Effects of neratinib on health-related quality of life (HRQoL) in early-stage HER2+ breast cancer: longitudinal analysis from the phase III ExteNET trial


Background
Neratinib Flxtrux® (Puma Biotechnology Inc.) is an irreversible tyrosine kinase inhibitor that has been approved for the extended adjuvant treatment of early-stage HER2+ breast cancer (HER2+). Early results showed that a 1-year course of neratinib given after trastuzumab-based adjuvant therapy was associated with worse health-related quality of life (HRQoL) compared with placebo after 2 years' follow-up (reported 0.47; 2.5% vs 0.01; 0.0% for HRQoL, p<0.05). Balancing the potential benefits and risks of any adjuvant therapy requires an understanding of the implications for patients, their caregivers and health-care providers, and the patient-reported outcomes (PROs).

We aimed to conduct a comprehensive analysis of HRQoL outcomes from the ExteNET trial, including a baseline (BL) and a 12-month follow-up assessment using PRO instruments, as well as further disaggregate the sensitivity analyses performed to assess the impact of differential early drop-outs (i.e. a transient decrease after the first month of therapy followed by a steady improvement).

Methods
Study design
ExteNET was an ongoing multicenter, randomized, double-blind, phase III trial comparing neratinib (Puma Biotechnology Inc.) with placebo, in patients with node-positive, HER2+ breast cancer following surgery and adjuvant trastuzumab plus chemotherapy.

Patient eligibility and analyses have been reported previously.2,4

Randomized patients were allocated to either neratinib 245 mg once daily or to placebo, for a planned duration of 12 months.

Patients
Women with histologically confirmed stage 1–3 disease (amended to 2–3, when 2–3 disease HER2+ patients were enrolled in the 12-month extension) were eligible. Full details of the patient population and treatment data have been described.2-5

Assessments
HRQoL was assessed using the FACT-B (version 4) and EQ-5D 5-index (EQ-5D).2,5

Eligible patients who provided informed consent were randomized to receive either neratinib 245 mg once daily or placebo over a 12-month period. The primary endpoint was the composite endpoint of disease recurrence or death. Secondary endpoints included time to recurrence, OS, and safety and tolerability measures.

We report the full longitudinal HRQoL data from the ExteNET study over multiple time points;7 for FACT-B, the primary HRQoL instrument, and for EQ-5D, the index measure of general HRQoL.

Results
A total of 2840 patients were randomized to study treatment and constituted the intention-to-treat population (neratinib, n=1410; placebo, n=1430).

Sensitivity analyses were done with no multiplicity adjustment.

Data were analyzed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Figure 1. ExteNET study CONSORT flowchart

Table 2: Compliance rules for FACT-B questionnaires

<table>
<thead>
<tr>
<th>Compliance</th>
<th>FACT-B Domain</th>
<th>FACT-B subscale</th>
<th>Domain-related subscales</th>
<th>Total score range</th>
<th>Baseline</th>
<th>Months 1</th>
<th>Months 3</th>
<th>Months 6</th>
<th>Months 9</th>
<th>Months 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excluded</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Assigned</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Table 3: Mean observed scores by treatment group over time

<table>
<thead>
<tr>
<th>Time point</th>
<th>FACT-B domain</th>
<th>FACT-B total score</th>
<th>FACT-B TOI-PFB score</th>
<th>EQ-5D Index score</th>
<th>EQ-5D Health state</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Months 1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Months 3</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Months 6</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Months 9</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Months 12</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>1.0</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Figure 2. Mean (SE) observed scores by treatment group over time

In conclusion, extended adjuvant therapy with neratinib in women with early-stage HER2+ breast cancer was associated with worse HRQoL outcomes; however, effects were only evident early in treatment and not sustained after month 1.

Acknowledgements
Grafius was supported by Roche Pharma and Puma Biotechnology. In turn, Puma Biotechnology funded all the provision of service support provided by MillMed Communications.

References

2. Bayse M, Eftestol B, Eton DT, et al. Final efficacy and safety results from E6297 (ExteNET), a phase III, randomized, double-blind study of the effects of extended adjuvant (i.e. a transient decrease after the first month of therapy followed by a steady improvement) therapy with neratinib or placebo in patients with node-positive, HER2+ breast cancer. J Clin Oncol. 2017;35:4s (suppl; abstr 4005).
6. Yost KJ, Eton DT. Functional assessment of cancer therapy–Breast; SE, standard error; TOI-ESB, trial outcome index with emotional well-being, social/family instrumental activities, a higher score indicates a better quality of life.

Conclusions

Over the course of study treatment, we observed a consistent pattern of HRQoL changes with neratinib on both the FACT-B and EQ-5D instruments (i.e. a transient decrease after the first month of therapy followed by a steady improvement).

For both the FACT-B and EQ-5D summary scores, the between-group difference was significant over the course of the trial and could not therefore be considered clinically significant.

The only exception was the FACT-B physical well-being domain, which showed a consistent pattern of HRQoL improvement through to month 12.

Sensitivity analyses, which used different imputation methods to investigate the impact of missing data and study drop-outs, were performed on the primary analysis. Inclusion, extended adjuvant therapy with neratinib in women with early-stage HER2+ breast cancer was associated with a transient reduction in EQ-5D scores.

Our interpretation is that patients are initially bothered by side effects immediately after treatment and later improve as the side effects subside. We have no data on the potential reasons for the increase in EQ-5D scores after month 7.

The ExteNET trial, a study of extended adjuvant therapy with neratinib, should inform the risk–benefit assessment of this treatment modality for patients with HER2+ breast cancer.

Response analysis

There were some differences in the proportions of patients showing improved or stable HRQoL between groups. None of these were significantly different between groups.

Sensitivity analyses

The sensitivity analyses performed to assess the impact of differential early drop-outs between treatment groups were supportive of the primary analysis.

The sensitivity analyses performed to assess the impact of differential early drop-outs showed that those patients who did not experience grade 2 deterioration had different drop-out profiles compared with those who did experience grade 2 deterioration (p=0.007). This analysis included patients with assessments at baseline and month 1.

Presented at the ESMO 2017 Congress, 8–12 September, Madrid, Spain.