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 anti-diarrheal prophylaxis was not protocol specified. 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, 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. 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 from CONTROL trial (see supplemental information for dosing)
- 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 to assess liver function
  - Consider monthly 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 medications with manufacturer voucher
- Consider providing Neratinib (Nerlynx®) Treatment Support Kit (TSK)
- Neratinib should be taken with food and around the same time each day

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References:

Supplemental Information:

Dosing Regimens from CONTROL study:

<table>
<thead>
<tr>
<th>Loperamide:</th>
<th>4 mg TID days 1-14, then 4 mg BID days 15-56</th>
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<tbody>
<tr>
<td>Budesonide</td>
<td>9 mg/day for 1 cycle</td>
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<td>+ loperamide 4 mg TID days 1-14, then 4 mg BID days 15-56</td>
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<tr>
<td>Colestipol</td>
<td>2 gm BID for 1 cycle + loperamide PRN</td>
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<td></td>
<td>+ loperamide 4 mg TID days 1-14, then 4 mg BID days 15-28</td>
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<tr>
<td>Neratinib</td>
<td>120 mg/day on days 1–7, then 160 mg/day on days 8–14, then 240 mg/day through day 364 or</td>
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<tr>
<td></td>
<td>160 mg/day on days 1–14, then 200 mg/day on days 15–28, then 240 mg/day through day 364</td>
</tr>
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Dose Escalation Regimen:

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

Note: Loperamide was given as needed in this arm of the CONTROL study.
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

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