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NCCN Guidelines Panel: Breast Cancer

On behalf of Puma Biotechnology (Puma), I respectfully request the NCCN Breast Cancer (BC) Guideline Panel to consider the enclosed data for neratinib for the extended adjuvant treatment of early-stage, Human Epidermal Growth Factor Receptor 2 overexpressed/amplified (HER2+) BC following adjuvant trastuzumab therapy.

Specific Changes: Please consider the available data on the use of neratinib for the extended adjuvant treatment of adult patients with early-stage, HER2+ BC following treatment with adjuvant trastuzumab therapy:

- **SYSTEMIC ADJUVANT TREATMENT – HER2-POSITIVE DISEASE (BINV-5, BINV-7, and BINV-K):**
 - **Add neratinib following adjuvant trastuzumab therapy**

FDA Clearance: On July 17, 2017, the FDA approved neratinib for extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy. Please refer to the enclosed full prescribing information for the FDA approved indication, including safety information.

Rationale: Neratinib, an oral, irreversible tyrosine kinase inhibitor of HER1 (EGFR), HER2, and HER4 receptors, has demonstrated efficacy as an extended adjuvant therapy in patients with HER2+ early-stage BC following treatment with adjuvant trastuzumab, including a significant reduction in the risk of BC recurrence or death determined by invasive Disease Free Survival (iDFS). The durability of neratinib efficacy has been maintained through the planned 5 year analysis.

Supporting Literature: Chan et al. reported results of a Phase 3, multicenter, randomized, double-blind, placebo controlled study (ExteNET) of neratinib in patients with HER2+, early-stage BC - the intent to treat (ITT) population - who had completed prior trastuzumab therapy (n=2,840) (1, 2, 3). The major efficacy outcome measure was iDFS, defined as the time between the date of randomization to the first occurrence of invasive recurrence (local/regional, ipsilateral or contralateral breast cancer), distant recurrence, or death from any cause at 2 years, with follow-up at 5 years. Patients were randomized 1:1 to take either neratinib or placebo, daily for 1 year. At 2 years, neratinib significantly reduced the risk of BC recurrence or death in patients by 34%. The iDFS rate was 94.2% (hazard ratio 0.66, p=0.008) in patients taking neratinib (n=1,420) compared to 91.9% in patients taking placebo (n=1,420). At 5 years, the iDFS rate for neratinib's ITT population was 90.2% (hazard ratio 0.73, p=0.008) versus 87.7% for placebo (4).

The overall safety profile of neratinib has been well characterized with >3,000 patients treated to date (4). In the ExteNET Study, the most common grade 1 or 2 adverse events of $\geq 5\%$ incidence were diarrhea, nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite, muscle spasms, dyspepsia, AST or ALT increase, nail disorder, dry skin, abdominal distention, weight decreased and urinary tract infection (1). Grade 3 diarrhea occurred in 40% of patients. One patient was reported to have Grade 4

diarrhea, however, upon investigation, criteria for Grade 4 was not met. The clinical course of neratinib-associated diarrhea is distinct. The majority of patients (93%) had diarrhea in the first month of treatment, the median time to first onset of Grade ≥ 3 diarrhea was 8 days (range, 1-350), and the median cumulative duration of Grade ≥ 3 diarrhea was 5 days (range, 1-139). However, anti-diarrheal prophylaxis upon initiation of neratinib was not protocol mandated (1, 2). There appears to be some adaptation to the effects of neratinib, as higher-grade diarrhea (grades 2 and 3) occurs early and does not typically recur (5). There was no evidence of hematopoietic, pulmonary, cardiac or increased risk for second malignancy.

The CONTROL Study, a Phase II, multicenter, open label study, characterized the incidence and severity of diarrhea with neratinib and anti-diarrheal prophylaxis. The trial demonstrated that prophylaxis improves tolerability and reduces the incidence and duration of diarrhea (5). The incidence of grade 3 diarrhea was reduced to 30.7%, 23.4%, and 11.5% in patients taking neratinib + loperamide, neratinib + loperamide + budesonide, or neratinib + loperamide + colestipol, respectively (5). Cumulative median duration of diarrhea, all grades, was reduced from 59 days seen in the ExteNET study, to 12 and 10 days for patients taking neratinib + loperamide and neratinib + loperamide + budesonide, respectively. Overall, the CONTROL study demonstrated that loperamide prophylaxis reduces the incidence, severity, and duration of neratinib-associated diarrhea.

Consistent with neratinib activity as extended adjuvant therapy in patients with early-stage BC, neratinib has also shown activity across other breast cancer treatment settings (6, 7, 8, 9, 10).

In summary, neratinib-associated diarrhea occurs early, is of short duration, and can be effectively managed with antidiarrheal prophylaxis and patient education, similar to other commonly used breast cancer therapies. Neratinib demonstrated a significant reduction in the risk of an iDFS event as extended adjuvant therapy for HER2+ patients with early-stage breast cancer following adjuvant therapy with trastuzumab. Furthermore, neratinib's benefit was durable, as confirmed through the 5-year final analysis.

The following key study publications are submitted, including the FDA prescribing information.

1. NERLYNX (neratinib) [package insert]. Los Angeles, CA: Puma Biotechnology, 2017.
2. Chan et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2016 Mar;17 (3):367-77.
3. Chan et al. Neratinib after adjuvant chemotherapy and trastuzumab in HER2-positive early breast cancer: Primary analysis at 2 years of a phase 3, randomized, placebo-controlled trial (ExteNET). *J Clin Oncol* 33, 2015 (suppl; abstr 508)
4. Oncologic Drugs Advisory Committee Sponsor Briefing Document, NERLYNX™ (NERATINIB), May 24, 2017, Puma Biotechnology
5. Ibrahim et al. Effects of adding budesonide or colestipol to loperamide prophylaxis on neratinib-associated diarrhea in patients (pts) with HER2+ early-stage breast cancer (eBC): the CONTROL trial. 2017 AACR Annual Meeting, Abstract and Poster CT128
6. Park et al. Adaptive Randomization of Neratinib in Early Breast Cancer. *N Engl J Med.* 2016 Jul 7;375(1):11-22.
7. Awada et al. Neratinib Plus Paclitaxel vs Trastuzumab Plus Paclitaxel in Previously Untreated Metastatic ERBB2-Positive Breast Cancer: The NEfERT-T Randomized Clinical Trial. *JAMA Oncol.* 2016 Dec 1;2(12):1557-1564.
8. Hyman et al. Neratinib in HER2- or HER3- mutant solid tumors: SUMMIT, a global, multi-histology, open-label, phase 2 "basket" study. AACR Annual Meeting 2017, Abstract CT001 and Presentation (Oral, Clinical Trials Plenary Session)
9. Hyman et al. Neratinib plus fulvestrant in ERBB2-mutant, HER2-non-amplified, estrogen receptor-positive, metastatic breast cancer: preliminary analysis from the phase II SUMMIT trial. 2016 CTRC-AACR San Antonio Breast Cancer Symposium (SABCS), Poster PD2-08 Discussion.
10. Ma et al. Neratinib Efficacy and Circulating Tumor DNA Detection of HER2 Mutations in HER2 Non-amplified Metastatic Breast Cancer. *Clin Cancer Res.* 2017 Jul 5. [Epub ahead of print].

Respectfully Submitted,



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