In the ExteNET adjuvant trial, where no mandatory anti-diarrheal prophylaxis was used, 40% of patients reported grade 3 diarrhea and 17% of patients discontinued neratinib due to diarrhea.

In the CONTROL trial, neratinib was administered as soon as possible after patients had received trastuzumab-based adjuvant therapy. All 12-week cycles commenced 1 week after the completion of trastuzumab-based adjuvant therapy.

Adoption of neratinib DE at the initiation of treatment, particularly the 2-week DE schedule (DE1), allowed patients to stay on treatment longer (Figure 2). At least 75% of patients receiving neratinib-DE1 tolerated 11.06–12.01 months of treatment compared with 7.46–11.99 months in the control arm. Adoption of the neratinib DE1 cohort also appeared to reduce the rate of grade 3 diarrhea and treatment discontinuations due to diarrhea compared with the DE2 cohort (Figure 3).

Final findings from the CONTROL trial show improved tolerability of neratinib with all diarrhoea prophylaxis strategies and suggest that neratinib DE1 with loperamide PRN allows patients to stay on treatment longer and receive the full benefit of neratinib therapy. The US package label for neratinib includes loperamide prophylaxis and has recently been amended to include the DE1 strategy from CONTROL.

**References**


**Acknowledgements and Disclosures**

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*Final findings from the CONTROL trial show improved tolerability of neratinib with all diarrhoea prophylaxis strategies and suggest that neratinib DE1 with loperamide PRN allows patients to stay on treatment longer and receive the full benefit of neratinib therapy. The US package label for neratinib includes loperamide prophylaxis and has recently been amended to include the DE1 strategy from CONTROL.*

**Figure 1. CONTROL trial DE cohorts: study schema**

**Figure 2. Treatment duration: CONTROL trial DE cohorts**

**Figure 3. Grade 3 diarrhea and treatment discontinuations due to diarrhea: CONTROL trial DE cohorts**

**Table 1. Patient disposition: CONTROL trial DE cohorts**

<table>
<thead>
<tr>
<th></th>
<th>DE cohort 1 (n=60)</th>
<th>DE cohort 2 (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient disposition (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed 1 year of treatment</td>
<td>47 (78.3)</td>
<td>46 (74.2)</td>
</tr>
<tr>
<td>Discontinued due to AE</td>
<td>13 (21.7)</td>
<td>15 (24.2)</td>
</tr>
<tr>
<td>Discontinued due to any AE</td>
<td>5 (8.3)</td>
<td>8 (12.9)</td>
</tr>
<tr>
<td>Discontinued due to diarrhea</td>
<td>2 (3.3)</td>
<td>4 (6.5)</td>
</tr>
<tr>
<td>Median duration of treatment, months</td>
<td>11.96</td>
<td>11.94</td>
</tr>
<tr>
<td>Q1–Q3</td>
<td>10.0–11.20</td>
<td>10.4–12.19</td>
</tr>
<tr>
<td>Range</td>
<td>0.2–17.0</td>
<td>0.2–14.5</td>
</tr>
</tbody>
</table>

**Impact of DE on diarrhoea**

Adoption of neratinib DE at the initiation of treatment, particularly the 2-week DE schedule (DE1), most likely contributed to the reduced incidence, severity, and duration of neratinib-associated grade 3 diarrhoea seen in the CONTROL trial.

- DE1 strategy reduced the incidence of grade 3 diarrhoea (DE1 3.3%; DE2 6.5%) compared with that seen in the ExteNET trial (historical control: 34.8%).
- No grade 4 diarrhoea was reported in any cohort.

The median cumulative duration of grade 3 diarrhoea ranged from 2 to 2.5 days across the CONTROL DE cohorts.

**Table 2. Diarrhea characteristics: CONTROL trial DE cohorts**

<table>
<thead>
<tr>
<th></th>
<th>DE cohort 1 (n=61)</th>
<th>DE cohort 2 (n=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>24 (40.0)</td>
<td>23 (37.1)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>27 (44.6)</td>
<td>23 (37.1)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>8 (13.1)</td>
<td>17 (27.4)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Median episodes of Grade 3 diarrhoea**

- DE1 cohort: 2
- DE2 cohort: 3

**Median time to first onset of Grade 3 diarrhoea, days**

- DE1 cohort: 45
- DE2 cohort: 19

**Medium cumulative duration of Grade 3 diarrhoea, per patient**

- DE1 cohort: 3.2
- DE2 cohort: 4.0

**Dose reductions due to diarrhoea, n (%)**

- DE1 cohort: 2 (3.3)
- DE2 cohort: 4 (6.5)

**Dose hold due to diarrhoea, n (%)**

- DE1 cohort: 2 (3.3)
- DE2 cohort: 7 (11.7)

**Hospitalizations due to diarrhoea, n (%)**

- DE1 cohort: 0
- DE2 cohort: 0

**Conclusions**

Adoption of neratinib DE1 + loperamide PRN during the first 2 weeks of treatment (DE1 cohort) was associated with the lowest rate of grade 3 diarrhoea observed in the trial compared with all other anti-diarrhoeal strategies investigated in CONTROL.

The DE2 cohort also had the lowest rate of diarrhoea-related discontinuations (3.3%) and dose hold (11.7%) compared with all previously mandated prophylaxis strategies investigated in CONTROL, the subsequent DE2 strategy, and also when compared with the neratinib arm in ExteNET.

Overall, the CONTROL trial DE1 strategy allowed patients to stay on treatment longer and receive the full benefit of neratinib therapy. The US package label for neratinib includes loperamide prophylaxis and has recently been amended to include the DE1 strategy from CONTROL.