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NCCN Guidelines Panel: Breast Cancer

On behalf of Puma Biotechnology, Inc., I respectfully request the NCCN Breast Cancer Guideline Panel review the enclosed FDA label for NERLYNX[®] (neratinib) + capecitabine for HER2-positive metastatic breast cancer.¹

Specific Changes: Please consider the following:

- BINV-Q1, “Other recommended regimens for HER2-Positive disease”
 - Please revise neratinib + capecitabine to a category 2A option
- BINV-Q4, “HER2-Positive Dose schedules for other recommended regimens”
 - Please revise neratinib + capecitabine to a category 2A option

FDA Clearance: neratinib is 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

Rationale: neratinib is an intracellular kinase inhibitor that irreversibly binds to epidermal growth factor (EGFR), HER2, and HER4.¹ Efficacy of neratinib + capecitabine in HER2-positive metastatic breast cancer has been shown in two studies that included patients who had received standard therapies including trastuzumab, T-DM1, pertuzumab, and lapatinib;^{2,3} additional safety results of this regimen are available from a third study.⁴ These studies demonstrate the safety and efficacy of neratinib + capecitabine as an effective option for patients with HER2-positive metastatic breast cancer.

Supporting Literature:

NALA^{1,2}

The safety and efficacy of neratinib + capecitabine vs. lapatinib + capecitabine was studied in NALA, a randomized, multicenter, open-label clinical trial in 621 patients with metastatic HER2-positive breast cancer who had received ≥ 2 prior HER2-directed regimens in the metastatic setting, including trastuzumab, T-DM1, and pertuzumab (31% of patients had ≥ 3 regimens). Patients with asymptomatic/stable brain mets were allowed to enroll. Centrally assessed progression free survival (PFS) favored neratinib + capecitabine (HR, 0.76; 95% CI, 0.63–0.93; $P=0.0059$). Numerical improvements were observed in median overall survival (21.0 vs. 18.7 months; HR, 0.88; 95% CI, 0.72–1.07), objective response rate (ORR) (32.8% vs. 26.7%), duration of response (8.5 vs. 5.6 months), and cumulative incidence of CNS mets (22.8% vs. 29.2%).

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The safety and efficacy of neratinib + capecitabine was studied in 2206, a phase 1/2 open-label, two-part trial. The phase 2 portion (part two) enrolled 72 patients with HER2-positive advanced breast cancer who had received prior trastuzumab-containing regimens; 7 received prior lapatinib. In part two, ORR was

64% in patients with no prior lapatinib and 57% in those who had prior lapatinib. Median PFS was 40.3 and 35.9 weeks, respectively. The maximum tolerated dose was determined to be neratinib 240 mg per day plus capecitabine 1,500 mg/m² (14/21 days).

Safety

Diarrhea is the main toxicity of neratinib and is common in absence of proactive management.¹ Prophylaxis was not mandated in study 2206; subsequent investigations of neratinib + capecitabine mandated loperamide during cycle 1; loperamide was used as needed after cycle 1.^{2,5} In NALA, the rate of grade ≥ 3 diarrhea in the neratinib arm was 24% and led to discontinuation in 2.6%; permanent discontinuation of neratinib due to any adverse reaction was 10.9% and neratinib dose reduction due to an adverse event of any grade occurred in 10%.

The following materials are submitted in support of this proposed change. We would like to acknowledge the contributions of NCCN panel members who are also co-authors on some of these publications or presentations.

1. NERLYNX® (neratinib) tablets [Prescribing Information]. Los Angeles, CA. Puma Biotechnology, Inc. <https://nerlynx.com/pdf/full-prescribing-information.pdf>
2. Saura C, Oliveira M, Feng YH, et al. Neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: Findings from the multinational, randomized, phase 3 NALA trial. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting. May 31-June 4, 2019; Chicago, IL. *J Clin Oncol*. 2019;37:(suppl; abstr 1002). <https://bit.ly/2XoWBxa>
3. Saura C, Garcia-Saenz JA, Xu B, et al. Safety and efficacy of neratinib in combination with capecitabine in patients with metastatic human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*. Nov 10 2014;32(32):3626-3633. <https://www.ncbi.nlm.nih.gov/pubmed/25287822>
4. Freedman RA, Gelman RS, Agar NYR, et al. Pre- and Postoperative Neratinib for HER2-Positive Breast Cancer Brain Metastases: Translational Breast Cancer Research Consortium 022. *Clin Breast Cancer*. Aug 22 2019 <https://www.ncbi.nlm.nih.gov/pubmed/31558424>
5. Freedman RA, Gelman RS, Anders CK, et al. TBCRC 022: A Phase II Trial of Neratinib and Capecitabine for Patients With Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer and Brain Metastases. *J Clin Oncol*. May 1 2019;37(13):1081-1089. <https://www.ncbi.nlm.nih.gov/pubmed/30860945>

Sincerely,



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