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RAD001 Shows Potential to Reverse Resistance to Herceptin®* in Metastatic Breast Cancer Patients, Leading to Phase III Trial

Dec 13, 2008

- - RAD001 combined with Herceptin and chemotherapy in two separate Phase I trials halted tumor growth in 77% and 62% of patients, respectively
- - Novartis to start Phase III clinical trial program to explore RAD001, an oral mTOR inhibitor, as combination treatment with Herceptin and chemotherapy

EAST HANOVER, N.J., Dec. 12 /PRNewswire/ -- New data from two early clinical studies show that RAD001® (everolimus) may overcome resistance to Herceptin® (trastuzumab)* in women with HER2-positive metastatic breast cancer. These results support the initiation of a Phase III clinical trial program to fully explore the potential of RAD001 (proposed brand name Afinitor®) in breast cancer.

Two Phase I studies were presented today during the CTRC-AACR San Antonio Breast Cancer Symposium. Initial results from both studies were released earlier this year at the American Society of Clinical Oncology (ASCO) annual meeting.

Updated results from the first Phase I trial show that the combination of RAD001 with Herceptin and weekly Taxol® (paclitaxel)** halted tumor growth in 77% of patients with HER2-positive metastatic breast cancer with documented resistance to Herceptin. In addition, the data demonstrated the first complete response in the trial.

In addition, updated data from the second Phase I study show promising anticancer activity for RAD001 in combination with Herceptin and Navelbine® (vinorelbine)*** in heavily pretreated Herceptin-resistant patients with HER2-positive metastatic breast cancer. In the study, RAD001 in combination with Herceptin and Navelbine halted tumor growth in 62% of patients.

"Data presented at this meeting affirm the potential of RAD001 to reverse Herceptin resistance and restore patient response to treatment," said Ruth O'Regan, MD, Emory University School of Medicine, Atlanta, GA. "These findings are important for patients with HER2-positive metastatic breast cancer who develop resistance to Herceptin."

Preclinical data have shown that RAD001, an inhibitor of mTOR, acts on the pathway that mediates Herceptin resistance and has the potential to help restore response in these patients. RAD001 works through direct antitumor activity and through its influence on two of the most important pathways for breast cancer, the erbB receptor and the HER2 pathways.

"We are encouraged by the benefit RAD001 provided to advanced breast cancer patients in these early trials," said Alessandro Riva, MD, Executive Vice President & Global Head of Development, Novartis Oncology. "Novartis is committed to further evaluating the potential of RAD001 in combination with Herceptin as a new treatment regimen in breast cancer, as well as studying its role in treating other tumor types."

Novartis will initiate a worldwide Phase III clinical trial program to further evaluate the potential of RAD001 in combination with Herceptin and chemotherapy in patients with HER2-positive metastatic breast cancer. To

learn more about the trial, please visit http://mail.breastcancerresearchstudy.com/, or speak to your doctor.

Study details: abstract #3119

An open-label, multicenter Phase I dose escalation trial evaluated daily RAD001 (5 mg, 10 mg) and weekly RAD001 (30 mg, 50 mg and 70 mg) regimens in combination with Taxol (80 mg/m2 IV over 60 min on days 1, 8 and 15 every 28 days) and Herceptin (2 mg/kg IV over 30 min) in heavily pretreated patients with HER2-positive metastatic breast cancer with prior resistance to Herceptin.

Across treatment arms, there was an overall disease control rate of 77% (complete response/ partial response/ stable disease greater than or equal to 16 weeks). Twenty-two heavily pretreated patients were evaluable for efficacy: treatment arms included five patients assigned to RAD001 5 mg daily, eight to RAD001 10 mg daily and nine to RAD001 30 mg weekly. Among the five patients evaluated in the 5 mg daily treatment arm, one patient had a complete response and four patients had partial responses. In the 10 mg daily treatment arm, one patient had a partial response, six patients had stable disease and one patient had progressive disease. Among the nine patients evaluated in the 30 mg weekly treatment arm, three patients had partial responses, five patients had stable disease and one patient had progressive disease. The critical dose- limiting toxicities occurring in the first cycle of treatment included febrile neutropenia, oral mucositis and confusion occurring in the 5 mg daily, 10 mg daily and 30 mg weekly treatment groups, respectively. The most commonly reported grade 3/4 adverse events (greater than or equal to 10%) suspected of being related to study treatment were neutropenia, lymphopenia, stomatitis, leukopenia, alopecia and anemia.

Study details: abstract #406

An open-label, multicenter Phase I trial evaluated daily RAD001 (2.5 mg, 5 mg and 10 mg) and weekly RAD001 (20 mg, 30 mg, 50 mg and 70 mg) in combination with Navelbine (25 mg/m2 IV over 10-15 min on days 1 and 8 every 21 days) and Herceptin (2 mg/kg IV over 30 min). All patients entering the study had progression on, or shortly after, treatment with Herceptin and all had received prior taxane. The median number of prior chemotherapy regimens was 3 (range: 1-5).

Across treatment arms, there was an overall disease control rate of 62%. Thirty-four heavily pretreated patients were evaluated to date (fifteen patients assigned to 5 mg daily, six to 20 mg weekly, and thirteen to 30 mg weekly). Among the fifteen patients in the 5 mg daily treatment arm, one patient had a complete response, two patients had partial responses, nine patients had stable disease and three patients had progressive disease. Among the six patients in the 20 mg weekly treatment arm, one patient had a partial response, three patients had stable disease and two patients had progressive disease. Among the thirteen patients evaluated in the 30 mg weekly treatment arm, two patients had partial responses, nine patients had stable disease and two patients had progressive disease. The critical dose-limiting toxicities (i.e., dose-limiting toxicities in cycle 1) occurring in the 5 mg daily treatment group included grade 3/4 neutropenia, grade 3 stomatitis, grade 3 fatigue and grade 3 anorexia. In the 30 mg weekly treatment group, grade 3/4 neutropenia was the only critical dose-limiting toxicity. There were no critical dose-limiting toxicities in the 20 mg weekly RAD001 treatment arm. The most commonly reported grade 3/4 adverse events (greater than or equal to 10%) suspected of being related to study treatment were neutropenia, stomatitis and leukopenia.

About breast cancer

In the US, invasive breast cancer affects one in eight women. It is the second most common cancer among women in the US and the second leading cause of cancer-related death in women. Breast cancer is expected to claim the lives of approximately 40,500 women in 2008.

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 nodes or to other parts of the body.

About RAD001

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

The safety and efficacy profile of RAD001 has not yet been established in oncology and there is no guarantee that RAD001 will become commercially available for oncology indications. The active ingredient in RAD001 is everolimus. The active ingredient everolimus, is available in different dosage strengths 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. Certican is not approved in the US.

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

Disclaimer

The foregoing release contains forward-looking statements that can be identified by terminology such as "potential," "to start," "to explore," "may," "to fully explore," "promising," "encouraged," "committed," "will," "to further evaluate," or similar expressions, or by express or implied discussions regarding potential regulatory filings or marketing approvals for RAD001 or regarding potential future revenues from RAD001. You should not place undue reliance on these statements. Such forward-looking statements reflect the current views of management 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 approved for sale for any oncology indication in any market. 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; competition in general; government, industry and general public pricing pressures; the impact that the foregoing factors could have on the values attributed to the Novartis Group's assets and liabilities as recorded in the Group's consolidated balance sheet, 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 Pharmaceuticals Corporation

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 which provides healthcare solutions that address the evolving needs of patients and societies. Focused solely on healthcare, Novartis offers a diversified portfolio to best meet these needs, innovative medicines, cost-saving generic pharmaceuticals, preventive vaccines, 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 97,000 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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* In the US, Herceptin is a registered trademark of Genentech, Inc. Internationally, Herceptin is a registered trademark of Roche.

** Taxol is a registered trademark of Bristol-Myers Squibb Company.

*** Navelbine is a registered trademark of Pierre Fabre Pharmaceuticals Inc.

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