxel (80 mg/m<sup>2</sup>, IV over 60 min on days 1, 8 and 15 q4w) and trastuzumab (4 mg/kg loading dose, IV over 90 min on day 1 [if patient was not already receiving trastuzumab], followed by weekly 2 mg/kg IV over 30 min) in heavily pretreated patients with HER2-overexpressing metastatic breast cancer with prior resistance to trastuzumab. Thirteen heavily pretreated patients were assessable for efficacy to date: treatment arms included five patients assigned to RAD001 5 mg daily, one to 10 mg daily and seven to 30 mg weekly. Among the five patients evaluated in the 5 mg daily arm, four patients had confirmed partial responses (including three complete responses, yet to be confirmed); the one patient on 10 mg daily showed stable disease at the first assessment; and of the seven patients evaluated in the RAD001 weekly treatment arm, two patients had confirmed partial response and four patients had long disease stabilization, including complete disappearance of brain metastasis in one patient. The most commonly reported adverse events were neutropenia and mouth sores.

"These preliminary results are very exciting given that the women in the study were heavily pretreated, had documented resistance to trastuzumab and most were also taxane-resistant," said Fabrice Andre, MD, PhD, Institut Gustave Roussy, Villejuif, France. "If confirmed in Phase II and III clinical trials, RAD001 will be a major addition to the existing arsenal of breast cancer therapy."

ABSTRACT #1057 - "Multicenter phase I clinical trial of daily and weekly RAD001 (everolimus) in combination with vinorelbine and trastuzumab in patients with HER2-overexpressing metastatic breast cancer with prior resistance to trastuzumab"

Guy H. Jerusalem, MD, Sart-Tilman, Liege, Belgium

This multicenter Phase I trial evaluated daily RAD001 (5 mg, 10 mg) and weekly RAD001 (20 mg, 30 mg, 50 mg and 70 mg) regimens. Patients were administered vinorelbine (25 mg/m<sup>2</sup>, IV over 10-15 min on days 1 and 8 q3w) and trastuzumab (4 mg/kg loading dose, IV over 90 min on day 1 [if patient was not already receiving trastuzumab], followed by weekly trastuzumab 2 mg/kg IV over 30 min). Twenty-two heavily pretreated patients were evaluated for efficacy to date: 11 allocated to RAD001 5 mg daily, six to RAD001 20 mg weekly and five to RAD001 30 mg weekly treatment arms. All patients entering the study had progression on or shortly after treatment with trastuzumab and all had received prior taxane. The median number of prior chemotherapy regimens was 3 (range: 1-5). A preliminary efficacy analysis in the 11 patients enrolled in the RAD001 5 mg treatment arm showed that one patient had a confirmed complete response (35+ weeks), one patient had a confirmed partial response (29+ weeks) and six patients had stable disease (9+, 12, 17+, 18+, 29, 39 weeks). Grade 2 and 3 mouth sores and grade 3 and 4 neutropenia were seen. Among 11 patients evaluated for preliminary efficacy in the RAD001 weekly arms, one had partial response (29+ weeks) and seven had stable disease (16+, 17+, 19, 27, 35+, 46+, 53+ weeks). Similar to the daily arm, grade 2 and 3 mouth sores and grade 3 and 4 neutropenia were seen.

#### About breast cancer

Breast cancer affects one in eight women in the US. It is the second leading cause of cancer-related death, expected to claim the lives of 41,000 people in 2008, and is the most common form of cancer accounting for 32% of cancer diagnoses. In fact, every three minutes a woman in the US is diagnosed with breast cancer.

Inside a breast there are many lobes, ducts and vessels that support several important functions in the body, including reproductive needs and fighting infection. In breast cancer, some of the cells in the breast begin growing abnormally and divide more rapidly than healthy cells. The quick division of cells may cause spreading through the breast, to the lymph or to other parts of the body.

#### About RAD001

RAD001, an oral inhibitor of mTOR, is an investigational drug being studied in multiple tumor types. In cancer cells, RAD001 inhibits mTOR, a protein that acts as a central regulator of tumor cell division, cell metabolism and blood vessel growth. RAD001 is a once-daily oral therapy that provides continuous inhibition of mTOR.

In addition to breast cancer, RAD001 is presently being evaluated in renal cell carcinoma; neuroendocrine tumors; lymphoma, lung, stomach and liver cancers, in addition to other cancers; and in tuberous sclerosis complex as a single agent or in combination with existing cancer therapies.

As an investigational compound, the safety and efficacy profile of RAD001 has not yet been established in oncology. Access to RAD001 is available only through carefully controlled and monitored clinical trials. These trials are designed to better understand the potential benefits and risks of the compound. Because of the uncertainty of clinical trials, there is no guarantee that RAD001 will ever be commercially available for oncology indications anywhere in the world. Everolimus is approved under the trade name Certican® for the prevention of organ rejection in heart and kidney transplant recipients. Certican was first approved in the EU in 2003 and is available in more than 60 countries.

#### About Femara

Femara® (letrozole tablets) is approved for the adjuvant (following surgery) treatment of postmenopausal women with hormone receptor-positive early stage breast cancer. The benefits of Femara in clinical trials are based on 24 months of treatment. Further follow-up will be needed to determine long-term results, safety and efficacy.

Femara is also approved for the extended adjuvant treatment of early stage breast cancer in postmenopausal women who are within three months of completion of five years of tamoxifen therapy. The benefits of Femara in clinical trials are based on 24 months of treatment. Further follow-up will be needed to determine long-term results, including side effects.

In addition, Femara is approved for the treatment of postmenopausal women with estrogen receptor-positive or estrogen receptor-unknown breast cancer that has spread to another part of the body (metastatic cancer).

#### Important Safety Information

You should not take Femara if you are premenopausal. Your doctor should discuss the need for adequate birth control if you have the potential to become pregnant, if you are not sure of your postmenopausal status, or if you recently became postmenopausal. Femara is only indicated in postmenopausal women. Talk to your doctor if you are allergic to Femara or any of its ingredients. You should not take Femara if you are pregnant as it may cause fetal harm. Some women reported fatigue and dizziness with Femara. Until you know how it affects you, use caution before driving or operating machinery. Some patients taking Femara had an increase in cholesterol. Additional follow-up is needed to determine the risk of bone fracture associated with long-term use of Femara.

In the adjuvant setting, commonly reported side effects are generally mild to moderate. The most common side effects seen with Femara include hot flashes, joint pain, night sweats, weight gain, nausea, tiredness, other heart-related events and bone fractures. Other less commonly reported side effects include vaginal bleeding, blood clots, other cancers, osteoporosis, stroke, heart attack and endometrial cancer.

In the extended adjuvant setting, commonly reported side effects are generally mild to moderate. Commonly reported side effects for Femara include hot flashes, fatigue, joint pain, headache, increase in sweating, swelling due to fluid retention, increase in cholesterol, dizziness, constipation, nausea, cardiovascular ischemic events, muscle pain, osteoporosis, arthritis and bone fracture.

In the metastatic cancer setting, commonly reported side effects are generally mild to moderate and may include bone pain, hot flashes, back pain, nausea, joint pain, shortness of breath, tiredness, coughing, constipation, limb pain, chest pain and headache.

#### Disclaimer

The foregoing release contains forward-looking statements that can be identified by terminology such as "potential," "suggest," "may," "to further explore," "will," "plans," "promising," or similar expressions, or by express or implied discussions regarding potential future regulatory filings or approvals for RAD001 or regarding potential future revenues from RAD001. Such forward-looking statements reflect the current views of the Company regarding future events, and involve known and unknown risks, uncertainties and other factors that may cause actual results with RAD001 to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that RAD001 will be submitted for approval, or approved for sale in any market for any oncology indication. Nor can there be any guarantee that RAD001 will achieve any particular levels of revenue in the future. In particular, management's expectations regarding RAD001 could be affected by, among other things, unexpected clinical trial results, including unexpected new clinical data and unexpected additional analysis of existing clinical data; unexpected

regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain patent or other proprietary intellectual property protection; government, industry and general public pricing pressures; competition in general, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those anticipated, believed, estimated, or expected. 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 Pharmaceuticals Corporation researches, develops, manufactures and markets leading innovative prescription drugs used to treat a number of diseases and conditions, including those in the cardiovascular, metabolic, cancer, organ transplantation, central nervous system, dermatological, GI and respiratory areas. The company's mission is to improve people's lives by pioneering novel healthcare solutions.

Located in East Hanover, New Jersey, Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG (NYSE: NVS), which provides healthcare solutions that address the evolving needs of patients and societies. Focused solely on growth areas in healthcare, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, cost-saving generic pharmaceuticals, preventive vaccines and diagnostic tools, and consumer health products. Novartis is the only company with leading positions in these areas. In 2007, the Group's continuing operations (excluding divestments in 2007) achieved net sales of USD 38.1 billion and net income of USD 6.5 billion. Approximately USD 6.4 billion was invested in R&D activities throughout the Group. Headquartered in Basel, Switzerland, Novartis Group companies employ approximately 98,000 full-time associates and operate in over 140 countries around the world. For more information, please visit <http://www.novartis.com/>.

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