Improved central nervous system outcomes in patients with early-stage HER2-positive breast cancer who receive neratinib for the recommended duration: Findings from the phase 3 ExteNET trial

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Background

- Non-adherence or early discontinuation of systemic adjuvant therapy has been documented in a substantial number of patients and is associated with higher disease recurrence and mortality.
- Neratinib, an oral irreversible pan-HER tyrosine kinase inhibitor, significantly improves invasive disease-free survival (iDFS) when given as extended adjuvant therapy after trastuzumab-based therapy in patients with early-stage HER2-positive (HER2+) breast cancer based on findings from the phase 3 ExteNET trial:[6,7]
  - Numerical improvements in CNS endpoints were also observed with neratinib compared to placebo.
- In ExteNET, which did not mandate anti-diarrheal prophylaxis, 28% of patients discontinued therapy early (≤3 months) primarily because of adverse events, most commonly diarrhea:[8]
  - The CONTROL trial has subsequently shown that the tolerability of neratinib may be improved with dose escalation of neratinib and anti-diarrheal prophylaxis.[9]
- Prior analyses from ExteNET have shown improved iDFS, distant disease-free survival and overall survival (OS) in patients who completed the planned duration of neratinib therapy.[8, 10–11]

Objectives

- To assess central nervous system (CNS) outcomes in patients from ExteNET who completed neratinib therapy as planned.
- Data are reported for the intention-to-treat (ITT) population, the patient population with hormone receptor-positive (HR+) disease who initiated neratinib within 1 year after prior trastuzumab (HR+/≤1-year post-trastuzumab; EU indication), as well as subgroups of clinical interest.

Methods

Study design

- ExteNET was a multicenter, randomized, double-blind, placebo-controlled phase 3 trial (Clinicaltrials.gov: NCT00878709).[6]
- Patients with early-stage HER2+ breast cancer received oral neratinib 240 mg/day or placebo for 12 months after trastuzumab-based (neo)adjuvant therapy.
- Patients who completed neratinib therapy (defined as treatment duration ≥11 months or cessation of neratinib if recurrence occurred prior to 11 months) were compared with placebo (all randomized patients).

Endpoints

- OS was defined as time from randomization to date of death of any cause.
- CNS-specific endpoints:
  - *Cumulative incidence of CNS recurrences*: defined as time from randomization to CNS recurrence as first distant recurrence. Any patient who was alive and for whom distant recurrence had not been observed by the data cut-off was censored at the date of their last physical examination (prespecified endpoint).
  - *CNS-disease-free survival (CNS-DFS)*: defined as time from randomization to any CNS recurrence (first or subsequent) or death from any cause (ad-hoc endpoint)

Statistical analyses

- Kaplan-Meier methods were used to estimate CNS-DFS and OS rates.
- Hazard ratios (HR) with 95% confidence intervals (CI) for neratinib versus placebo were estimated using a Cox proportional hazards model.
- Cumulative incidence competing risks analysis was performed for CNS recurrences.
- Data cut-offs:
  - CNS-specific endpoints: March 2017.
  - OS: July 2019 (median follow-up 8.0 years; range 0–9.8 years).

Results

Patients

- 2840 patients were randomly assigned to study treatment (1420 per group):
  - 1631 patients (57%) had HR+ disease, of whom 1334 (82%) initiated study treatment within 1 year of prior trastuzumab and comprised the HR+/≤1-year population (EU indication).
- Key baseline characteristics are presented in **Table 1**.

Exposure

- Cumulative doses for neratinib and placebo over the duration of the study are presented in **Table 2**.
  - Cumulative dose of neratinib was increased by ~45% in patients who completed ≥11 months of therapy versus the corresponding overall randomized population.

Table 1. Key baseline characteristics

	ITT population		HR+/≤1-year[a] population (EU indication)	
	Neratinib completed therapy[b] (N=872)	Placebo overall (N=1420)	Neratinib completed therapy[b] (n=402)	Placebo overall (n=664)
Median age, years (range)	51 (26–83)	52 (23–82)	50 (26–83)	51 (23–78)
HR status, n (%)				
Positive	485 (56)	815 (57)	402 (100)	664 (100)
Negative	387 (44)	605 (43)	–	–
Nodal status, n (%)				
Negative	174 (20)	336 (24)	60 (15)	125 (19)
Positive	698 (80)	1084 (76)	342 (85)	539 (81)
Prior trastuzumab regimen, n (%)				
Concurrent	530 (61)	886 (62)	247 (61)	415 (63)
Sequential	342 (39)	534 (38)	155 (39)	249 (38)

[a]HR+ and ≤1-year after prior trastuzumab.
[b]Defined as ≥11 months of neratinib therapy or ended neratinib treatment due to disease recurrence prior to 11 months.
EU, European Union; HR, hormone receptor; HR+, hormone receptor-positive; ITT, intention-to-treat.

Table 2. Cumulative dose (Safety population)

	ITT population			HR+/≤1-year[a] population (EU indication)		
	Neratinib		Placebo	Neratinib		Placebo
	Overall (n=1408)	Completed therapy[b] (n=872)	Overall (n=1408)	Overall (n=662)	Completed therapy[b] (n=402)	Overall (n=657)
Actual dose intensity,[c] mg/day						
Mean (SD)	210 (43)	219 (31)	235 (12)	210 (44)	221 (30)	236 (11)
Cumulative dose, mg						
Mean (SD)	54,194 (34,205)	78,410 (11,965)	76,749 (20,842)	53,709 (34,866)	79,025 (11,410)	76,606 (21,482)
Median (range)	70,200 (240–92,400)	84,000 (13,920–92,400)	85,200 (960–95,040)	69,800 (240–92,400)	84,240 (13,920–92,400)	85,440 (960– 94,080)

[a]HR+ and ≤1-year after prior trastuzumab; [b]Defined as ≥11 months of neratinib therapy or ended neratinib treatment due to disease recurrence prior to 11 months; [c]Defined as actual cumulative dose divided by treatment duration.
EU, European Union; HR+, hormone receptor-positive; ITT, intention-to-treat, SD, standard deviation.

Efficacy

Cumulative incidence of CNS as first site of recurrence

- The reduction in CNS events seen in the neratinib arm was independent of duration of therapy, although event numbers were small (**Table 3**).
- Cumulative incidence of CNS recurrences at 5 years:
  - In the ITT population was 1.3% (16 events) with neratinib and 1.4% (12 events) in those who completed planned duration of therapy versus 1.8% (23 events) with placebo.
  - In the HR+/≤1-year population was 0.7% (4 events) with neratinib and 0.8% (3 events) in those who completed planned duration of therapy versus 2.1% (12 events) with placebo.

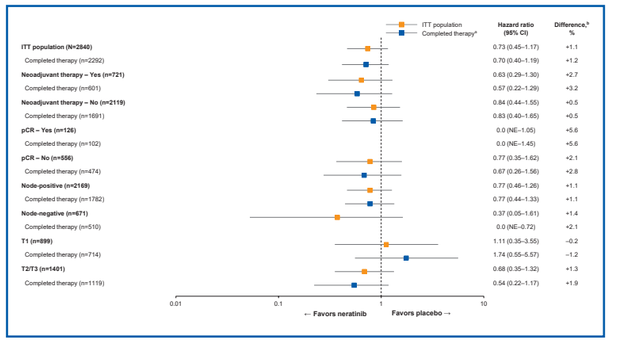
CNS-DFS

- For CNS-DFS, a composite endpoint that accounts for both first and subsequent CNS recurrences as well as death from any cause, the HR was improved in patients who completed the planned duration of treatment (**Table 4**).
  - In the ITT population, the HR for CNS-DFS changed from 0.73 to 0.70 in patients who completed planned duration of therapy.
  - In the HR+/≤1-year population, the HR for CNS-DFS changed from 0.41 to 0.27 in patients who completed planned duration of therapy.

Overall survival

- Numerical improvements in OS were also observed upon completion of neratinib therapy (**Table 4**).

Figure 1. Subgroup analyses of CNS-DFS (ITT population)



[a]Completed therapy defined as ≥11 months of therapy or ended treatment due to disease recurrence prior to 11 months (neratinib arm), and all randomized subjects (placebo arm); [b]Difference in event-free survival estimates (neratinib vs placebo). CI, confidence interval; CNS-DFS, central nervous system disease-free survival; ITT, intention-to-treat; NE, not estimable because there were no events in the neratinib arm; pCR, pathologic complete response.

Table 3. Cumulative incidence of CNS events as first site of recurrence

			First site of CNS recurrence at 5 years			
			Events, n		Cumulative incidence of CNS recurrences (95% CI), %	
Population or subgroup	Neratinib	Placebo	Neratinib	Placebo	Neratinib	Placebo
ITT population	1420	1420	16	23	1.3 (0.8–2.1)	1.8 (1.2–2.7)
Completed therapy[a]	872	1420	12	23	1.4 (0.8–2.4)	1.8 (1.2–2.7)
HR+/≤1-year population[b] (EU indication)	670	664	4	12	0.7 (0.2–1.7)	2.1 (1.1–3.5)
Completed therapy[a]	402	664	3	12	0.8 (0.2–2.1)	2.1 (1.1–3.5)

Cut-off date: March 2017.
[a]Defined as ≥11 months of neratinib therapy or ended neratinib treatment due to disease recurrence prior to 11 months.
[b]HR+ and ≤1-year after prior trastuzumab.
CI, confidence interval; CNS, central nervous system; HR+, hormone-receptor-positive; ITT, intention-to-treat.

Table 4. CNS-DFS and OS

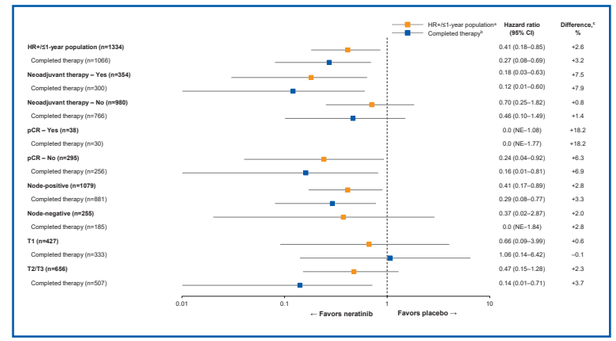
	N		CNS-DFS rate (5-year analysis)		OS rate[a]	
Population or subgroup	Neratinib	Placebo	Difference, %[b]	HR (95% CI)	Difference, %[b]	HR (95% CI)
ITT population	1420	1420	+1.1	0.73 (0.45–1.17)	–0.1	0.95 (0.75–1.21)[c]
Completed therapy[d]	872	1420	+1.2	0.70 (0.40–1.19)	+2.0	0.78 (0.58–1.04)
HR+/≤1 year[e] population (EU indication)	670	664	+2.6	0.41 (0.18–0.85)	+2.1	0.79 (0.55–1.13)
Completed therapy[d]	402	664	+3.2	0.27 (0.08–0.69)	+5.8	0.49 (0.29–0.78)

[a]OS analysis after a median follow-up of 8.0 years (range, 0–9.8); [b]Difference in event-free survival estimates (neratinib vs placebo); [c]Stratified by randomization stratification factors; [d]Defined as ≥11 months of neratinib therapy or ended neratinib treatment due to disease recurrence prior to 11 months; [e]HR+ and ≤1 year after prior trastuzumab.
CI, confidence interval; HR, hazard ratio; CNS-DFS, central nervous system disease-free survival; HR+, hormone receptor-positive; ITT, intention-to-treat; OS, overall survival.

Subgroup analyses

- The numerical improvements observed with neratinib versus placebo for CNS-DFS were greater in a number of higher-risk patient subgroups who completed neratinib therapy, as compared to the corresponding overall randomized patient group (**Figures 1 and 2**).

Figure 2. Subgroup analyses of CNS-DFS (HR+/≤1-year population)



[a]Completed therapy defined as ≥11 months of therapy or ended treatment due to disease recurrence prior to 11 months (neratinib arm), and all randomized subjects (placebo arm); [b]Difference in event-free survival estimates (neratinib vs placebo). CI, confidence interval; CNS-DFS, central nervous system disease-free survival; NE, not estimable because there were no events in the neratinib arm; pCR, pathologic complete response.

Conclusions

- These descriptive findings suggest greater benefits in patients who completed neratinib therapy as planned:
  - Greater numerical improvements were seen for CNS-DFS, consistent with improvements previously reported for iDFS, DDFS and OS.
- Optimal anti-diarrheal management to minimize diarrhea and increase likelihood of completing planned treatment is recommended.[9,12]

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