Continued efficacy of neratinib in patients with HER2-positive early-stage breast cancer: Final overall survival analysis from the randomized phase 3 ExteNET trial

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Background

- Neratinib (NERLYNX®), a small-molecule irreversible pan-HER tyrosine kinase inhibitor (TKI), significantly improves invasive disease-free survival (iDFS) compared with placebo when given as extended adjuvant therapy for 1 year in patients with HER2-positive (HER2+) early breast cancer after trastuzumab-based adjuvant therapy:[1]
  - The benefit with neratinib in the extended adjuvant setting as demonstrated by the ExteNET trial is in contrast to the HERA trial in which the use of trastuzumab for 2 years did not improve outcomes.[2] Neratinib and trastuzumab are thought to be non-cross-resistant, possibly due to differing mechanisms of action.
- In the phase 3 ExteNET trial, an absolute iDFS benefit of 2.5% and distant disease-free survival (DDFS) benefit of 1.7% was observed with neratinib *vs* placebo in the intention-to-treat (ITT) population after 5 years' follow-up (**Table 1**):[3]
  - More marked benefits in iDFS and DDFS were seen in patients with hormone receptor-positive (HR+) disease who initiated treatment within 1 year of completing trastuzumab (HR+/≤1-year; EU indication), and in the high-risk patient group with residual disease after neoadjuvant therapy (HR+/≤1-year no pCR).[4]

Table 1. Effects of neratinib vs placebo on iDFS and DDFS in the ExteNET trial at 5 years[3,4]

ExteNET population	5-year iDFS absolute benefit	HR (95% CI)	5-year DDFS absolute benefit	HR (95% CI)
Intention-to-treat (n=2840)	2.5%	0.73 (0.57–0.92)	1.7%	0.78 (0.60–1.01)
HR+/≤1-year (EU indication) (n=1334)	5.1%	0.58 (0.41–0.82)	4.7%	0.57 (0.39–0.83)
HR+/≤1-year no pCR (n=295)	7.4%	0.60 (0.33–1.07)	7.0%	0.61 (0.32–1.11)

CI, confidence interval; DDFS, distant disease-free survival; HR, hazard ratio; HR+, hormone receptor-positive; iDFS, invasive disease-free survival; pCR, pathologic complete response.

- In the metastatic setting, neratinib has shown central nervous system (CNS) efficacy in 3 trials, demonstrating reduced time to intervention for CNS metastases,[5] clinically significant response rates in patients with progressive brain metastases,[6] and prevention of new CNS metastases.[7]
- In the adjuvant setting, no HER2-directed therapy (antibody or reversible TKI) has been shown to prevent CNS metastases (**Table 2**).[8–10]

Table 2. CNS as site of first recurrence in early-stage HER2+ breast cancer trials

Study	Follow-up, years	Patient population	CNS recurrences, %			
			Control group		Experimental group	
ALTTO[8]	3	Early-stage HER2+ (n=8381)	Trastuzumab	2	Trastuzumab + lapatinib	2
APHINITY[9]	6	Early-stage HER2+ (n=4804)	Trastuzumab	2	Pertuzumab + trastuzumab	2
KATHERINE[10]	3	High-risk early-stage HER2+ (no pCR) (n=1486)	Trastuzumab	4.3	Trastuzumab emtansine	5.9

CNS, central nervous system; HER2+, HER2-positive; pCR, pathologic complete response.

- Therapies that prevent CNS recurrence as first iDFS event remain an unmet need in HER2+ breast cancer.[10,11]

Objectives

- We report the final protocol-defined analysis of overall survival (OS) from the ExteNET trial in the ITT population.
- In addition, we present descriptive analyses of OS and CNS outcomes in subgroups of clinical interest:
  - HR+/≤1-year population, per the approved indication of neratinib in Europe.[12]
  - Subgroups at higher risk of relapse, including HR+/≤1-year no pCR.

Methods

Study design

- ExteNET was a multicenter, randomized, double-blind, placebo-controlled phase 3 trial (Clinicaltrials.gov: NCT00878709). The study design has been described in detail previously:[1]
  - Randomization was stratified by locally determined HR status (HR+ vs HR–), schedule of trastuzumab administration (sequential vs concurrent administration with chemotherapy), and nodal status (0, 1–3 or ≥4 positive nodes).
  - Patients were randomly assigned to oral neratinib 240 mg/day or placebo for 1 year; antidiarrheal prophylaxis was not mandated in ExteNET.

Patients

- Women with stage 1–3c HER2+ primary breast cancer who received locoregional treatment and completed trastuzumab-based adjuvant therapy (with or without prior neoadjuvant therapy) within 2 years of randomization were eligible:
  - Recruitment was restricted in February 2010 (protocol amendment 3) to higher-risk patients with stage 2–3c disease, completion of trastuzumab within 1 year of randomization, and no pCR for patients who completed neoadjuvant therapy.

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 or death from any cause (ad-hoc endpoint).

Statistical analyses

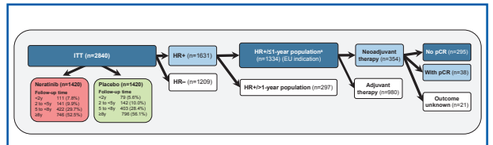
- Preplanned analyses of OS were performed in the ITT population, which were powered for 248 events and hazard ratio (HR) of 0.70 with 80% power and one-sided 0.025 type I error rate.
- Descriptive analyses of OS and 5-year CNS outcomes were performed in the HR+/≤1-year population and high-risk subgroups.
- Survival rates for OS and CNS-DFS were estimated by the Kaplan-Meier method. HR and 95% confidence intervals (CI) for were estimated from Cox proportional hazards models, and tested with a log-rank test (OS only).
- Cumulative incidence of CNS recurrences was analysed by competing risks analysis, and tested via Gray's method.

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 constituted the HR+/≤1-year population (**Figure 1**).
  - 354 patients of the HR+/≤1-year population (27%) had received neoadjuvant therapy, of whom 295 patients had residual invasive disease (no pCR) at study entry (**Figure 1**).
  - Baseline characteristics in the HR+/≤1-year population and no pCR subgroup were balanced between treatment groups and similar to the ITT population (**Table 3**).
- Median duration of follow-up for OS was 8.1 (range, 0.0–9.9) years:
  - A total of 1542 patients (54.3%) completed at least 8 years of follow-up.

Figure 1. Overall survival analysis: patient flowchart



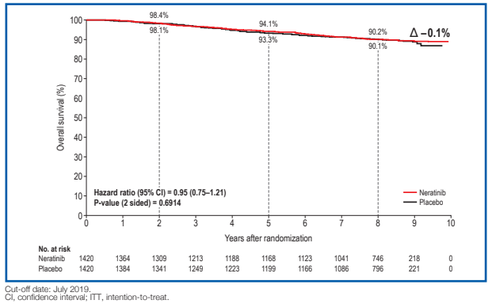
[a]Patients with HR+ breast cancer who initiated study treatment within 1 year of completing prior trastuzumab-based therapy.
HR+, hormone receptor-positive; HR–, hormone receptor-negative; ITT, intention-to-treat; pCR, pathologic complete response.

Table 3. Key baseline characteristics

	Intention-to-treat population (n=2840)		HR+/≤1-year population[a] (EU indication) (n=1334)		HR+/≤1-year[a] no pCR (n=295)	
	Neratinib (n=1420)	Placebo (n=1420)	Neratinib (n=670)	Placebo (n=664)	Neratinib (n=131)	Placebo (n=164)
Median age (range), years	52 (25–83)	52 (23–82)	51 (25–83)	51 (23–78)	49 (25–76)	49 (26–76)
Hormone receptor status, n (%)						
Positive	816 (57)	815 (57)	670 (100)	664 (100)	131 (100)	164 (100)
Negative	604 (43)	605 (43)	–	–	–	–
Nodal status, n (%)						
Negative	335 (24)	336 (24)	130 (19)	125 (19)	15 (12)	20 (12)
Positive	1085 (76)	1084 (76)	540 (81)	535 (81)	116 (89)	144 (88)
Prior trastuzumab regimen, n (%)						
Concurrent	884 (62)	886 (62)	411 (61)	415 (63)	90 (69)	111 (68)
Sequential	536 (38)	534 (38)	259 (39)	249 (38)	41 (31)	53 (32)

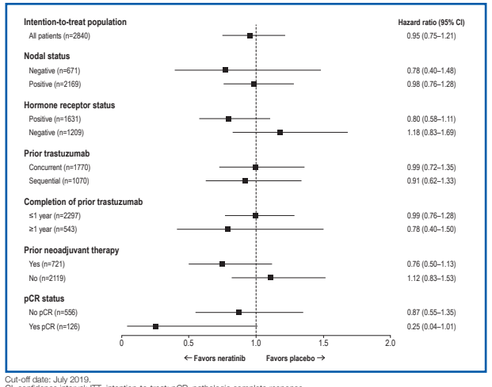
[a]Patients with HR+ breast cancer who initiated study treatment within 1 year of completing prior trastuzumab-based therapy.
HR+, hormone receptor-positive; pCR, pathologic complete response

Figure 2. Overall survival (ITT population)



Cut-off date: July 2019.
CI, confidence interval; ITT, intention-to-treat.

Figure 3. Overall survival forest plot (ITT population)

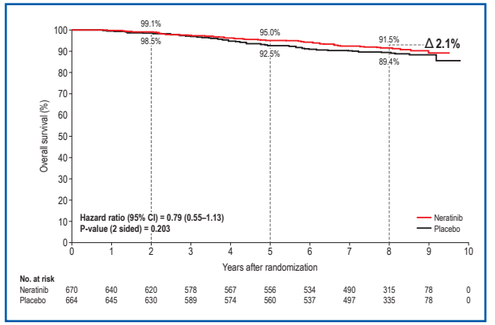


Cut-off date: July 2019.
CI, confidence interval; ITT, intention-to-treat; pCR, pathologic complete response.

Overall survival

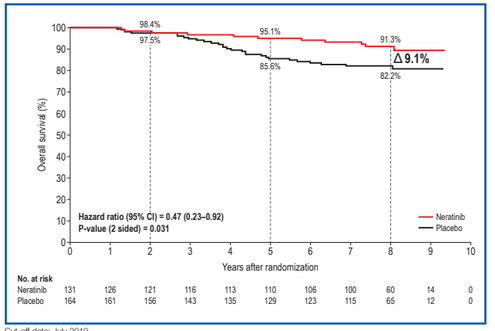
- In the ITT population:
  - At the analysis cut-off date (July 2019), 127 of 1420 patients (8.9%) in the neratinib group and 137 of 1420 patients (9.6%) in the placebo group died.
  - Estimated 8-year OS rates were 90.1% in the neratinib group and 90.2% in the placebo group (stratified HR 0.95; 95% CI 0.75–1.21; p=0.6916; **Figure 2**).
- Subgroup analyses of OS were consistent with iDFS results (**Figure 3**):
  - Neratinib numerically improved OS in patients with HR+ disease (n=1631): 8-year OS rates were 91.6% in the neratinib group and 90.1% in the placebo group (HR 0.80; 95% CI 0.58–1.12).
  - Neratinib did not appear to improve OS in patients with HR– disease (n=1209): 8-year OS rates were 88.1% in the neratinib group and 90.3% in the placebo group (HR 1.18; 95% CI 0.83–1.69).
- In the HR+/≤1-year population:
  - 53 of 670 patients (7.9%) in the neratinib group and 68 of 664 patients (10.2%) in the placebo group died.
  - Estimated 8-year OS rates were 91.5% in the neratinib group and 89.4% in the placebo group, corresponding to a 2.1% absolute benefit (HR 0.79; 95% CI 0.55–1.13; **Figure 4**).
- Within the HR+/≤1-year population by pCR status:
  - In patients with no pCR (n=295), 8-year OS rates were 91.3% in the neratinib group and 82.2% in the placebo group, corresponding to a 9.1% absolute benefit (HR 0.47; 95% CI 0.23–0.92; **Figure 5**).
  - In patients with a pCR (n=38), 8-year OS rates were 93.3% in the neratinib group and 73.7% in the placebo group, corresponding to a 19.6% absolute benefit (HR 0.40; 95% CI 0.06–1.88).

Figure 4. Overall survival (HR+/≤1-year population)[a]



Cut-off date: July 2019.
[a]Patients with HR+ breast cancer who initiated study treatment within 1 year of completing prior trastuzumab-based therapy.
CI, confidence interval; HR+, hormone receptor-positive.

Figure 5. Overall survival (HR+/≤1-year no pCR)



Cut-off date: July 2019.
CI, confidence interval; HR+, hormone receptor-positive.

CNS outcomes

- CNS outcomes in the HR+/≤1-year population and subgroups are presented in **Tables 4 and 5**:
  - Patients in the neratinib group had a lower number of CNS events in all populations: ITT, HR+/≤1-year, and patients who received neoadjuvant therapy (pCR and no pCR).

Table 4. Cumulative incidence of CNS recurrences at 5 years

Population or subgroup	Events, n		Cumulative incidence of CNS recurrences (95% CI), %	
	Neratinib	Placebo	Neratinib	Placebo
Intention-to-treat population[3] (n=2840)	16	23	1.3 (0.8–2.1)	1.8 (1.2–2.7)
HR+/≤1-year population[3] **(EU indication)** (n=1334)	4	12	0.7 (0.2–1.7)	2.1 (1.1–3.5)
Prior neoadjuvant therapy (n=1334)				
No (n=980)	3	6	0.7 (0.2–2.0)	1.5 (0.6–3.0)
Yes (n=354)	1	6	0.7 (0.1–3.3)	3.7 (1.5–7.4)
pCR status (n=354)[b]				
No (n=295)	1	5	0.8 (0.1–4.0)	3.6 (1.3–7.8)
Yes (n=38)[c]	0	1	0 (NE)	5.0 (0.3–21.2)

Cut-off date: March 2017. CI, confidence interval; CNS, central nervous system; NE, not estimable; pCR, pathologic complete response.
[a]Patients with HR+ breast cancer who initiated study treatment within 1 year of completing prior trastuzumab-based therapy.
[b]Among the 354 patients who had received neoadjuvant therapy, 295 patients had no pCR, 38 patients achieved a pCR, and 21 patients had no outcome reported.
[c]Small patient numbers, interpret with caution.

Table 5. CNS disease-free survival at 5 years

Population or subgroup	Events, n		Kaplan-Meier estimate at 5 years (95% CI), %		Hazard ratio (95% CI)
	Neratinib	Placebo	Neratinib	Placebo	
Intention-to-treat population (n=2840)	29	42	97.5 (96.4–98.3)	96.4 (95.2–97.4)	0.73 (0.45–1.17)
HR+/≤1-year population[a] **(EU indication)** (n=1334)	9	23	98.4 (96.8–99.1)	95.7 (93.6–97.2)	0.41 (0.18–0.85)
Prior neoadjuvant therapy (n=1334)					
No (n=980)	7	10	98.2 (96.3–99.2)	97.5 (95.3–98.6)	0.70 (0.25–1.82)
Yes (n=354)	2	13	98.7 (94.8–99.7)	91.2 (85.1–94.8)	0.18 (0.03–0.63)
pCR status (n=354)[b]					
No (n=295)	2	10	98.4 (93.6–99.6)	92.0 (85.6–95.7)	0.24 (0.04–0.92)
Yes (n=38)[c]	0	3	100 (100–100)	81.9 (53.1–93.9)	0 (NE, 1.08)

Cut-off date: March 2017. CI, confidence interval; CNS, central nervous system; NE, not estimable; pCR, pathologic complete response.
[a]Patients with HR+ breast cancer who initiated study treatment within 1 year of completing prior trastuzumab-based therapy.
[b]Among the 354 patients who had received neoadjuvant therapy, 295 patients had no pCR, 38 patients achieved a pCR, and 21 patients had no outcome reported.
[c]Small patient numbers, interpret with caution.

Follow-up anti-cancer therapy

- In the ITT population, uptake of anti-cancer medications during follow-up was balanced in both groups (neratinib, 25.2% vs placebo, 28.2%; **Table 6**).

Table 6. Common follow-up anti-cancer medications (ITT population)

	Neratinib (n=1420)	Placebo (n=1420)
Any medication	358 (25.2)	400 (28.2)
Endocrine therapy	276 (19.4)	282 (19.9)
HER2-directed agents	89 (6.3)	119 (8.4)
Chemotherapeutic agents	86 (6.1)	126 (8.9)
Other	48 (3.4)	61 (4.3)

Safety

- Safety analysis from ExteNET has been published previously.[1]
- Neratinib dose-escalation strategy has since been shown in the phase 2 CONTROL study[13] to reduce the rate of grade 3 diarrhea (13.3% vs 40% in ExteNET[1]) and rate of discontinuation due to diarrhea (3.3% vs 17% in ExteNET[1]).

Conclusions

- In the final protocol-defined analysis, there were fewer deaths in the neratinib arm, but no significant improvement in OS (HR 0.95; 95% CI 0.75–1.21) in the ExteNET ITT population after 8 years of follow-up:
  - The data suggest an association between neratinib and improved OS in patients with HR+ disease (HR 0.80; 95% CI 0.58–1.12) when compared with patients with HR– tumors (HR 1.18; 95% CI 0.83–1.69), which is consistent with the primary 2-year and 5-year analyses of iDFS and DDFS.
- Descriptive analyses also suggest that neratinib may be associated with longer OS in subgroups of clinical interest including the HR+/≤1-year population (HR 0.79; 95% CI 0.55–1.13), and in the high-risk patient subgroup with residual disease after neoadjuvant therapy (HR 0.47; 95% CI 0.23–0.92):
  - Clinically meaningful improvements were consistently observed across the endpoints (iDFS, DDFS, OS).
- Neratinib is the first HER2-directed agent to show a trend towards improved CNS outcomes in early-stage HER2+ breast cancer:
  - In all groups (ITT, HR+/≤1-year, and no pCR), consistently fewer CNS events were observed in the neratinib arm compared with placebo.

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