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

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Background

- Neratinib (Nerlynx®, Puma Biotechnology Inc.) is an irreversible tyrosine kinase inhibitor of HER1, HER2 and HER4[1] that has been FDA-approved for the extended adjuvant treatment of early-stage HER2+ breast cancer.
  - Primary analysis of the ExteNET trial, which provided the basis for drug approval, showed that a 1-year course of neratinib given after trastuzumab-based adjuvant treatment significantly improved invasive disease-free survival (iDFS) compared with placebo after 2 years' follow-up (hazard ratio 0.67; 95% CI 0.50–0.91; p=0.0091).[2]
- Balancing the potential risks and benefits of any adjuvant therapy requires an objective evaluation of expected disease relapse benefits versus adverse events and patient-reported outcomes (PROs).
  - While in advanced disease, medical interventions may improve patient health-related quality of life (HRQoL), the main challenge in the adjuvant setting is to improve survival outcomes without HRQoL impairment.
  - PRO assessments are particularly important when treatment is given for an extended period, such as in the adjuvant setting in breast cancer.[3-5]
- ExteNET included a detailed exploratory evaluation of HRQoL outcomes throughout treatment using two validated questionnaires and multiple repeated assessments.
- We report the full longitudinal HRQoL data from the ExteNET study over 12 months of treatment with neratinib or placebo, and further disaggregate the Functional Assessment of Cancer Therapy–Breast FACT-B questionnaire to identify specific-interest changes in FACT-B subscales.

Methods

Study design

- ExteNET is an ongoing multicentre, randomized, double-blind, phase III trial (Clinicaltrials.gov identifier: NCT00878709).
- Primary efficacy and safety analyses have been reported previously.[2]
- Patient follow-up is ongoing, with the 5-year efficacy analysis presented at ESMO 2017.[6]

Patients

- Women with histologically confirmed stage 1 to 3c disease (amended to 2 to 3c disease) HER2+ breast cancer.
- Completed surgery and trastuzumab-based adjuvant therapy.

Treatment

- Oral neratinib 240 mg once daily continuously or matching placebo for 1 year.
- No formal management plan or primary prophylaxis for diarrhoea, but early treatment for diarrhoea was recommended.

Assessments

- Patient-reported HRQoL was assessed using the FACT-B (version 4) and EuroQol 5-Dimensions (EQ-5D).
- Patients completed HRQoL questionnaires at baseline, and months 1, 3, 6, 9 and 12.
- Collection of HRQoL data was no longer required after protocol amendment 9 (October 2011).
- Changes in HRQoL scores were considered to be meaningful to patients if greater than important differences (ID) reported in the literature.[7-9]

Statistical analysis

- Descriptive statistics for observed scores were presented by treatment group at each time point, and mean scores (± standard error) were presented as plots over time.
- For the primary HRQoL analysis, evaluable patients were required to have a baseline HRQoL assessment and at least one post-baseline HRQoL assessment.
- A series of sensitivity analyses were done to assess the impact of early drop-outs and missing data on HRQoL outcomes.
- Statistical analyses were done with no multiplicity adjustment.
- Data were analyzed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

- A total of 2840 patients were randomized to study treatment and constituted the intention-to-treat population (neratinib, n=1420; placebo, n=1420).
- 2407 of the 2840 patients completed FACT-B questionnaires at baseline and at least one post baseline visit (neratinib, n=1171; placebo, n=1236), and 2427 of 2840 patients completed EQ-5D questionnaires at baseline and at least one post-baseline visit (neratinib, n=1186; placebo, n=1241, **Figure 1**).
- Baseline characteristics of HRQoL evaluable patients were well balanced between treatment groups and similar to the intention-to-treat population (**Table 1**).

Table 1. Baseline patient demographics and characteristics: intention-to-treat and HRQoL evaluable populations

	Intention-to-treat population (n=2840)		HRQoL population[a] (n=2429)	
Characteristic	Neratinib (n=1420)	Placebo (n=1420)	Neratinib (n=1186)	Placebo (n=1243)
Median (range) age, years	52 (25–83)	52 (23–82)	52 (25–83)	53 (23–81)
Race, n (%)				
White	1165 (82)	1135 (80)	957 (81)	978 (79)
Black	27 (2)	47 (3)	20 (2)	41 (3)
Asian	188 (13)	197 (14)	174 (15)	185 (15)
Other	40 (3)	41 (3)	35 (3)	39 (3)
Region, n (%)				
Asia Pacific, Eastern Europe and South America	414 (29)	411 (29)	371 (31)	377 (30)
North America	519 (37)	477 (34)	446 (38)	432 (35)
Western Europe, Australia and South Africa	487 (34)	532 (38)	369 (31)	434 (35)
Nodal status, n (%)				
Negative	335 (24)	336 (24)	286 (24)	305 (25)
1–3 positive nodes	664 (47)	664 (47)	546 (46)	581 (47)
≥4 positive nodes	421 (30)	420 (30)	354 (30)	357 (29)
Hormone receptor status, n (%)				
Positive	816 (58)	815 (57)	670 (56)	705 (57)
Negative	604 (43)	605 (43)	516 (44)	538 (43)
Prior trastuzumab regimen, n (%)				
Concurrent	884 (62)	886 (62)	734 (62)	777 (63)
Sequential	536 (38)	534 (38)	452 (38)	466 (37)
Prior neoadjuvant therapy, n (%)	342 (24)	379 (27)	285 (24)	339 (27)

[a] Defined as patients who had a baseline assessment and at least one post-baseline assessment for at least one of the two questionnaires (FACT-B and EQ-5D).

Withdrawals and questionnaire compliance rates

- The median duration of treatment was similar in both treatment groups (neratinib: 353 days, range, 1–406; placebo: 360 days, range, 4–401).
- More patients in the neratinib group (n=127) than in the placebo group (n=44) ended treatment early (i.e. within 3 months), mainly because of early adverse events.
- FACT-B questionnaire compliance rates were similar in both groups and exceeded 85% at all time-points prior to protocol amendment 9 (which removed the requirement for HRQoL data collection) (**Table 2**).
- Overall compliance rates (i.e. including data after amendment 9) were also balanced between treatment groups at all time-points, although rates in both groups were lower at later time-points (**Table 2**). Compliance rates for EQ-5D showed similar patterns to those observed with FACT-B.

Figure 1. ExteNET study: CONSORT flowchart

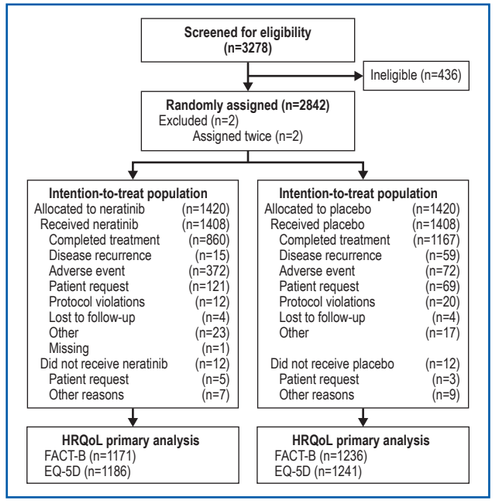


Table 2. Compliance rates for FACT-B questionnaires

	With consideration for protocol amendment 9[ab]				Without consideration for protocol amendment 9[bc]			
	Neratinib		Placebo		Neratinib		Placebo	
	N[d]	Compliance, n (%)[e]	N[d]	Compliance, n (%)[e]	N[d]	Compliance, n (%)[e]	N[d]	Compliance, n (%)[e]
Baseline	1408	1259 (89.4)	1408	1266 (89.9)	1408	1259 (89.4)	1408	1266 (89.9)
Month 1	1408	1200 (85.2)	1408	1274 (90.5)	1408	1200 (85.2)	1408	1274 (90.5)
Month 3	1011	913 (90.3)	1279	1177 (92.0)	1074	955 (88.9)	1356	1230 (90.7)
Month 6	831	759 (91.3)	1112	1025 (92.2)	973	830 (85.3)	1292	1121 (86.8)
Month 9	692	622 (89.9)	941	859 (91.3)	913	708 (77.6)	1228	973 (79.2)
Month 12 / EOT	575	516 (89.7)	811	729 (89.9)	863	598 (69.3)	1165	841 (72.2)

[a] With protocol amendment 9 (implemented in October 2011), patient enrolment was stopped and collection of HRQoL data was no longer required.

[b] Patients were not expected to submit questionnaires after protocol amendment 9. Questionnaires obtained after amendment 9 were not used.

[c] Patients expected to submit questionnaires until the end of treatment (i.e. ignoring protocol amendment 9). All questionnaires were used.

[d] Number of patients expected to submit questionnaires at each visit.

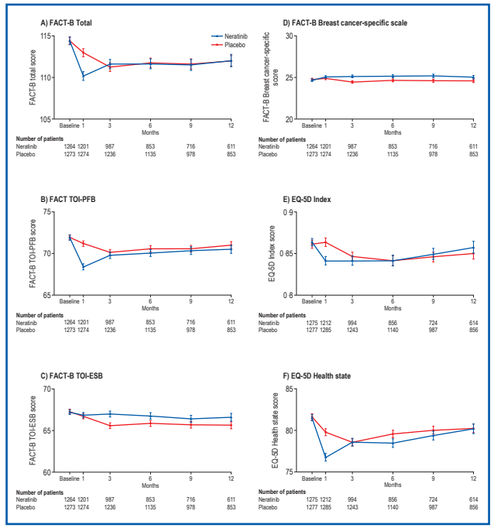
[e] Compliance = actual number of HRQoL assessments/expected number of HRQoL assessments while on study treatment. Note: all questionnaires were complete, as all questions had to be answered in order for patients to submit their HRQoL assessment.

Abbreviations: EOT, end of treatment; FACT-B, Functional Assessment of Cancer Therapy – Breast.

Longitudinal HRQoL changes from baseline

- HRQoL scores at baseline were similar in the neratinib and placebo groups. Mean observed scores by treatment group over time for key FACT-B and EQ-5D scores are shown in **Figure 2**.
- For FACT-B total score, the most pronounced between-group difference occurred at month 1; the adjusted mean difference of change was –2.9 points (95% CI, –3.7, –2.0; p<0.0001) favouring the placebo group.
- After month 1, FACT-B total scores in the neratinib group recovered towards baseline levels and differences between groups were minimal (p>0.05) and less than the ID range (**Figure 2A**).
- A similar pattern was evident for TOI-PFB, (**Figure 2B**) and also in the question about degree of bother with side effects on the physical well-being (PWB) subscale (**Figure 3**).
- For TOI-ESB, differences between treatment groups were minimal at all time-points (**Figure 2C**), although patients receiving neratinib showed small positive changes in the breast cancer-specific subscale, although these were not clinically significant (**Figure 2D**).
- The pattern of changes for the EQ-5D index and health state scores over time were similar to those observed with FACT-B (**Figures 2E and 2F**).
- Results from a mixed model analysis, which assumed that missing data were missing at random, were consistent with the primary analysis.

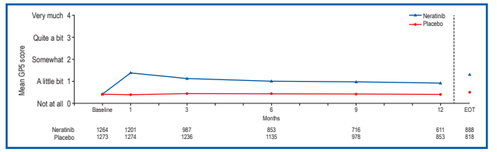
Figure 2. Mean (SE) observed scores by treatment group over time



Important differences: FACT-B total, 7–8 points;[7] FACT-B TOI, 5–6 points;[7] FACT-B subscales, 2–3 points;[7,8] EQ 5D health index, 0.09–0.10 units;[9] and EQ health state score, 7–10 units.[9] Important difference = group score difference or change that is likely to be meaningful to patients. For both instruments, a higher score indicates a better quality of life.

Abbreviations: EQ-5D, EuroQol 5-Dimensions; FACT-B, Functional Assessment of Cancer Therapy – Breast; SE, standard error; TOI-ESB, trial outcome index with emotional well-being, social/family well-being and breast cancer-specific subscales; TOI-PFB, trial outcome index with physical well-being, functional well-being and breast cancer-specific subscales.

Figure 3. Mean responses to FACT-B physical well-being question 5 'I am bothered by side effects of treatment.'



Responder analysis

- There were some differences in the proportions of patients showing improved, stable and worsened HRQoL at month 1 according to FACT-B total score (9.2%, 58.1% and 32.7% with neratinib *vs* 11.5%, 66.2% and 22.3% with placebo, respectively), which were no longer evident at later time-points.

Sensitivity analyses

- Findings from sensitivity analyses performed to assess the impact of differential early drop-out rates between treatment groups were supportive of the primary analysis.
- These included an analysis using last value carried forward (since patients who ended treatment early due to adverse events/subject request were likely to post their worst HRQoL scores at treatment end), a pattern mixture model (which assumed that patients who did/did not experience grade ≥2 diarrhea had different drop-out patterns), and a completer's analysis (which included patients with assessments at baseline, months 1 and 12).

Conclusions

- Over the course of study treatment, we observed a consistent pattern of HRQoL changes with neratinib therapy on both the FACT-B and EQ-5D instruments (i.e. a transient decrease after the first month of therapy followed by a steady recovery towards baseline).
- For both the FACT-B and EQ-5D summary scores, the between-group differences were consistently less than the accepted ID values reported for these instruments and could not therefore be considered clinically significant.
  - The only exception was for the FACT-B physical well-being subscale at month 1 (mean difference between groups, –2.4 points) which was of borderline clinical significance (ID range, 2–3 points).
- Sensitivity analyses, which used different imputation methods to investigate the impact of missing data and early drop-outs, were supportive of the primary analysis.
- In conclusion, extended adjuvant therapy with neratinib in women with early-stage HER2+ breast cancer was associated with a transient reduction in HRQoL during the first month of treatment, before recovering thereafter.
- Our interpretation is that patients are initially bothered by side effects (mainly diarrhoea) but that this dissipates rapidly after month 1 and remains subclinical thereafter for those who remain on therapy.
- The ongoing CONTROL study is evaluating loperamide-based prophylaxis regimens to reduce the incidence, severity and duration of neratinib-associated diarrhea.

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