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. 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 of patients (95%) experienced diarrhea in the first month of treatment in ExteNET. The 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 initiating treatment using dose escalation regimen (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 monthly CMP (including ALT, AST, bilirubin, and alkaline phosphatase) for the first 3 months then every 3 months as clinically indicated

Patient-Centered Activities:

- Provide neratinib Oral Chemotherapy Education (OCE) Sheet and managing diarrhea Oral Chemotherapy Education Supplemental Sheet
- Express importance of diarrhea prophylaxis and ensure patients to obtain anti-diarrheal medications
- 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 (ExteNET trial)

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- 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].

Supplemental Information:
Antidiarrheal dosing regimens from the CONTROL study

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Loperamide</th>
<th>Budesonide</th>
<th>Colestipol</th>
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<tbody>
<tr>
<td>Dosing</td>
<td>4 mg TID days 1-14, then 4 mg BID days 15-56, from day 57 on 4 mg PRN not to exceed 16 mg per day; titrate dosing to achieve 1–2 bowel movements per day</td>
<td>9 mg/day for 1 cycle + loperamide 4 mg TID days 1-14, then 4 mg BID days 15-56</td>
<td>2 gm BID for 1 cycle + loperamide PRN + loperamide 4 mg TID days 1-14, then 4 mg BID days 15-28</td>
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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
- If diarrhea has improved to ≤ 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

**Figure 1: CONTROL Trial: Strategies for Diarrhea Management**

![Figure 1: CONTROL Trial: Strategies for Diarrhea Management](image-url)
Figure 2: CONTROL Trial: Rates of Discontinuation due to Diarrhea

Incidence of Discontinuation due to Treatment-Emergent Diarrhea

Data for the neotradin dose-escalation cohort included those who did not complete.

At 60 Apr 2017, study treatment had been discontinued in 96% of patients, except for the ceritinib + loperamide (76.3%) and ceritinib dose escalation + loperamide (73%) cohorts.

(Adapted from S. Hoshiai et al. 2017. J Clin Oncol; 35(21) 2097.)