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NCCN Guidelines Panel: Breast Cancer

On behalf of Puma Biotechnology, Inc., I respectfully request the NCCN Breast Cancer Guideline Panel to consider the enclosed data for NERLYNX® (neratinib) for extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy.

Specific Changes: Please consider the following:

- Inclusion of neratinib in the treatment algorithm (as opposed to the footnote) as extended adjuvant treatment following treatment with adjuvant trastuzumab-based therapy per FDA indication in the following:
 - Systemic Adjuvant Treatment – Hormone Receptor-Positive – HER2-Positive Disease (BINV-5)
 - Preoperative Systemic Therapy: Adjuvant Therapy (BINV-13)
 - Preoperative Systemic Therapy for Inoperable or Locally Advanced Breast Cancer (Non-Inflammatory) (BINV-15)
- Inclusion of neratinib in HER2+ Preferred and Other Adjuvant Regimens to follow trastuzumab-based regimens (BINV-K; Page 1)
- Inclusion of neratinib in HER2+ Preferred and Other Adjuvant Regimens to follow trastuzumab-based regimens (BINV-K; Pages 4,5)

FDA Status: NERLYNX® (neratinib) has been approved for extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy (3).

Rationale:

- Consider inclusion of neratinib in the treatment algorithms for HER2+ adjuvant therapy based upon:
 - Neratinib is the only treatment that has demonstrated significant, durable risk reduction after standard-of-care trastuzumab-based adjuvant treatment.
 - The Breast Cancer Guideline Panel’s placement of other adjuvant therapies such as pertuzumab.
- Consider moving neratinib from footnote to treatment algorithm, based on:
 - No increased risk of long-term toxicity was observed in the ExteNET study.
 - Diarrhea is the main tolerability issue with neratinib. Results from the Phase II CONTROL study indicate that structured prophylaxis anti-diarrheal regimens reduces the incidence, severity and duration of diarrhea with improved tolerability leading to fewer dose holds, reductions and discontinuations. The combination of loperamide and colestipol was particularly effective, as reflected in the attached poster presented at SABCS 2017.
 - New updated CONTROL Phase II study results include 163 patients that have been treated with prior pertuzumab.
- Consider removing the statements recommending the limitation of neratinib to HR-positive patients “with a perceived high risk of recurrence (such as stage II-III)”. The ExteNET analysis included all stages I-III. No data exist suggesting stage I be excluded, or low-risk patients be excluded.

Supporting Literature:

The ExteNET study, recently published in Lancet Oncology in November 2017, demonstrated a significant invasive disease-free survival (iDFS) benefit in patients with early-stage HER2+ breast cancer after a median follow-up of 5 years (1).

- The iDFS rate in patients with HR+ disease was 91.2% in the neratinib group and 86.8% in the placebo group, with an absolute difference of 4.4% (HR 0.60; 95% CI 0.43-0.83; p=0.002) (1).
- After a median follow-up of 5.2 years (IQR 2: 1-5.3), patients in the neratinib group had significantly fewer invasive disease-free survival events than those in the placebo group (116 vs 163 events; stratified hazard ratio 0.73, 95% CI 0.57-0.92, p=0.0083). The 5-year invasive disease-free survival was 90.2% (95% CI 88.3-91.8) in the neratinib group and 87.7% (85.7-89.4) in the placebo group (1).
- Neratinib, when given in combination with endocrine therapy in patients with HR+ tumors, may result in prevention of HER2-ER crosstalk which potentially allows an escape mechanism when only one pathway is inhibited (1).
- At the 5-year follow-up, 1 year of extended adjuvant therapy with neratinib, administered after chemotherapy and trastuzumab, significantly reduced the proportion of clinically relevant breast cancer relapses - ie, those that might lead to death, such as distant and locoregional relapses outside the preserved breast – without increasing the risk of long-term toxicity (1).

New, improved side-effect management data for the CONTROL Study, a Phase II, multicenter, open label study, characterized the incidence and severity of diarrhea with neratinib and anti-diarrheal prophylaxis (2):

- The addition of colestipol to loperamide prophylaxis, administered in cycle 1, resulted in the greatest reduction in diarrhea incidence, severity and cumulative duration, compared to that observed in the ExteNET trial, and may further diminish the duration of diarrhea. Incidence of grade 3 diarrhea in the loperamide plus colestipol cohort was 10.8% (95% CI 5.9-17.8) with median episodes/patient of 1 and cumulative duration of 3.0 days. Diarrhea episodes generally occur in the first month of treatment (2).
- Colestipol may also improve tolerability as shown by the decreased rate of other adverse events (including fatigue, headache, and abdominal pain) and fewer neratinib dose holds, dose reductions, and discontinuations (2).

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

1. Martin et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2017 Dec;18(12):1688-1700; published Online Nov 13, 2017. [http://dx.doi.org/10.1016/S1470-2045\(17\)30717-9](http://dx.doi.org/10.1016/S1470-2045(17)30717-9).
2. Hurvitz S, et al. Effects of adding budesonide or colestipol to loperamide prophylaxis on neratinib-associated diarrhea in patients with HER2+ early-stage breast cancer: the CONTROL trial. #P3-14-01 San Antonio Breast Cancer Symposium (SABCS) 2017. San Antonio, Texas December 4-December 9, 2017.
3. NERLYNX (neratinib) [package insert]. Los Angeles, CA: Puma Biotechnology, 2017.

Respectfully Submitted,



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