VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Nerlynx™ (neratinib tablets – Puma Biotechnology)

DATE REVIEWED: 09/25/2019; selected revision 03/04/2020

OVERVIEW

Nerlynx is indicated for the extended adjuvant treatment of adult patients with early-stage human epidermal growth factor receptor 2 (HER2) overexpressed/amplified (i.e., HER2 positive [HER2+]) breast cancer, to follow adjuvant trastuzumab -based therapy.[1] It is also indicated 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. Nerlynx is a kinase inhibitor that irreversibly binds to epidermal growth factor receptors (EGFR), HER2, and HER4. *In vitro* studies showed Nerlynx has antitumor activity in EGFR and/or HER2 expressing carcinoma cell lines.

Clinical Efficacy

The efficacy of Nerlynx was established in one Phase III, randomized, double-blind, placebo-controlled, multicenter, pivotal study (ExteNET, Extended Adjuvant Treatment of Breast Cancer with Neratinib) in women with early stage HER2+ breast cancer (n = 2,840).[1,2] Patients had completed adjuvant treatment with Herceptin and were without evidence of recurrence. Placebo or Nerlynx was given continuously for 12 months. The ExteNET trial underwent multiple amendments, and was a time driven analysis rather than event driven. Invasive disease-free survival (iDFS) within 2 years and 28 days was 94.2% (95% confidence interval [CI]: 92.6%, 95.4%) on Nerlynx vs. 91.9% (95% CI: 90.2%, 93.2%) on placebo (stratified hazard ratio [HR] 0.66; 95% CI: 0.49, 0.90; P =0.008). In a prespecified exploratory subgroup analysis of iDFS, Nerlynx was more beneficial in patients with HR+ breast cancer (unstratified hazard ratio 0.49; 95% 0.31, 0.75) than in patients with HR-negative disease (unstratified hazard ratio 0.93; 95% CI: 0.60, 1.43). In another analysis after a median follow-up of 5.2 years (interquartile range 2.1-5.3), patients who received Nerlynx had significantly fewer iDFS events than those in the placebo group (116 vs. 163 events; stratified HR 0·73; 95% CI: 0.57, 0.92; P = 0.0083).[3] The 5-year iDFS survival was 90·2% (95% CI: 88.3%, 91.8%) in the Nerlynx group and 87·7% ((95% CI: 85.7%, 89.4%) in the placebo group.

An exploratory analysis was conducted to understand why the subgroup of patients with HR-negative disease did not show statistical significance for efficacy in the ExteNET trial.[5] It is hypothesized that the risk of disease recurrence is highest during the first 6 months following completion of trastuzumab therapy in patients with HR-negative, HER2+ disease; so the greatest benefit with Nerlynx would likely also be in this subgroup of patients completing trastuzumab within 6 months of initiating Nerlynx in the study. The 5-year iDFS for patients with interval 0 to 6 months between prior trastuzumab therapy and Nerlynx randomization in the study was 88.9% for Nerlynx and 86.1% for placebo (HR 0.73; 95% CI: 0.47, 1.14). For interval duration > 6 months, the iDFS for Nerlynx at 5 years was 88.7% compared with 92.7% for placebo (HR 1.52; 95% CI: 0.82, 2.88).

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines on breast cancer (version 2.2020 – February 5, 2020) notes that Nerlynx can be considered as extended adjuvant therapy following adjuvant trastuzumab-containing therapy in patients with HR+, HER2+ disease with a perceived high risk of recurrence (such as Stage II or III breast cancer) [category 2A].[4] The benefits or toxicities associated with extended Nerlynx in patients who have received Perjeta is unknown. The guidelines do not include recommendations for using Nerlynx extended adjuvant therapy in patients with HR-negative, HER2+. For

the treatment of recurrent or metastatic disease, Nerlynx + capecitabine is listed as a category 2B recommended option.

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of Nerlynx. Coverage with Nerlynx is recommended for 1 year (total) of a patient's lifetime.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Nerlynx is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Breast Cancer – Adjuvant Therapy.** Approve for 1 year (total) if the patient meets the following criteria (A and B):
   - **A)** Patient has human epidermal growth factor receptor 2 (HER2)-positive breast cancer; AND
   - **B)** The patient meets ONE of the following criteria (i or ii):
     - **i.** The medication is requested for extended adjuvant therapy after the patient has completed 1 year of adjuvant therapy with trastuzumab intravenous products; OR
     - **ii.** The patient has tried adjuvant therapy with trastuzumab intravenous products and could not tolerate 1 year of therapy, according to the prescriber.

2. **Breast Cancer – Advanced or Metastatic Disease.** Approve for 3 years if the patient meets the following criteria (A, B, and C):
   - **A)** The patient has human epidermal growth factor receptor 2 (HER-2)-positive breast cancer; AND
   - **B)** The medication is used in combination with capecitabine; AND
   - **C)** The patient has tried at least two prior anti-HER2 based regimens in the metastatic setting.
     Note: Examples include Perjeta (pertuzumab injection for intravenous use) + trastuzumab + docetaxel, Perjeta + trastuzumab + paclitaxel; Kadcyla (ado-trastuzumab emtansine for intravenous use), trastuzumab + capecitabine, Tykerb (lapatinib tablets) + capecitabine, trastuzumab + Tykerb.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Nerlynx has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Concurrent Use of Nerlynx with Other Medications for Adjuvant or Neoadjuvant Treatment of HER2-Positive Breast Cancer:** Nerlynx is not indicated in combination with other medications for adjuvant or neoadjuvant (preoperative) HER2 positive breast cancer (e.g., Herceptin, Perjeta). Studies are not available for this use. Patients with HR+ early breast can receive concurrent adjuvant endocrine therapy.[2]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Nerlynx™ tablets [prescribing information]. Los Angeles, CA: Puma Biotechnology, Inc.; February 2020.
2. Chan A, Delaloge S, Holmes FA, et al; ExteNET Study Group. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2016;17:367-377.
3. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 2.2020 – February 5, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on March 2, 2020.
4. Martin M, Holmes FA, Ejlertsen B, et al; for the ExteNet Study Group. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18(12):1688-1700.
5. Ejlertsen B, Barrios CH, Gokmen E, et al. Timing of initiation of neratinib after trastuzumab-based adjuvant therapy in early-stage HER2+ hormone receptor (HR)-negative breast cancer: exploratory analysis from the phase III ExteNET trial [Abstract 549]. Presented at 2018 ASCO Annual Meeting. June 2, 2018.

HISTORY

Type of Revision	Summary of Changes*	Date Reviewed
New policy	New policy	08/23/2017
Selected revision	Breast cancer in women and in men: added the patient has hormone receptor-positive (that is, estrogen- and/or progesterone-positive) breast cancer. In Conditions Not Recommended for Approval, added Use of Nerlynx For a Total of No Greater than 1 Year Duration During a Patient's Lifetime.	01/03/2018
Update	02/12/2018: Conditions Not Recommended for Approval: In Concurrent Use of Nerlynx with Other Medications for Adjuvant or Neoadjuvant Treatment of HER2-Positive Breast Cancer, the last sentence was revised to replace the word"estrogen" with "endocrine".	NA
Annual revision	No criteria changes	09/19/2018
Annual revision	Deleted "Breast Cancer in Men" condition since the criteria are the same for all adult patients. Deleted "in Women" for the approval condition "Breast Cancer". Changed approval duration to "1 year (total)" from "up to 1 year". Deleted criteria "The patient has early stage disease", since it is not needed. Deleted "Herceptin" and referred to it by chemical name due to the availability of biosimilars. Added criteria that "The medication is requested for extended adjuvant therapy" after the patient has 1 year of trastuzumab therapy. Changed from "prescribing physician" to "prescriber".	09/25/2019
Selected revision	The requirement specifying Nerlynx use only in hormone receptor-positive disease was removed.	12/18/2019
Selected revision	Added new FDA approved indication for Nerlynx use in advanced or metastatic breast cancer. Deleted condition for 1-year maximum lifetime approval listed under "Conditions Not Recommended for Approval", since this is covered in the criteria for approval already.	03/04/2020

NA - Not applicable.