National Community Oncology Dispensing Association, Inc.
PASSION FOR PATIENTS

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Positive Quality Intervention: Neratinib Diarrhea Management

Description: Diarrhea is the main toxicity of neratinib (Nerlynx ®) treatment occurring in 95% of patients in the ExteNET trial on the Neratinib arm in which antidiarrheal prophylaxis was not protocol specified.[1] Various prevention and treatment strategies for diarrhea have been studied and will be discussed in this PQI.

Background: Neratinib is indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab based therapy. The majority (93%) of patients experienced diarrhea in the first month of treatment in ExteNET. Median time to onset of any grade diarrhea is 2 days (8 days for Grade 3) and median cumulative duration of diarrhea was 59 days (5 days for Grade 3).

The Phase 2 CONTROL trial was designed to investigate various approaches to preventing and managing diarrhea in patients on neratinib, including various anti-diarrheal combinations, as well as a dose escalation arm. Mature data is available for budesonide and colestipol; interim data are available for dose escalation in Phase 2 CONTROL trial[4].All preventative strategies from the CONTROL trial reduced the incidence, duration, and severity of diarrhea, and also reduced neratinib discontinuation when compared to the pivotal ExteNET trial.

PQI Process:

Upon receipt of Neratinib prescription:

- Counsel patient on the importance of diarrhea prophylaxis and remind them that diarrhea occurs in 95% of the patients without prophylaxis protocol.
- The clinician should exercise his/her best professional judgment in making recommendations for interventions for individual patients.
- Begin prophylaxis with the first dose or neratinib and continue for 2 cycles depending on the regimen selected and the patient response.
- Ensure patient has instructions and supply of loperamide and consider colestipol or budesonide (*see Supplemental Information for dosing*).
- Consider dose escalation based on interim data from CONTROL trial (*see Supplemental Information for dosing).* Educate on PRN use of loperamide.
- Identify drug-drug interactions and side effect profiles of loperamide, colestipol, and budesonide when making clinical recommendations
- Avoid concomitant use of PPIs. If H2-antagonists must be used, administer neratinib 2 hours before or 10 hours after. Other antacids (Tums, Maalox) should be separated by at least 3 hours
- Verify in EMR that patient is scheduled for CMP to assess liver function

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Patient Centered Activities:

- Consider weekly assessment of diarrhea throughout the first 2 cycles
- Express importance of diarrhea prophylaxis and enable patients to obtain anti-diarrheal medications with manufacturer voucher
- Advise patients to call office if diarrhea is uncontrolled with anti-diarrheal regimen (more than 4 loose stools per day over baseline).
- Neratinib should be taken with food and all six tablets(240mg) should be taken as one dose around the same time with food each day.
- Maintain adequate oral hydration throughout treatment unless otherwise indicated by physician
- Consider monthly CMP for the first 3 months then every 3 months as clinically indicated.
- Counsel on other possible side effects are nausea(43%), abdominal pain(36%), vomiting(26%) and stomatitis (14%).
- Assess if patient is having uncontrolled nausea or is developing stomatitis or another AE.
- Clinicians should be aware of these new options for patients and the availability of a voucher for 3-months of anti-diarrheal medication at no charge from the manufacturer.

Dosage Adjustment for Diarrhea:

Grade 1 or 2 (<5 days) or Grade 3 (<2 days)

- Maximize use of antidiarrheal agents and assess diet and aggravating substances
- When diarrhea has improved to ≤ grade 1 or baseline, initiate loperamide 4 mg with each subsequent neratinib dose.

Grade 2 (>5 days) or Grade 3 (>2 days) or any grade with complicating features of dehydration, fever, hypotension, renal failure, or grade 3/4 neutropenia)

- Interrupt treatment. Modify diet; maintain fluid intake of ~2 L.
- If diarrhea improves to ≤ grade 1 in 1 week or less, resume neratinib at the same dose.
- If diarrhea improves to ≤ grade 1 in more than 1 week, resume neratinib at the next lower dose.
- When diarrhea has improved to ≤ grade 1 or baseline, initiate loperamide 4 mg with each subsequent neratinib dose.

Recurrent Grade 2 or more occurring at 120mg once daily dose, or, Grade 4 diarrhea:

- Permanently discontinue neratinib.

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References:

1. NERLYNX [Package Insert]. Los Angeles, CA: Puma Biotechnology, Inc; 2017.
2. Hurvitz S, Chan A, Iannotti N, 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. Presented at: 40th Annual San Antonio Breast Cancer Symposium; December 5–9, 2017; San Antonio, TX. Poster P3-14-01.
3. Martin M, Holmes FA, Ejlertsen B, et al. 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. Dec 2017;18(12):1688-1700. https://www.ncbi.nlm.nih.gov/pubmed/29146401
4. Barcenas CH, Hurvitz SA, Di Palma J, et al. Effect of prophylaxis on neratinib-associated diarrhea and tolerability in patients with HER2+ early-stage breast cancer: Phase II CONTROL 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 548). https://bit.ly/2Xu86DO

Supplemental Information

Dosing Regimens from CONTROL study Loperamide:	• 4mg TID days 1-14, then 4mg BID days 15-56
Budesonide	• 9mg/day for 1 cycle • + loperamide 4mg TID days 1-14, then 4mg BID days 15-56
Colestipol	• 2gm BID for 1 cycle + loperamide PRN or • + loperamide 4mg TID days 1-14, then 4mg BID days 15-28
Neratinib	• 120 mg/day on days 1–7, then 160 mg/day on days 8–14, then 240 mg/day through day 364, or • 160 mg/day on days 1–14, then 200 mg/day on days 15–28, then 240 mg/day through day 364

Dose Escalation Regimen:

- 160mg (4 tablets) daily days 1-14
- 200mg (5 tablets) daily days 15-28
- 240mg (6 tablets) daily days 29+

Note: Loperamide was given PRN in this arm of the CONTROL study

Financial Assistance:

- 3-month voucher available for anti-diarrheal agents.
- Traditional financial assistance for high medication costs available through PumaPatientLynx. https://nerlynx.com/access-and-support

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Figure 1: CONTROL Trial: Strategies for Diarrhea Management

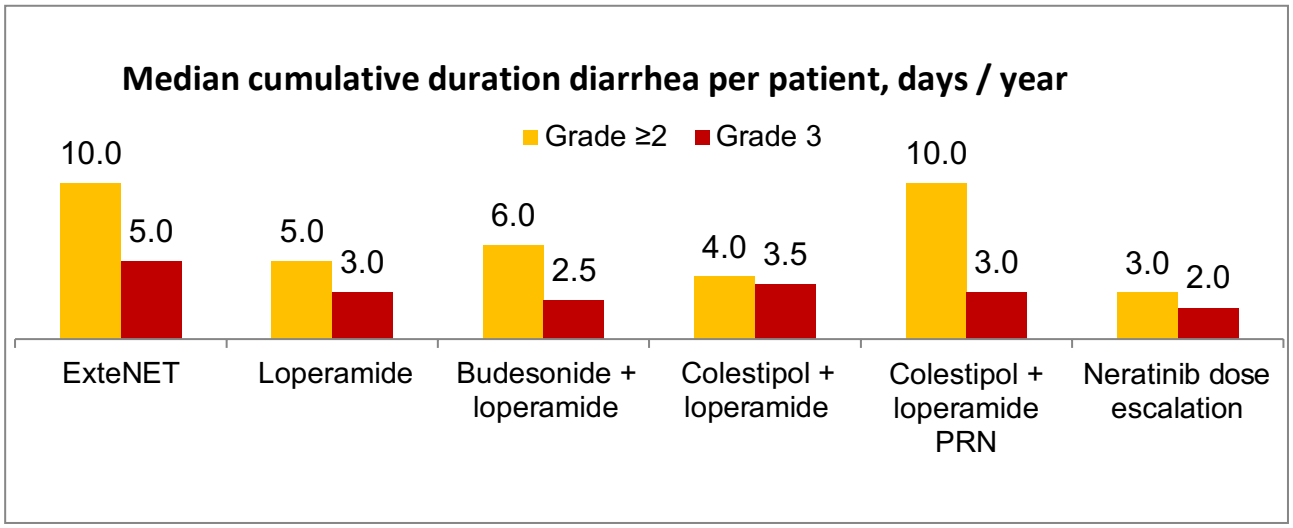

Figure 2: CONTROL Trial: Rates of Discontinuation due to Diarrhea