Puma Biotechnology Announces I-SPY 2 Phase II Study of Neratinib Published in The New England Journal of Medicine

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LOS ANGELES--(BUSINESS WIRE)--Puma Biotechnology, Inc. (NYSE: PBYI), a biopharmaceutical company, announced that the positive results from the I-SPY 2 Phase II clinical trial of neratinib for the neoadjuvant treatment of breast cancer were published in the July 7 issue of *The New England Journal of Medicine*.

The I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis 2) is a randomized Phase II clinical trial for women with newly diagnosed Stage 2 or higher (tumor size at least 2.5 cm) breast cancer that addresses whether adding investigational drugs to standard chemotherapy in the neoadjuvant setting is better than standard chemotherapy. The primary endpoint is pathological complete response (pCR) in the breast and the lymph nodes at the time of surgery. The goal of the trial is to match investigational regimens with patient subsets on the basis of molecular characteristics (referred to as biomarker signatures) that benefit from the regimen. The trial enrolled patients who had a high risk of relapse using up-front tumor profiling (including tumor size, hormone receptor status (HR), HER2 status, and the MammaPrint 70-gene signature test).

The I-SPY 2 TRIAL involves an adaptive trial design based on Bayesian predictive probability that a regimen will be shown to be statistically superior to standard neoadjuvant therapy in an equally randomized 300-patient confirmatory trial. Regimens that have a high Bayesian predictive probability of showing superiority in at least one of 10 predefined signatures graduate from the trial. Regimens are dropped for futility if they show a low predictive probability of showing superiority over standard therapy in all 10 signatures. A maximum total of 120 patients can be assigned to each experimental regimen. A regimen can graduate early and at any time after having 60 patients assigned to it.

The neratinib-containing regimen (neratinib plus paclitaxel followed by doxorubicin and cyclophosphamide) graduated from the I-SPY 2 TRIAL based on having a high probability of success in Phase III with a signature of HER2-positive/HR-negative. In this group, treatment with the neratinib-containing regimen resulted in an estimated pCR rate of 55.6% compared to the control arm (standard neoadjuvant chemotherapy: paclitaxel in combination with Herceptin (trastuzumab) followed by doxorubicin and cyclophosphamide) which had an estimated pCR rate of 32.6%. The Bayesian probability of superiority for the neratinib-containing regimen (compared to standard therapy) is 94.9%, which is analogous to a one-sided p-value of 0.051. In addition, the Bayesian predictive probability of showing statistical superiority in a 300-patient Phase III randomized trial of paclitaxel plus neratinib versus paclitaxel plus trastuzumab, both followed by doxorubicin/cyclophosphamide, is 79.1%.

There were 115 patients assigned to neratinib in the trial, including 65 patients who were HER2-positive. For the patients in the trial who were HER2-positive (including those who were either hormone receptor-positive or negative), treatment with the neratinib-containing regimen resulted in an estimated pCR rate of 39.4% compared to the control arm, which demonstrated an estimated pCR rate of 22.8%. The Bayesian probability of superiority for the neratinib-containing regimen is 95.4%, which is analogous to a p-value of 0.046. In addition, the Bayesian predictive probability of showing statistical superiority in a 300-patient Phase III randomized trial of paclitaxel plus neratinib versus paclitaxel plus trastuzumab is 72.7%.

Patients in the I-SPY 2 TRIAL were screened using the MammaPrint 70-gene signature test. The median MammaPrint score from the patients in the previous I-SPY 1 TRIAL who fit the eligibility criteria for I-SPY2 was used as a predefined stratification factor for the I-SPY 2 TRIAL. Patients in I-SPY 2 were stratified as either MammaPrint High (below the median from I-SPY 1) or MammaPrint Ultra High (above the median from I-SPY 1). For the 41 neratinib treated patients in the trial who were MammaPrint Ultra High (80.5% of which were HER2 negative), treatment with the neratinib-containing regimen resulted in an estimated pCR rate of 47.5% compared to the control arm, which demonstrated an estimated pCR rate of 29.4%. The Bayesian probability of superiority for the neratinib-containing regimen is 93.3%, which is analogous to a p-value of 0.067. In addition, the Bayesian predictive probability of showing statistical superiority in a 300-patient Phase III randomized trial of paclitaxel plus neratinib versus paclitaxel, alone for HER2-negative patients or in combination with trastuzumab for the HER2-positive patients, is 71.8%.

The most frequently observed severe adverse event in the trial was diarrhea. In the neratinib treated arm of the trial 38% of the patients experienced grade 3/4 diarrhea while 4% of the patients in the control arm experienced grade 3/4 diarrhea. In several clinical trials subsequent to I-SPY 2, high dose loperamide significantly reduced the incidence of grade 3/4 diarrhea.

The I-SPY 2 TRIAL is a collaborative effort among academic investigators from approximately 20 major cancer research centers across the country, the U.S. Food and Drug Administration, Quantum Leap Healthcare Collaborative, and the Foundation for the National Institutes of Health (FNIH) Cancer Biomarkers Consortium. Major supporters include The Safeway

Foundation and the Bill Bowes Foundation.

“I-SPY 2 is an innovative adaptive clinical trial that enabled the investigators to evaluate several agents in the neoadjuvant setting,” said Alan H. Auerbach, Chief Executive Officer and President. “We were very pleased with the activity of neratinib in I-SPY 2 as it represents the first clinical data on neratinib in the neoadjuvant treatment of breast cancer and suggests that the combination of paclitaxel plus neratinib has potent activity for the treatment of HER2-positive breast cancer and a subset of patients with HER2-negative breast cancer.”

I-SPY 2 Principal Investigators Dr. Laura Esserman, Director of the Carol Franc Buck Breast Care Center and Co-Leader of the Breast Oncology Program at the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, and Dr. Donald Berry, Professor of the Department of Biostatistics at the University of Texas MD Anderson Cancer Center, both expressed their enthusiasm for moving successful agents into confirmatory Phase 3 trials. "We are excited for the opportunity to confirm these promising results in I-SPY 3 in our quest to get better treatments to those women who stand to benefit most. I SPY 3 represents a much needed approach to the conduct of Phase 3 trials,” said Laura Esserman.

About Puma Biotechnology

Puma Biotechnology, Inc. is a biopharmaceutical company with a focus on the development and commercialization of innovative products to enhance cancer care. The Company in-licenses the global development and commercialization rights to three drug candidates—PB272 (neratinib (oral)), PB272 (neratinib (intravenous)) and PB357. Neratinib is a potent irreversible tyrosine kinase inhibitor that blocks signal transduction through the epidermal growth factor receptors, HER1, HER2 and HER4. Currently, the Company is primarily focused on the development of the oral version of neratinib, and its most advanced drug candidates are directed at the treatment of HER2-positive breast cancer. The Company believes that neratinib has clinical application in the treatment of several other cancers as well, including non-small cell lung cancer and other tumor types that over-express or have a mutation in HER2.

Further information about Puma Biotechnology can be found at www.pumabiotechnology.com.

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