# News Release

## Puma Biotechnology Announces Publication of Interim Results of Phase II CONTROL Trial in Annals of Oncology

*- CONTROL Trial Investigates Anti-diarrheal Strategies Including Dose Escalation in Neratinib-treated Patients with Early Stage HER2-positive Breast Cancer*

*- Dose Escalation Resulted in Reduced Rate, Severity and Duration of Grade ≥3 Diarrhea Compared to Phase III ExteNET Trial, Lower Diarrhea-related Discontinuations and Dose Reductions in Multiple CONTROL Cohorts*

**LOS ANGELES, Calif., Aug. 19, 2020** – Puma Biotechnology, Inc. (NASDAQ: PBYI), a biopharmaceutical company, announced the publication of interim results from its Phase II CONTROL trial of neratinib in the September 2020 Issue (Volume 31, Issue 9) of *Annals of Oncology*. The publication entitled, "Improved Tolerability of Neratinib in Patients with HER2+ Early-Stage Breast Cancer: Diarrheal Toxicity in the CONTROL Trial," can also be accessed online here.

Previous studies of neratinib in HER2-positive early stage breast cancer showed that diarrhea was the most common adverse event (AE) associated with neratinib treatment.

The international, open-label, sequential-cohort Phase II CONTROL trial is investigating several strategies to improve neratinib tolerability. Researchers used data on incidence, duration and onset of diarrhea in the pivotal, multi-center, randomized, double-blind, placebo-controlled Phase III ExteNET trial as a historical comparison. In the ExteNET trial, prophylactic use of anti-diarrheal medication was not mandatory.

The interim results of the CONTROL trial discussed in this publication demonstrate that neratinib tolerability can be significantly improved using a variety of anti-diarrheal strategies. The most significant impact was seen using a dose escalation strategy with loperamide as needed, which included utilizing a lower dose of neratinib during the first two weeks of a 52-week treatment period. In the dose escalation cohort, of which patients completed one year of treatment or had the highest median treatment duration compared to other cohorts, grade 3 diarrhea was reduced by over 60% (CONTROL 15% versus ExteNet 40%), discontinuations by over 80% (CONTROL 3% versus ExteNet 17%), the need to dose reduce by almost 90% (CONTROL 3% versus ExteNet 26%) and no patients were hospitalized.

"Achieving a balance between treatment benefit and adverse events is an important clinical consideration in breast cancer, and the CONTROL trial demonstrates that neratinib tolerability can be most optimally improved with dose escalation, which can ultimately improve patient adherence to treatment," said Carlos H. Barcenas, M.D., M.S., associate professor in the department of breast medical oncology at The University of Texas MD Anderson Cancer Center. "These results, and specifically the lessened discontinuation of patients in early neratinib treatment, suggest that managing diarrhea during neratinib treatment allows more patients to receive the potential efficacy benefits of extended adjuvant neratinib therapy."

Alan H. Auerbach, Chief Executive Officer and President of Puma Biotechnology, said, "We are pleased with the marked reduction in both the incidence of grade 3 diarrhea and the decrease in discontinuation of

therapy demonstrated in the dose-escalation cohort of the CONTROL trial. We believe these are important results and should lead to improved tolerability for neratinib in early stage breast cancer patients. We remain committed to the fight against breast cancer, both in the early stage as well as in the metastatic setting."

The CONTROL trial initially tested high-dose loperamide prophylaxis given for the first two cycles (56 days) of adjuvant treatment (12 mg on days 1-14, 8 mg on days 15-56 and as needed thereafter). The CONTROL trial was then expanded to include four additional cohorts. One cohort received the combination of loperamide and budesonide, the second cohort received the combination of loperamide plus colestipol, the third cohort received colestipol plus loperamide as needed and the fourth cohort did not use any antidiarrheal drugs as mandatory prophylaxis but instead used a dose escalation schedule plus loperamide as needed during the first month of neratinib treatment. Budesonide is a locally acting corticosteroid that Puma believes targets the inflammation identified in a preclinical model of neratinib-induced diarrhea, and colestipol is a bile acid sequestrant that Puma believes targets potential bile acid malabsorption that could result from such inflammation. The dose escalation schedule involved treating with neratinib with loperamide as needed at 120 mg per day for the first week, 160 mg per day for the second week and 240 mg per day starting at week three and until the end of treatment.

**About HER2-Positive Breast Cancer**

Up to 20% of patients with breast cancer tumors over-express the HER2 protein (HER2-positive disease) and in the ExteNET study, 57% of patients were found to have tumors that were hormone-receptor positive. HER2-positive breast cancer is often more aggressive than other types of breast cancer, increasing the risk of disease progression and death. Although research has shown that trastuzumab can reduce the risk of early stage HER2-positive breast cancer recurring, up to 25% of patients treated with trastuzumab experience recurrence within 10 years, the majority of which are metastatic recurrences.

**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. Puma in-licenses the global development and commercialization rights to PB272 (neratinib, oral), PB272 (neratinib, intravenous) and PB357. Neratinib, oral was approved by the U.S. Food and Drug Administration in 2017 for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, following adjuvant trastuzumab-based therapy, and is marketed in the United States as NERLYNX® (neratinib) tablets. In February 2020, NERLYNX was also approved by the FDA in combination with capecitabine for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. NERLYNX was granted marketing authorization by the European Commission in 2018 for the extended adjuvant treatment of adult patients with early stage hormone receptor-positive HER2-overexpressed/amplified breast cancer and who are less than one year from completion of prior adjuvant trastuzumab-based therapy. NERLYNX is a registered trademark of Puma Biotechnology, Inc.

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

**IMPORTANT SAFETY INFORMATION**

**NERLYNX® (neratinib) tablets, for oral use**

**INDICATIONS AND USAGE:** NERLYNX is a kinase inhibitor indicated:

- As a single agent, for the extended adjuvant treatment of adult patients with early-stage HER2-positive breast cancer, to follow adjuvant trastuzumab-based therapy.
- In combination with capecitabine, for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer, who have received two or more prior anti-HER2 based regimens in the metastatic setting.

**CONTRAINDICATIONS:** None

**WARNINGS AND PRECAUTIONS:**

- **Diarrhea:** Aggressively manage diarrhea. If diarrhea occurs despite recommended prophylaxis, treat with additional antidiarrheals, fluids, and electrolytes as clinically indicated. Withhold NERLYNX in patients experiencing severe and/or persistent diarrhea. Permanently discontinue NERLYNX in patients experiencing Grade 4 diarrhea or Grade ≥ 2 diarrhea that occurs after maximal dose reduction.
- **Hepatotoxicity:** Monitor liver function tests monthly for the first 3 months of treatment, then every 3 months while on treatment and as clinically indicated. Withhold NERLYNX in patients experiencing Grade 3 liver abnormalities and permanently discontinue NERLYNX in patients experiencing Grade 4 liver abnormalities.
- **Embryo-Fetal Toxicity:** NERLYNX can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception.

**ADVERSE REACTIONS:**

The most common adverse reactions (reported in ≥ 5% of patients) were:

- NERLYNX as a single agent: Diarrhea, nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite, muscle spasms, dyspepsia, AST or ALT increased, nail disorder, dry skin, abdominal distention, epistaxis, weight decreased, and urinary tract infection.
- NERLYNX in combination with capecitabine: Diarrhea, nausea, vomiting, decreased appetite, constipation, fatigue/asthenia, weight decreased, dizziness, back pain, arthralgia, urinary tract infection, upper respiratory tract infection, abdominal distention, renal impairment, and muscle spasms.

**To report SUSPECTED ADVERSE REACTIONS, contact Puma Biotechnology, Inc. at 1-844-NERLYNX (1-844-637-5969) and www.NERLYNX.com or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.**

**DRUG INTERACTIONS:**

- Gastric acid reducing agents: Avoid concomitant use with proton pump inhibitors. When patients require gastric acid reducing agents, use an $H_2$-receptor antagonist or antacid. Separate NERLYNX by at least 3 hours with antacids. Separate NERLYNX by at least 2 hours before or 10 hours after $H_2$-receptor antagonists.
- Strong CYP3A4 inhibitors: Avoid concomitant use.
- Moderate CYP3A4 and P-glycoprotein (P-gp) dual inhibitors: Avoid concomitant use.
- Strong or moderate CYP3A4 inducers: Avoid concomitant use.
- P-glycoprotein (P-gp) substrates: Monitor for adverse reactions of narrow therapeutic agents that are P-gp substrates when used concomitantly with NERLYNX.

**USE IN SPECIFIC POPULATIONS:**

• **Lactation:** Advise women not to breastfeed.

**Please see Full Prescribing Information for additional safety information.**

To help ensure patients have access to NERLYNX, Puma has implemented the Puma Patient Lynx support program to assist patients and healthcare providers with reimbursement support and referrals to resources that can help with financial assistance. More information on the Puma Patient Lynx program can be found at

www.NERLYNX.com or 1-855-816-5421.

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