



## 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.<sup>1</sup> 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 dose escalation. The neratinib full prescribing information was updated in June 2021 to include dose escalation.

**PQI Process:** Upon receipt of neratinib prescription:

- Consider dose escalation (see *Supplemental Information*)
- Diarrhea Prophylaxis:
  - Begin prophylaxis with the first dose of neratinib and continue for 2 cycles depending on the regimen selected and the patient response
  - Ensure patient has instructions and supply of antidiarrheals (see *Supplemental Information*)
  - 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 (from ExteNET trial)

**Important notice:** NCODA has developed this Positive Quality Intervention platform. This platform represents a brief summary of medication uses and therapy options derived from information provided by the drug manufacturer and other resources. This platform is intended as an educational aid and does not provide individual medical advice and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication discussed in the platform and is not intended as a substitute for the advice of a qualified healthcare professional. The materials contained in this platform are for informational purposes only and do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA, which assumes no liability for and does not ensure the accuracy of the information presented. NCODA does not make any representations with respect to the medications whatsoever, and any and all decisions, with respect to such medications, are at the sole risk of the individual consuming the medication. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional. *Updated 2.16.22*



- Diarrhea (95%)
    - Advise patients to call office if diarrhea is uncontrolled with anti-diarrheal
  - Nausea (43%)
  - Abdominal pain (36%)
  - Vomiting (26%)
  - Stomatitis (14%)
- Patient Assistance: [NCODA Financial Assistance Tool](#)

**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, Ejlerlsen 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

**Dosage Adjustment for Diarrhea:**

Grade 1 or 2 ( $\leq 5$  days) or Grade 3 ( $\leq 2$  days)

- Maximize use of antidiarrheal agents and assess diet and aggravating substances
- When diarrhea has improved to  $\leq$  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  $\leq$  Grade 1 in 1 week or less, resume neratinib at the same dose
- If diarrhea improves to  $\leq$  Grade 1 in more than 1 week, resume neratinib at the next lower dose
- If diarrhea has improved to  $\leq$  Grade 1/baseline, initiate loperamide 4 mg with each subsequent dose

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

- Permanently discontinue neratinib

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Figure 1: CONTROL Trial: Strategies for Diarrhea Management

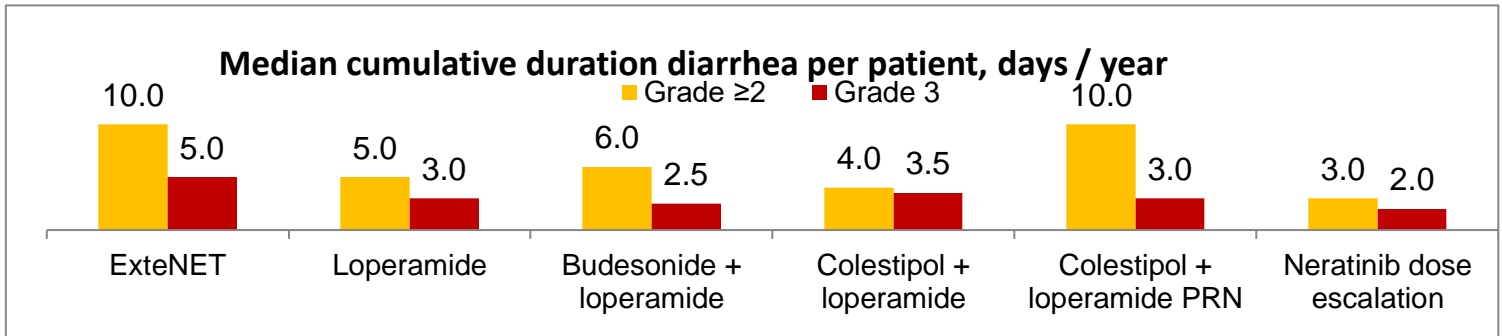
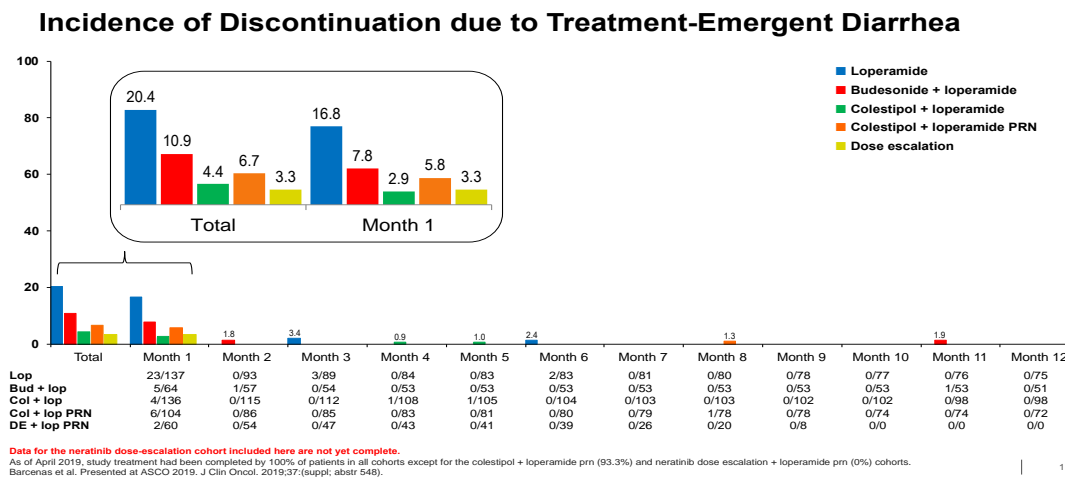


Figure 2: CONTROL Trial: Rates of Discontinuation due to Diarrhea



Data for the neratinib dose-escalation cohort included here are not yet complete. As of April 2019, study treatment had been completed by 100% of patients in all cohorts except for the colestipol + loperamide prn (93.3%) and neratinib dose escalation + loperamide prn (0%) cohorts. Barcenas et al. Presented at ASCO 2019. J Clin Oncol. 2019;37(suppl; abstr 548).

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