Effects of adding budesonide or colestipol to loperamide prophylaxis on neratinib-associated diarrhea in patients with HER2+ early-stage breast cancer: the CONTROL trial


Background

Neratinib (Puma Biotechnology, Inc.) is an irreversible pan HER2 tyrosine kinase inhibitor.

- Results from the randomized, Phase II ExteNET study demonstrated that neratinib delivered as 12 weeks of daily oral treatment in patients with HER2-positive breast cancer reduced the risk of disease recurrence or death by 33% relative to placebo after 2 years’ follow-up in women with HER2-positive early-stage breast cancer.

- Neratinib dose reductions and dose holds due to diarrhea occurred in 20.4% and 23.5% of patients, respectively.

- In 2017, neratinib-associated diarrhea was characterized in ExteNET by the ExteNET study (Protocol Amendment 3).

Methods

Study design

- CONTROL (Puma HER-022) is an international, open-label, phase II study investigating the effects of loperamide prophylaxis in a backbone, locally acting corticosteroid, on diarrhea in patients with HER2-positive breast cancer.

- All analyses were descriptive and were performed in the safety population.

Baseline characteristics are presented in Table 1.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CONTROL</th>
<th>EXTENET (control)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study arm</strong></td>
<td>350</td>
<td>350</td>
</tr>
<tr>
<td><strong>Sex, M/F (%)</strong></td>
<td>51.7/48.3</td>
<td>51.4/48.6</td>
</tr>
<tr>
<td><strong>Race, %</strong></td>
<td>90.1/10 (9/0)</td>
<td>94.1/1 (6/0)</td>
</tr>
<tr>
<td><strong>Median age (years)</strong></td>
<td>50.0</td>
<td>51 (35–78)</td>
</tr>
<tr>
<td><strong>Documentation HER2 overexpression or amplification, %</strong></td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

- Baseline characteristics are presented in Table 1.

Results

A total of 112 patients were included in the intent-to-treat analysis of the loperamide cohort (original loperamide schedule, n=28; modified loperamide schedule, n=109).

- The proportion of patients requiring neoplastic dose holds and dose reductions did not differ between cohort with or without budesonide and colestipol.

- The occurrence and severity of diarrhea in the CONTROL study over the course of study treatment may not have been impacted by diarrhea prophylaxis given without or with budesonide or colestipol.

Conclusions

- Controlling early diarrheal events, effective diarrhea prophylaxis may help to improve the tolerability of neratinib, enhance long-term adherence to treatment, and ensure that the efficacy benefits of neratinib are realized.

- Adding loperamide prophylaxis regimen, for one or two cycles and with or without the addition of budesonide or colestipol for a single cycle, reduced the incidence, severity, and duration of neratinib-related diarrhea compared with events observed in the ExteNET study.

- The addition of colestipol and loperamide prophylaxis appears to offer an incremental decrease in diarrhea incidence and severity compared with loperamide prophylaxis given with or without budesonide or colestipol in ExteNET.

- The occurrence and severity of diarrhea in patients treated with budesonide or colestipol did not differ between study treatment arms, and did not differ compared with patients treated with loperamide prophylaxis alone.

- Further studies are needed to examine the optimal duration of diarrhea prophylaxis, how it may differ for patients with or without pre-existing diarrhea, and how it may further reduce incremental decreases in diarrhea incidence and severity.

References


- Puma Biotechnology Inc. website.