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Positive Quality Intervention: Neratinib (Nerlynx®) Diarrhea Management

Description: Diarrhea is the main toxicity of neratinib 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 document.

Background: Neratinib is indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, following adjuvant trastuzumab based therapy. Neratinib is also indicated in combination with capecitabine in metastatic/advanced HER2-positive breast cancer following 2 or more anti-HER2 based regimens. The majority (95%) 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, as well as dose escalation from the 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:

- Consider dose escalation based on data update FDA approved updated package insert *(see Supplemental Information)*
- Diarrhea Prophylaxis - Diarrhea occurs in 95% of the patients without prophylaxis protocol
    - 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*)
    - Refer to Oncolytic Induced Diarrhea PQI
    - Identify drug-drug interactions and side effect profiles of loperamide, colestipol, and budesonide when making clinical recommendations
    - Consider weekly assessment of diarrhea throughout the first 2 cycles
- Drug-Drug Interactions
    - 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 for the first 3 months then every 3 months as clinically indicated

Patient Centered Activities:

- Provide Oral Chemotherapy Education (OCE) Sheet and Oral Chemotherapy Education Supplemental Sheet
- Express importance of diarrhea prophylaxis and enable patients to obtain anti-diarrheal
- Consider providing Neratinib (Nerlynx®) Treatment Support Kit (TSK)
- Neratinib should be taken with food and around the same time each day
    - Dose escalation – Take three tablets (120 mg) daily for 7 days, then four tablets (160 mg) daily for 7 days, then six tablets (240 mg) daily thereafter

    - Initiation without escalation – Take six tablets (240 mg daily) with loperamide during the first 56 days, then loperamide as needed to maintain daily bowel movements
- Maintain adequate oral hydration throughout treatment unless otherwise indicated
- Counsel on other possible side effects
    - Diarrhea (95%)
        - Voucher for 3-months of anti-diarrheal medication from the manufacturer
        - Advise patients to call office if diarrhea is uncontrolled with anti-diarrheal
    - Nausea (43%)
    - Abdominal pain (36%)
    - Vomiting (26%)
    - Stomatitis (14%)
- Financial Assistance:
    - 3-month voucher available for anti-diarrheal agents
    - Traditional financial assistance for high medication costs available through PumaPatientLynx

References:

1. NERLYNX® [Package Insert]. Los Angeles, CA: Puma Biotechnology, Inc.
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: CONTROL trial. Presented at: 40th Annual San Antonio Breast Cancer Symposium; Dec 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	4 mg TID days 1-14, then 4 mg BID days 15-56
Budesonide	9 mg/day for 1 cycle + loperamide 4 mg TID days 1-14, then 4 mg BID days 15-56
Colestipol	2 gm BID for 1 cycle + loperamide PRN + loperamide 4 mg TID days 1-14, then 4 mg 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:

- 120 mg (3 tablets) daily days 1-7
- 160 mg (4 tablets) daily days 8-14
- 240 mg (6 tablets) daily thereafter

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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 120 mg once daily dose, or, Grade 4 diarrhea:

- Permanently discontinue neratinib

Figure 1: CONTROL Trial: Strategies for Diarrhea Management

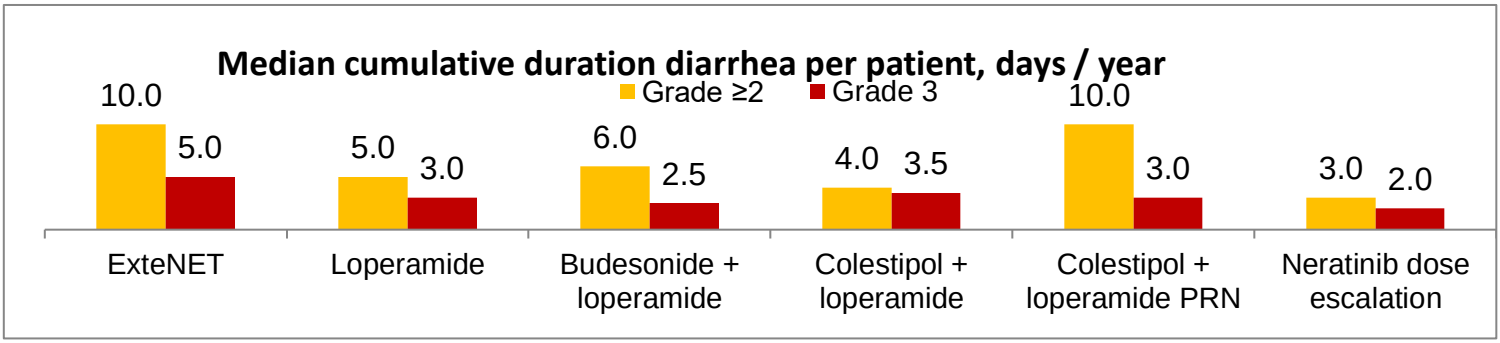

Figure 2: CONTROL Trial: Rates of Discontinuation due to Diarrhea