Deepa Lalla, B.Pharm, PhD
Head of Medical Affairs
Puma Biotechnology, Inc.
10880 Wilshire Blvd., Suite 2150, Los Angeles, CA 90024
424-248-6500
dlalla@pumabiotechnology.com

April 5, 2019

NCCN Guidelines Panel: CNS Cancers

On behalf of Puma Biotechnology, Inc., I respectfully submit recently published clinical data on NERLYNX® (neratinib) + capecitabine to the Central Nervous System Cancers Panel for consideration:

- 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. Mar 12 2019:JCO1801511.

Specific Changes: We respectfully request that the recommendation for neratinib + capecitabine be changed from a 2B to 2A option for breast cancer with brain metastases (recurrent disease, BRAIN-D).

FDA Clearance: 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.[1] Neratinib is not approved for use in locally advanced / metastatic disease.

Rationale:

TBCRC 022 is a an active, currently recruiting phase 2, multi-center, open-label, single-arm, two-stage study in subjects with HER2-positive breast cancer with CNS progression. Findings from Cohort 3 were recently published.[2,3]

Subjects with measurable, progressive, HER2-positive brain metastases were included. Most (92%) subjects had prior local CNS therapy; 33% had ≥2 lines of chemotherapy for metastatic disease. Prior HER2 directed therapy for metastatic disease (not mutually exclusive) included trastuzumab (82%), pertuzumab (49%), and T-DM1 (27%). Subjects with no prior lapatinib were assigned to cohort 3A (n=37) and those who had were assigned to cohort 3B (n=12; cohort closed for slow accrual). Prior neratinib and capecitabine were not allowed. Subjects in these two cohorts received neratinib + capecitabine until disease progression, unacceptable toxicity, or patient request / provider discretion.

In cohort 3A the composite CNS objective response rate was 49% (95% CI, 32–66%) and in cohort 3B was 33% (95% CI, 10–65%). Median progression free survival was 5.5 and 3.1 months in cohorts 3A and 3B, respectively and median overall survival was 13.3 and 15.1 months, respectively. 57% of study subjects continued to receive study therapy for ≥6 cycles. Diarrhea was the most common grade 3 toxicity (29%).

Sincerely,

Deepa Lalla

Deepa Lalla, B.Pharm, PhD
Head of Medical Affairs
Puma Biotechnology, Inc.

References

1. NERLYNX® (neratinib) tablets [Prescribing Information, June 2018] Puma Biotechnology, Inc. https://nerlynx.com/pdf/full-prescribing-information.pdf

2. 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.* Mar 12 2019:JCO1801511. https://www.ncbi.nlm.nih.gov/pubmed/30860945

3. Hurvitz SA. Neratinib Plus Capecitabine Provides a Glimmer of Hope for a Daunting Disease. *J Clin Oncol.* Mar 15 2019:JCO1900083. https://www.ncbi.nlm.nih.gov/pubmed/30875278