Neratinib in the extended adjuvant treatment of patients from Asia with early stage HER2-positive breast cancer after trastuzumab-based therapy: exploratory analyses from the phase III ExteNET trial

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P1-13-11

Introduction

- Neratinib, an irreversible tyrosine kinase inhibitor of HER1, HER2 and HER4,[1] is used for the extended adjuvant treatment of early-stage HER2-positive (HER2+) breast cancer after trastuzumab-based adjuvant therapy.
  - The primary analysis of the international, randomized, placebo-controlled phase III ExteNET trial showed that 1 year of neratinib given after trastuzumab-based (neo)adjuvant therapy significantly improved 2-year invasive disease-free survival (iDFS) compared with placebo in women with early-stage HER2-positive breast cancer (stratified hazard ratio [HR] 0.67; 95% confidence intervals [CI] 0.50–0.91; p=0.0091).[2]
  - Furthermore, the significant iDFS benefits of neratinib were maintained after a median of 5 years' follow-up (stratified hazard ratio 0.73; 95% CI 0.57–0.92; p=0.008).[3]
- Current knowledge about breast cancer is based largely on studies conducted in western populations.[4]
  - As the genetic background, socio-economic profile, lifestyle, and health beliefs of Asian and western women differ, the findings from such studies may not be applicable to Asian women.[4]
  - We report exploratory analyses from the ExteNET trial of patients enrolled from Asian centers to better understand the efficacy and safety of neratinib compared with placebo in Asian women with early-stage HER2-positive breast cancer.

Methods

Study overview

- ExteNET is a multicenter, randomized, double-blind, parallel, placebo-controlled, phase III trial.
- Patients were enrolled from centers in 40 countries in Europe, North and South America, Asia, and Australasia.
- The final study design comprised 3 parts:
  - Part A: primary efficacy analysis at 2 years (July 2014)[2]
  - Part B: sensitivity analysis of efficacy at 5 years (March 2017)[3]
  - Part C: analysis of overall survival which is planned after 248 events.
- ExteNET is registered on Clinicaltrials.gov (identifier, NCT00878709).

Patients

- Women with confirmed stage 2–3c (1–3c in original protocol) HER2-positive breast cancer.
- Clinical and radiologic assessments were required to be negative for recurrences or metastatic disease at study entry.
- Patients had received (neo)adjuvant therapy with trastuzumab completed within 1 year (2 years in original protocol) before randomization.

Treatment

- Women were randomly assigned to oral neratinib 240 mg once daily continuously or matching placebo for 1 year.
- Prophylaxis for the prevention of neratinib-associated diarrhea was not mandatory.

Assessments

- During years 1 and 2, physical examinations were performed at month 1, every 3 months during year 1, and every 4 months during year 2, mammograms were performed annually where appropriate, and computed tomography or bone scans were performed if clinically indicated.
- During years 3 to 5, physical examination and mammogram schedules were based on standard of care, and details of recurrent disease events and deaths were obtained from medical records.

Outcomes

- The primary study endpoint was iDFS after 2 years of follow-up.
- Secondary endpoints included disease-free survival including ductal carcinoma *in situ* (DCIS), time to distant recurrence, distant disease-free survival, cumulative incidence of central nervous system (CNS) recurrences, and safety.

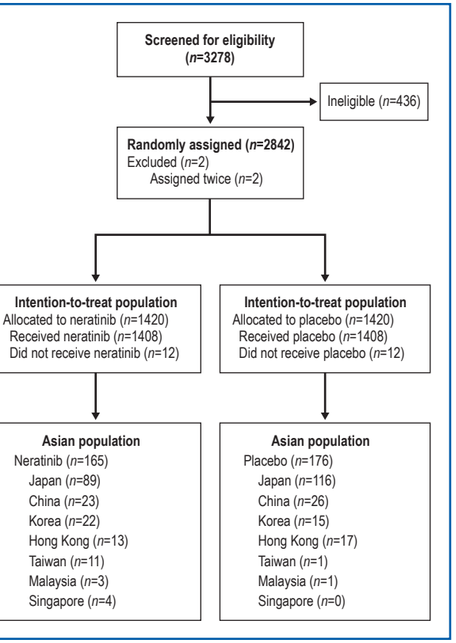
Statistical analysis

- Exploratory analyses were performed in the subpopulation of patients enrolled from Asian countries (i.e. China, Hong Kong, Japan, Korea, Malaysia, Singapore, and Taiwan).
- Patients of Asian ethnicity enrolled from non-Asian countries (n=44) were not included in the Asian subpopulation.
- Efficacy analyses were by intention-to-treat and performed at 2 and 5 years post-randomization.
- Kaplan Meier methods were used to analyze time-to-event endpoints, and a unstratified Cox proportional-hazards model was used to estimate HR with 95% CI for neratinib versus placebo.

Results

- 2840 women were randomly assigned to study treatment and constituted the intention to-treat population (neratinib, n=1420; placebo, n=1420).
- 341 women were enrolled from centers in Asia (neratinib, n=165; placebo, n=176) [**Figure 1**].

Figure 1. ExteNET analysis flowchart



- Patient demographics and characteristics at baseline were generally balanced between treatment groups in the Asian population (**Table 1**).
- Compared with the intention-to-treat population, Asian patients (neratinib and placebo combined) were more likely to have node-negative disease (28.7% *vs* 23.6%) and hormone receptor-negative tumors (52.2% *vs* 42.6%).
- Asian patients were also less likely to have received trastuzumab concurrently with chemotherapy (41.3% *vs* 62.3% in the intention-to-treat population), but more likely to have received an anthracycline plus taxane (81.2% *vs* 67.9%).

Table 1. Baseline characteristics in Asian and intention-to-treat populations

	Asian population		Intention-to-treat population	
Variable	Neratinib (n=165)	Placebo (n=176)	Neratinib (n=1420)	Placebo (n=1420)
Age, years, median (range)	52 (26–81)	53 (27–72)	52 (25–83)	52 (23–82)
Body mass index, kg/m² mean (SD)	22.6 (3.8)	23.1 (3.3)	27.4 (5.8)	27.5 (5.8)
Nodal status*				
Negative	43 (26.1)	55 (31.3)	335 (23.6)	336 (23.7)
1–3 positive node	75 (45.5)	74 (42.0)	664 (46.8)	664 (46.8)
4+ positive nodes	47 (28.5)	47 (26.7)	421 (29.6)	420 (29.6)
Hormone receptor status*				
Positive	77 (46.7)	86 (48.9)	816 (57.5)	815 (57.4)
Negative	88 (53.3)	90 (51.1)	604 (42.5)	605 (42.6)
Previous trastuzumab regimen*				
Concurrent	66 (40.0)	75 (42.6)	884 (62.3)	886 (62.4)
Sequential	99 (60.0)	101 (57.4)	536 (37.7)	534 (37.6)
Menopausal status at diagnosis				
Premenopausal	90 (54.5)	83 (47.2)	663 (46.7)	664 (46.8)
Postmenopausal	75 (45.5)	93 (52.8)	757 (53.3)	756 (53.2)
Prior (neo)adjuvant therapy				
Trastuzumab	165 (100)	176 (100)	1420 (100)	1420 (100)
Anthracycline only	17 (10.3)	21 (11.9)	136 (9.6)	135 (9.5)
Anthracycline plus taxane	136 (82.4)	141 (80.1)	962 (67.7)	965 (68.0)
Taxane only	12 (7.3)	13 (7.4)	318 (22.4)	316 (22.3)
Non-anthracycline or taxane	0	1 (0.6)	4 (0.3)	4 (0.3)

Data are presented as n (%), unless otherwise stated. SD, standard deviation.
*Stratification factor.

Efficacy

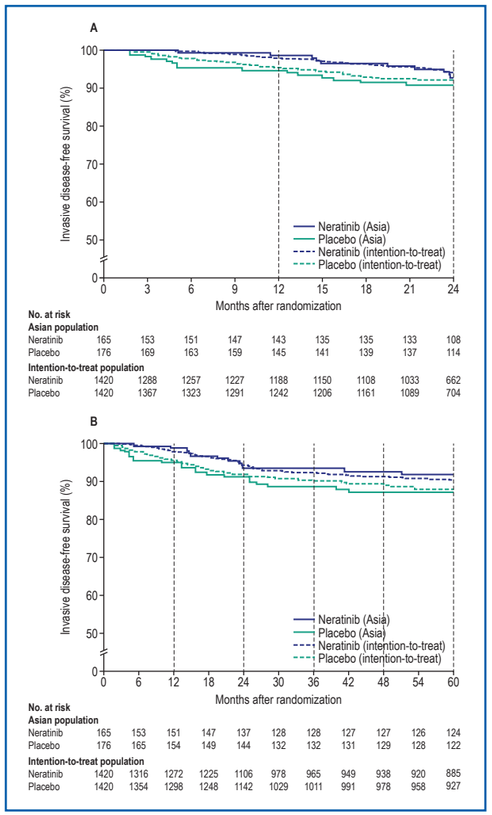
- Efficacy findings are summarized in **Table 2** and Kaplan-Meier curves for iDFS are presented in **Figure 2**.
- After 2 years' follow-up, the iDFS rate in the Asian population was 92.8% in the neratinib group and 90.8% in the placebo group (HR 0.71; 95% CI 0.31–1.57), corresponding with an absolute between-group difference of 2.0%.
- For other secondary endpoints, the trend favoring neratinib treatment was also consistently observed (**Table 2**).
- After 5 years' follow-up, the iDFS rate in the Asian population was 91.9% in the neratinib group and 87.2% in the placebo group (HR 0.54; 95% CI 0.26–1.08), corresponding with an absolute between-group difference of 4.7%.
- The number of CNS recurrences was numerically smaller in the neratinib group than in the placebo group at both time-points (1 *vs* 4 events, respectively).

Table 2. Efficacy findings after 2 and 5 years in the Asian and intention-to-treat populations

	Asian population	Intention-to-treat population	
Parameter	Hazard ratio (95% CI)	Hazard ratio (95% CI)	P value (2-sided)
Primary 2-year analysis			
Invasive disease-free survival	0.70 (0.31–1.55)	0.66 (0.49–0.90)	0.008
Disease-free survival with DCIS	0.66 (0.29–1.43)	0.61 (0.45–0.83)	0.001
Distant disease-free survival	0.59 (0.20–1.54)	0.74 (0.52–1.05)	0.094
Time to distant recurrences	0.59 (0.20–1.54)	0.73 (0.51–1.04)	0.087
5-year analysis			
Invasive disease-free survival	0.57 (0.27–1.13)	0.73 (0.57–0.92)	0.008
Disease-free survival with DCIS	0.55 (0.26–1.08)	0.71 (0.56–0.89)	0.004
Distant disease-free survival	0.50 (0.21–1.07)	0.78 (0.60–1.01)	0.065
Time to distant recurrences	0.50 (0.21–1.07)	0.79 (0.60–1.03)	0.078

CNS, central nervous system; CI, confidence intervals; DCIS, ductal carcinoma *in situ*.

Figure 2. iDFS in Asian and intention-to-treat populations at 2 years (A) and 5 years (B)



Treatment exposure

- In the Asian population, the median duration of treatment was similar in both treatment arms (neratinib, 11.5 months; placebo, 11.6 months).
- However, Asian patients were more likely to complete study treatment (neratinib, 70.3%; placebo, 85.8%) than patients in the overall study population (62.1% *vs* 82.9%, respectively).

Safety

- In the Asian population, diarrhea was the most common adverse event with neratinib (**Table 3**); no grade 4 diarrhea occurred in either treatment group.
- All other grade 3 events occurred in single patients only with neratinib.
- Grade 4 events were reported in 1 patient (0.6%) in the neratinib group (anemia) and 3 patients (1.7%) in the placebo group (brain edema, n=1; amylase increased, abnormal hepatic function, cholestatic jaundice, n=1; gastric cancer, n=1). No grade 4 event was considered to be treatment related.
- One grade 5 event (gastric cancer) occurred in the placebo group.

Table 3. Treatment-emergent adverse events in the Asian safety population (≥10% incidence)

	Neratinib (n=165)		Placebo (n=176)	
Adverse event, n (%)	Any-grade	Grade 3	Any-grade	Grade 3
Diarrhea	162 (98.2)	76 (46.1)	82 (46.6)	3 (1.7)
Nausea	58 (35.2)	1 (0.6)	30 (17.0)	0
Fatigue	31 (18.8)	0	19 (10.8)	0
Vomiting	51 (30.9)	1 (0.6)	14 (8.0)	0
Abdominal pain	28 (17.0)	0	20 (11.4)	0
Headache	27 (16.4)	0	27 (15.3)	0
Abdominal pain upper	27 (16.4)	1 (0.6)	11 (6.3)	0
Rash	51 (30.9)	1 (0.6)	17 (9.7)	0
Decreased appetite	29 (17.6)	1 (0.6)	7 (4.0)	0
Dizziness	15 (9.1)	1 (0.6)	21 (11.9)	1 (0.6)
Stomatitis	40 (24.4)	1 (0.6)	14 (8.0)	0
Nasopharyngitis	25 (15.2)	0	54 (30.7)	0
Paronychia	24 (14.5)	1 (0.6)	0	0
Influenza-like illness	23 (13.9)	0	22 (12.5)	0
Weight decreased	21 (12.7)	1 (0.6)	2 (1.1)	0
Pyrexia	17 (10.3)	0	10 (5.7)	0
Palmar-plantar erythrodysesthesia	17 (10.3)	0	2 (1.1)	0

Note: Adverse events were graded according to National Cancer Institute Common Terminology Criteria, version 3.0.

- With the exception of lower rates of dizziness and nasopharyngitis, Asian patients treated with neratinib experienced higher rates of all-grade adverse events compared with those who received placebo.
- Grade 3 diarrhea was also more common with neratinib in Asian patients (46.1%) compared with the rate seen in the overall safety population (39.8%).

Conclusions

- In ExteNET, the benefits of neratinib appeared to be similar among Asian patients than in the intention-to-treat population at both the 2-year and 5-year timepoints.
- Asian patients treated with neratinib experienced a higher rate of most adverse events compared with those receiving placebo, although this did not appear to impact on treatment duration or efficacy outcome.
- Despite small patient numbers, our analyses suggest that the findings from ExteNET are applicable to Asian patients.

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Acknowledgements

ExteNET was sponsored by Wyeth, Pfizer, and Puma Biotechnology Inc.
Puma Biotechnology Inc. also funded the provision of editorial support provided by Miller Medical Communications.

Presented at the 40th Annual San Antonio Breast Cancer Symposium (SABCS), Dec 5–9, 2017 in San Antonio, TX