The CONTROL study is investigating the effectiveness of rationally structured antidiarrheal prophylaxis or neratinib dose escalation in the prevention and treatment of neratinib-associated diarrhea and tolerability in patients with HER2-positive stage I–IIIc breast cancer. Phase II CONTROL trial

Background

Neratinib (NERLYNX®, PNG-00006) is a novel, irreversible pan-HER tyrosine kinase inhibitor that is currently approved for the treatment of HER2-positive advanced breast cancer following adjuvant trastuzumab-based therapy.

- The ExteNET trial, which demonstrated a benefit for neratinib over placebo for a 12.8-month course of first-line neoadjuvant/adjuvant treatment, had a 12-month course of neratinib after trastuzumab-based adjuvant therapy without improvement in overall survival. However, diarrhea was a dose-limiting toxicity in ExteNET and the 2-year risk of grade 3 or higher diarrhea was 39.9%.6
- In ExteNET, where antidiarrheal prophylaxis was not mandated, the study design allowed for a flexible approach to managing diarrhea. Treatment-emergent diarrhea occurred in 39.9% of patients (n=104) during the first year of neratinib treatment and 26.8% (n=136) during the second year. Among the first year’s patients, 15% of patients experienced a grade 3 or higher event.3
- In ExteNET, diarrhea events were associated with a median duration of 15 days (range, 1 to 17) across all cohorts (Table 3), with a median time to onset of 7 to 66 days across all cohorts.
- On neratinib treatment, n (%)

Methods

CONTROL (Clinicaltrials.gov NCT02400476) is an international multi-cohort, open-label, phase II study (Figure 1). The primary objective of this study was to evaluate the safety and tolerability of a rationally structured regimen of loperamide prophylaxis for one or two cycles of pertuzumab or neratinib treatment in patients with HER2-positive breast cancer with a median age of 52 (range, 26–86) years and a median time from last trastuzumab dose to enrollment ranging from 1 to 17 months (range, 0.1–13.1).

Table 1. Study overview

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No diarrhea</td>
<td>26 (19.0%)</td>
<td>42 (30.9%)</td>
<td>76 (55.5%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>64 (100.0%)</td>
<td>34 (53.1%)</td>
<td>55 (85.9%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>23/137</td>
<td>2/83</td>
<td>0/104</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>136 (100.0%)</td>
<td>41 (30.9%)</td>
<td>39 (37.5%)</td>
</tr>
</tbody>
</table>

Table 2. Incidence of treatment-emergent diarrhea by worst grade

In addition to loperamide prn, treatment-emergent diarrhea was managed with loperamide-based prophylaxis; 3) colestipol + loperamide prophylaxis; 4) colestipol + loperamide prn; and 5) control (neratinib only).

Results

- From February 2015 to August 2016, a total of 501 patients have been enrolled and treated in 19 countries with HER2-positive (at least 25% by IHC), hormone receptor-positive or triple-negative breast cancer.
- Most patients (n=498; 99.4%) were women, with a median age of 52 (range, 26–86) years and a median time from last trastuzumab dose to enrollment ranging from 1 to 17 months (range, 0.1–13.1).
- On neratinib treatment, n (%)

Table 3. Overall summary of TEAE

Figure 2. Treatment-emergent diarrhea leading to discontinuation by month

The majority of discontinuations due to diarrhea in all cohorts occurred in the first month of treatment (53.1%) for pertuzumab treatment (57.1%) and the second month of treatment (53.9%) for neratinib. A significantly increased number of patients required neratinib dose holds and dose reductions for diarrhea when compared with the ExteNET trial (historical control: 39.9%),6 all preventive strategies were compared with the control group in this study endpoint (Table 2).

Conclusions and future directions

A rationally structured regimen of loperamide prophylaxis for one or two cycles substantially reduces the incidence, severity, and duration of neratinib-associated diarrhea compared with that observed in the ExteNET trial.3

The clinical development of loperamide prophylaxis is expected to reduce the risk of grade 3 or higher diarrhea in patients treated with pertuzumab or neartinib.

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References