PUMA BIOTECHNOLOGY, INC.
Form 8-K
April 06, 2017

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, DC 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d)

of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): April 2, 2017

PUMA BIOTECHNOLOGY, INC.

(Exact Name of Registrant as Specified in its Charter)

Delaware	**001-35703**	**77-0683487**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

10880 Wilshire Boulevard, Suite 2150

Los Angeles, California 90024

(Address of principal executive offices) (Zip Code)

(424) 248-6500

(Registrant s telephone number, including area code)

N/A

(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Item 8.01 Other Events.

Expanded Access Program for PB272 (Neratinib) for U.S. Patients with HER2-Positive Breast Cancer or HER2-Mutated Cancers

On April 2, 2017, Puma Biotechnology, Inc. (the Company) announced that it has initiated an expanded access program (EAP) in the United States to provide its investigational therapy, PB272 (neratinib), to patients with HER2-positive breast cancer or HER2-mutated cancers. The program will provide access to neratinib for the treatment of early stage HER2-positive breast cancer (extended adjuvant setting), HER2-positive metastatic breast cancer and HER2-mutated solid tumors. Patients must not be able to participate in any ongoing neratinib clinical trial to qualify for the Company s expanded access program.

The U.S. Food and Drug Administration (FDA) permits expanded access to investigational drugs for treatment use for patients with serious or immediately life-threatening diseases or conditions who do not otherwise qualify for participation in a clinical trial and lack satisfactory therapeutic alternatives.

Caligor Opco LLC, which administers the managed access program for neratinib, will also manage the U.S. expanded access program by providing regulatory and logistical support.

Phase II SUMMIT Trial of PB272 for ERBB2 (HER2) Mutant, HER2 Non-Amplified, Metastatic Cancer

On April 2, 2017, the Company announced that results from an ongoing Phase II clinical trial of neratinib were presented at the 2017 American Association for Cancer Research Annual Meeting (the 2017 AACR Annual Meeting). The presentation entitled, Neratinib in HER2 or HER3 mutant solid tumors: SUMMIT, a global, multi-histology, open-label, phase 2 basket study, was presented as a plenary session by David Hyman, M.D., Director of Developmental Therapeutics at Memorial Sloan Kettering Cancer Center (MSK), and principal investigator of the trial.

The Phase II SUMMIT basket trial is an open-label, multicenter, multinational study to evaluate the safety and efficacy of PB272 administered daily to patients who have solid tumors with activating HER2 or HER3 mutations. All patients received loperamide (16 mg per day initially) prophylactically for the first cycle of treatment in order to reduce the neratinib-related diarrhea.

Included in the presentation were data on 141 patients enrolled in the neratinib monotherapy arm of the trial, including 124 patients with HER2 mutations and 17 patients with HER3 mutations. This included patients with 21 unique tumor types, with the most common being breast, lung, bladder and colorectal cancer. There were also 30 distinct HER2 and 12 distinct HER3 mutations observed among these patients, with the most frequent HER2 variants involving S310, L755, A755_G776insYVMA and V777.

In the HER2-mutant cohort, clinical responses were observed in tumors with S310, L755, V777, P780_Y781insGSP and A775_G776insYVMA mutations. When stratified by tumor type, responses were observed in patients with breast, cervical, biliary, salivary and non-small-cell lung cancers, which led to cohort expansions in these tumor types. No activity was observed in the HER3-mutant cohort. A more detailed presentation of the data is presented in Table 1 below:

Table 1: SUMMIT Trial Efficacy Summary

	$HER2^{mut}$ Breast	**$HER2^{mut}$ Bladder**	**$HER2^{mut}$ Lung**	**$HER2^{mut}$ Colorectal**	**$HER2^{mut}$ Biliary tract**	**$HER2^{mut}$ Cervical**	**$HER3^{mut}$ NOS**

	(n=25)	**(n=16)**	**(n=26)**	**(n=12)**	**(n=9)**	**(n=5)**	**(n=17)**
ORR at week 8, n (%)	8 (32.0)	0 (0.0)	1 (3.8)	0 (0.0)	2 (22.2)	1 (20.0)	0 (0.0)
(95% CI)	(14.9 53.5)	(0.0 20.6)	(0.1 19.6)	(0.0 26.5)	(2.8 60.0)	(0.5 71.6)	(0.0 20.6)
Clinical benefit rate, n (%)	10 (40.0)	3 (18.8)	11 (42.3)	1 (8.3)	3 (33.3)	3 (60.0)	2 (11.8)
(95% CI)	(21.1 61.3)	(4.0 45.6)	(23.4 63.1)	(0.2 38.5)	(7.5 70.1)	(14.7 94.7)	(1.6 38.3)
Median PFS, months	3.5	1.8	5.5	1.8	2.8	20.1	1.7
(95% CI)	(1.9 4.3)	(1.7 3.5)	(2.7 10.9)	(1.4 1.9)	(0.5 3.7)	(0.5 NA)	(1.4 2.0)

The neratinib safety profile observed in the SUMMIT study is consistent with that observed previously in metastatic patients with HER2 amplified tumors. With anti-diarrheal prophylaxis and management, diarrhea was not a treatment-limiting side effect in SUMMIT. The interim safety results of the study showed that the most frequently observed adverse event was diarrhea. For the 141 patients enrolled in the neratinib monotherapy arm with safety data available, 31 patients (22%) reported grade 3 diarrhea. The median duration of grade 3 diarrhea for those patients was 2 days. 4 patients (2.8%) permanently discontinued neratinib due to diarrhea and 21 patients (14.9%) temporarily discontinued neratinib due to diarrhea and then restarted after the diarrhea subsided.

Interim Results of Phase Ib/II FB-10 Trial of PB272 in Combination with Trastuzumab Emtansine (T-DM1) in HER2-Positive Metastatic Breast Cancer

On April 2, 2017, the Company announced that interim results from the Phase Ib/II FB-10 clinical trial of neratinib given in combination with the antibody drug conjugate T-DM1 (Kadcyla, ado-trastuzumab emtansine) were presented at the 2017 AACR Annual Meeting. The presentation entitled, NSABP FB-10: Phase Ib dose-escalation study evaluating trastuzumab emtansine (T-DM1) with neratinib in women with metastatic HER2-positive breast cancer was selected for an oral presentation.

The trial enrolled patients with HER2-positive metastatic breast cancer who had previously been treated with chemotherapy and the combination of trastuzumab (Herceptin) and pertuzumab (Perjeta). Study treatment consisted of the standard dose of T-DM1 at 3.6 mg/kg administered intravenously every 3 weeks and neratinib administered orally at escalating doses of 120, 160, 200 and 240 mg per day continuously. Primary diarrhea prophylaxis with high dose loperamide was administered.

For the 16 patients who were evaluable for efficacy, the objective response (CR/PR) rate was 56%. More specifically, the efficacy results from the trial demonstrated that 3 patients had a complete response (CR) lasting 17.1 months, 11.9 months and 12+ months; 6 patients had a partial response (PR); 3 patients had stable disease (SD); and 4 patients had progressive disease (PD). The number and types of response per dose cohort are summarized in the table below:

Neratinib Dose	**No. of Objective Responses (CR/PR)**
(mg/day)	**/ No. of Evaluable (CR/PR/SD/PD)**
120	5/5 (CR 2, PR 3)
160	2/4 (CR 1, PR 1, PD 2)
200	1/5 (PR 1, SD 2, PD 2)
240	1/2 (PR 1, SD 1)

The waterfall plot for the trial, % Change in Size of Target Lesions, is shown in Figure 1 below:

The safety results of the study showed that the most frequently observed grade 3 adverse events were diarrhea, nausea, thrombocytopenia and hypertension. More specifically, for the 21 patients with available safety assessments, grade 3 diarrhea was reported in 4 patients (19%), grade 3 nausea was reported in 3 patients (14%), grade 3 thrombocytopenia was reported in 3 patients (14%), and grade 3 hypertension was reported in 2 patients (10%). There was 1 dose limiting toxicity (DLT) at the 120 mg dose (1 of 6 patients), 3 DLTs at the 200 mg dose (3 of 8) and 2 DLTs at the 240 mg dose (2 of 3). Additional patients are currently being accrued at the 160 mg dose in order to define the recommended Phase II dose.

Interim Results of Phase II CONTROL Trial of PB272 in Extended Adjuvant Treatment of HER2-Positive Early Stage Breast Cancer

On April 4, 2017, the Company announced that interim results from a Phase II clinical trial of neratinib were presented at the 2017 AACR Annual Meeting. The presentation entitled, Effects of adding budesonide or colestipol to loperamide prophylaxis on neratinib-associated diarrhea in patients with HER2-positive early stage breast cancer: the CONTROL trial, was presented as a poster presentation.

The main adverse event that has been seen to date in clinical trials of neratinib is diarrhea and more specifically grade 3 diarrhea. In the Phase III ExteNET trial of neratinib as extended adjuvant treatment of HER2-positive early stage breast cancer that has previously been treated with adjuvant Herceptin, 95.4% of the patients experienced all grade diarrhea and 39.8% of the patients experienced grade 3 or higher diarrhea (there was one event of grade 4 diarrhea). The CONTROL trial is an international, open-label, Phase II study investigating the use of loperamide prophylaxis with or without other agents in the reduction of neratinib-associated diarrhea that has a primary endpoint of the incidence of grade 3 diarrhea.

In the CONTROL trial, patients with HER2-positive early stage breast cancer who had completed trastuzumab-based adjuvant therapy received neratinib daily for a period of one year. High dose loperamide prophylaxis was given for the first 2 cycles (56 days) of treatment. Initially, the loperamide dosing used was 16 mg on day 1, then 12 mg on days 2 and 3 and then 6-8 mg on days 4-56 (original dosing). The protocol was later amended to simplify the regimen such that patients took 12 mg on days 1-14 and 8 mg on days 15-56 (modified dosing). The CONTROL trial was also expanded to include two additional cohorts. One cohort received the combination of loperamide and budesonide and the other cohort received the combination of loperamide plus colestipol. Budesonide is a locally acting corticosteroid that the Company believes targets the inflammation identified in a preclinical model of neratinib-induced diarrhea and colestipol is a bile acid sequestrant that the Company believes targets the bile acid malabsorption also seen in preclinical models of neratinib-induced diarrhea.

The interim analysis of the trial presented in the poster included a total of 137 patients who received neratinib plus loperamide prophylaxis (28 patients taking the original dosing and 109 patients taking the modified dosing), 64 patients who received neratinib plus loperamide prophylaxis for 2 cycles and budesonide for 1 cycle, and 26 patients who received neratinib plus loperamide prophylaxis for 1 cycle and colestipol for 1 cycle.

The results of the trial showed that the incidence of grade 3 diarrhea for the 137 patients who received the loperamide prophylaxis was 30.7%. For the 137 patients who received the loperamide prophylaxis, the median number of grade 3 diarrhea episodes per patient was 1 and the median cumulative duration of grade 3 diarrhea was 3 days. For the 137 patients who received loperamide prophylaxis, 20.4% discontinued neratinib due to diarrhea.

For the 64 patients who received the combination of loperamide plus budesonide, the results of the trial showed that the incidence of grade 3 diarrhea was 23.4%. The median number of grade 3 diarrhea episodes per patient was 1 and the median cumulative duration of grade 3 diarrhea was 2 days. For the 64 patients who received loperamide plus budesonide prophylaxis, 9.4% discontinued neratinib due to diarrhea.

For the 26 patients who received the combination of loperamide plus colestipol, the results of the trial showed that the incidence of grade 3 diarrhea was 11.5%. The median number of grade 3 diarrhea episodes per patient was 2 and the median cumulative duration of grade 3 diarrhea was 2 days. For the 26 patients who received loperamide plus colestipol prophylaxis, no patient (0%) discontinued neratinib due to diarrhea. Further information is provided in Table 1 below:

Table 1: Characteristics of Treatment-Emergent Diarrhea

Study	**CONTROL**			**ExteNET**
Antidiarrheal prophylaxis	**Loperamide (original + modified)**	**Budesonide + loperamide**	**Colestipol + loperamide**	**Loperamide prn**
N (at data cut-off)	137	64	26	1408
Diarrhea, %				
Any grade	77.4	79.7	57.7	95.4
Grade 1	24.1	26.6	30.8	22.9
Grade 2	22.6	29.7	15.4	32.5
Grade 3	30.7	23.4	11.5	39.8
Grade 4	0	0	0	0.1
Median cumulative duration of diarrhea, days				
Any grade	12.0	10.0	8.0	59.0
Grade ³2	4.0	3.0	2.0	10.0
Grade ³3[a]	3.0	2.0	2.0	5.0
Median episodes of diarrhea per patient, n				
Any grade	2.0	4.0	3.0	8.0
Grade ³2	2.0	2.0	2.0	3.0
Grade ³3[a]	1.0	1.0	2.0	2.0
Median duration of neratinib treatment, months				
Median	10.6	5.1	1.7	11.6
Tolerability related to neratinib diarrhea				
Neratinib dose hold due to diarrhea, %	14.6	14.1	7.7	33.9
Neratinib dose reductions due to diarrhea, %	7. 3	1.6	3.8	26.4
Neratinib discontinuations due to diarrhea, %	20.4	9.4	0	16.8
Hospitalization due to diarrhea, %	1. 5	0	0	1.4

[a] No grade 4 events in the CONTROL study; one grade 4 event in the ExteNET study.

In the ExteNET trial, higher grade (grade 2 and grade 3) diarrhea occurred early and persisted throughout the duration of the 12-month treatment period. In the CONTROL trial, in the loperamide prophylaxis, loperamide plus budesonide prophylaxis and loperamide plus colestipol prophylaxis arms, the results showed that higher grade diarrhea (grades 2 and 3) occurred early but did not typically recur. This is shown in more detail in Figure 1: Treatment Emergent Diarrhea below:

During the course of the CONTROL trial there has been an increase in the proportion of patients previously treated with pertuzumab (mainly in the neoadjuvant setting). For the 55 patients in the loperamide prophylaxis cohort who received prior pertuzumab, the grade 3 diarrhea rate was 38.2% (Table 2). For the 82 patients who did not receive prior pertuzumab, the grade 3 diarrhea rate was 25.6%. For the 39 patients in the budesonide cohort who received prior pertuzumab, the grade 3 diarrhea rate was 10.3%. For the 25 patients in the budesonide cohort who did not receive prior pertuzumab, the grade 3 diarrhea rate was 36.0%. This analysis suggests that prior pertuzumab exposure may have led to a higher rate of grade 3 diarrhea in the CONTROL trial that was not effectively managed by loperamide prophylaxis alone but was more effectively managed by loperamide plus budesonide.

Table 2: Incidence of Grade 3 Diarrhea in CONTROL by Prior Pertuzumab Treatment

	Loperamide Cohort		**Budesonide Cohort**	
	Yes (n = 55)	No (n = 82)	Yes (n = 39)	No (n = 25)
Grade 3 Diarrhea	38.2%	25.6%	10.3%	36.0%

Forward-Looking Statements

This Current Report on Form 8-K contains forward-looking statements, including statements regarding the Company s the expanded access program for PB272 (neratinib) for the treatment of early stage HER2-positive breast cancer (extended adjuvant setting), HER2-positive metastatic breast cancer and HER2-mutated solid tumors and the development of the Company s drug candidates. All forward-looking statements included in this Current Report on Form 8-K involve risks and uncertainties that could

cause the Company s actual results to differ materially from the anticipated results and expectations expressed in these forward-looking statements. These statements are based on current expectations, forecasts and assumptions, and actual outcomes and results could differ materially from these statements due to a number of factors, which include, but are not limited to, the fact that the Company has no product revenue and no products approved for marketing, the Company s dependence on PB272, which is still under development and may never receive regulatory approval, the challenges associated with conducting and enrolling clinical trials, the risk that the results of clinical trials may not support the Company s drug candidate claims, even if approved, the risk that physicians and patients may not accept or use the Company s products, the Company s reliance on third parties to conduct its clinical trials and to formulate and manufacture its drug candidates, the Company s dependence on licensed intellectual property, and the other risk factors disclosed in the periodic reports filed by the Company with the Securities and Exchange Commission from time to time, including the Company s Annual Report on Form 10-K for the year ended December 31, 2016. Readers are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. The Company assumes no obligation to update these forward-looking statements, except as required by law.

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

PUMA BIOTECHNOLOGY, INC.

Date: April 6, 2017

By: /s/ Alan H. Auerbach
Alan H. Auerbach
Chief Executive Officer and President