Efficacy of neratinib in hormone receptor-positive patients who initiated treatment within 1 year of completing trastuzumab-based adjuvant therapy in HER2+ early stage breast cancer: subgroup analyses from the phase III ExteNET trial

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Introduction

- Neratinib, an irreversible pan-HER tyrosine kinase inhibitor, is approved in the US for the extended adjuvant treatment of adult patients with early-stage HER2-overexpressed/amplified (HER2+) breast cancer, to follow adjuvant trastuzumab-based therapy.[1]
- It has been recently granted marketing authorization by the European Commission (EC) for the extended adjuvant treatment of adult patients with early-stage hormone receptor-positive (HR+) HER2+ breast cancer who are less than 1 year from the completion of prior adjuvant trastuzumab-based therapy.[2]
- The international, randomized, placebo-controlled phase III ExteNET trial (NCT00878709)[3] showed that 1 year of neratinib 240 mg/day after trastuzumab-based (neo)adjuvant therapy significantly improved 2-year invasive disease-free survival (iDFS) (hazard ratio 0.66; 95% confidence intervals [CI] 0.49–0.90; p=0.008),[1] and also had a durable iDFS benefit after 5 years' follow-up (hazard ratio 0.73; 95% CI 0.57–0.92; p=0.008).[4]
- A protocol-defined subgroup analysis of ExteNET after 2 years showed greater benefit with neratinib in patients with HR+ breast cancer,[3] which was also durable at 5 years.[4]
- Dual inhibition of HER2/estrogen receptor crosstalk[5] may be responsible for the enhanced efficacy seen in the HR+ subset (95% of the HR+ study population received concurrent endocrine therapy).

Objectives

- To present exploratory analyses from ExteNET examining the efficacy and safety of neratinib in patients with early-stage HR+ HER2+ breast cancer who are less than 1 year from the completion of prior adjuvant trastuzumab-based therapy.
- Exploratory analyses of patients from this population who were treated with neoadjuvant therapy but did not achieve a pathologic complete response (pCR) are also presented.

Methods

Study design and treatment

- 2840 women aged ≥18 years with early-stage HER2+ breast cancer who had completed trastuzumab-based (neo)adjuvant therapy without evidence of recurrence were treated with oral neratinib 240 mg once daily or placebo for 1 year.
- Randomization was stratified by HR status (determined locally before trial entry according to local criteria), schedule of trastuzumab administration, and nodal status.
- 94% and 95% of patients with HR+ disease in the neratinib and placebo groups, respectively, received concurrent endocrine therapy.
- Antidiarrheal prophylaxis was not mandated by the study protocol.

Endpoints and statistical analysis

- Primary: iDFS, defined as time from randomization to first occurrence of invasive ipsilateral tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence or death from any cause.
- Secondary: disease-free survival including ductal carcinoma in situ (DFS-DCIS); distant disease-free survival (DDFS); time to distant recurrence (TDR); incidence of central nervous system (CNS) recurrences; overall survival; and safety.
- Efficacy analyses were done by intent-to-treat (ITT), and safety analyses included all patients who received ≥1 dose of study treatment. Cut-off dates: 2-year analysis, July 2014; 5-year analysis, March 2017.
- Analyses were exploratory, although both variables used to define the population of interest (i.e. HR status and ≤1 year from completion of prior trastuzumab-based therapy) were prespecified individually in the statistical analysis plan.
- Time-to-event efficacy endpoints were tested with a 2-sided log-rank test, and hazard ratios (95% CI) were estimated using a Cox proportional hazards model. Kaplan Meier methods were used to estimate 2-year and 5-year event-free rates.
- Cumulative incidence of CNS recurrence as first distant recurrence was analyzed by competing risks analysis and compared via Gray's method.
- Exploratory subgroup analyses of iDFS were performed to examine the effects of baseline factors of interest (i.e. nodal status, schedule of trastuzumab administration, and no pCR after neoadjuvant therapy) on treatment effect.

Results

- Of the 2840 women in the ITT population (neratinib, n=1420; placebo, n=1420), 1334 had HR+ tumors and were randomized to start study treatment within 1 year of completing trastuzumab (neratinib, n=670; placebo, n=664).
- Among patients in this population:
  - Key baseline characteristics were balanced between treatment groups, and similar to those observed in the ITT population (Table 1).
  - The median interval from last dose of trastuzumab to randomization was 3.1 (range, 0.2–12) months in the neratinib group and 3.3 (range, 0.3–12) months in the placebo group.

Table 1. Baseline characteristics

	ITT population (n=2840)		HR+ and ≤1 year from last dose of trastuzumab to randomization (n=1334)		HR+ and ≤1 year from last dose of trastuzumab to randomization and no pCR after neoadjuvant therapy (n=295)	
Study population	Neratinib (n=1420)	Placebo (n=1420)	Neratinib (n=670)	Placebo (n=664)	Neratinib (n=131)	Placebo (n=164)
Median (range) age, years	52 (25–83)	52 (23–82)	51 (25–83)	51 (23–78)	49 (25–76)	49 (26–76)
Race, n (%)						
White	1165 (82)	1135 (80)	564 (84)	544 (82)	98 (75)	130 (79)
Asian	188 (13)	197 (14)	77 (11)	88 (13)	24 (18)	26 (16)
Black	27 (2)	47 (3)	11 (2)	19 (3)	3 (2)	3 (2)
Other	40 (3)	41 (3)	18 (3)	13 (2)	6 (5)	5 (3)
Nodal status,[a] n (%)						
Negative	335 (24)	336 (24)	130 (19)	125 (19)	15 (11)	20 (12)
Positive	1085 (76)	1084 (76)	540 (81)	539 (81)	116 (89)	144 (88)
Hormone receptor status,[ab] n (%)						
Positive	816 (57)	815 (57)	670 (100)	664 (100)	131 (100)	164 (100)
Negative	604 (43)	605 (43)	–	–	–	–
Prior trastuzumab regimen,[a] 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)
Median (range) time from last trastuzumab dose to randomization, months	4.4 (0.2–30.9)	4.6 (0.3–40.6)	3.1 (0.2–12.0)	3.3 (0.3–12.0)	3.0 (0.4–12.0)	2.8 (0.3–11.9)
Prior neoadjuvant therapy, n (%)	342 (24)	397 (27)	162 (24)	192 (29)	131 (100)	164 (100)
pCR	61 (4)	65 (5)	17 (3)	21 (3)	–	–
No pCR	258 (18)	298 (21)	131 (20)	164 (25)	131 (100)	164 (100)
Unknown	23 (2)	16 (1)	14 (2)	7 (1)	–	–

[a]Stratification factor; [b]HR+ defined as estrogen receptor (ER)+ and/or progesterone receptor (PR)+, and HR-negative as ER negative and PR negative.
Note: percentages may not add up to 100 due to rounding.
Abbreviations: pCR, pathologic complete response; ITT, intention-to-treat.

Efficacy

- Among patients with HR+ tumors who started neratinib within 1 year of completing trastuzumab:
  - There was an absolute iDFS benefit of 4.5% with neratinib after 2 years' follow-up [hazard ratio 0.49; 95% CI 0.30–0.78; p=0.002].
  - Treatment benefit was durable with an absolute iDFS benefit of 5.1% with neratinib after 5 years' follow-up [hazard ratio 0.58; 95% CI 0.41–0.82; p=0.002].
  - Kaplan-Meier curves for iDFS (2 and 5 years) separated early and maintained separation (Figure 1).
  - Other secondary time-to-event endpoints were also significantly improved with neratinib compared with placebo at both 2 and 5 years (Figure 2).
  - An absolute DDFS benefit of 3.2% was evident with neratinib after 2 years [hazard ratio 0.53; 95% CI 0.31–0.88; p=0.015], and 4.7% after 5 years [hazard ratio 0.57; 95% CI 0.39–0.83; p=0.003] (Figure 3).
  - The number of CNS recurrence events was low at both 2 years (neratinib, n=2; placebo, n=6) and 5 years (neratinib, n=4; placebo, n=12); the cumulative incidence of CNS recurrences at 2 years was 0.34% with neratinib and 1.01% with placebo (p=0.187), and at 5 years was 0.69% and 2.09% (p=0.055), respectively.
  - Follow up for overall survival is ongoing.

Figure 1. Invasive disease-free survival in patients with HR+ tumors and ≤1 year from last dose of trastuzumab to randomization (n=1334)

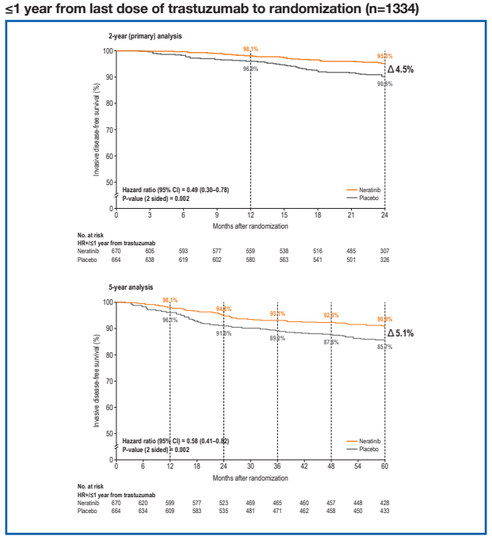
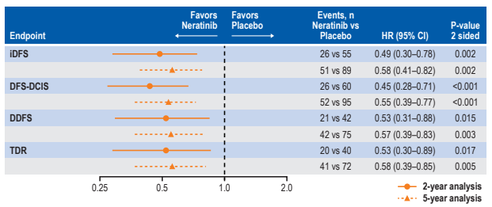


Figure 2. Efficacy outcomes in patients with HR+ tumors and ≤1 year from last dose of trastuzumab to randomization (n=1334)



Abbreviations: DDFS, distant disease-free survival; DFS-DCIS, disease-free survival including ductal carcinoma *in situ*; iDFS, invasive disease-free survival; TDR, time to distant recurrence.

Subgroup analyses

- A subgroup analysis of iDFS showed that the efficacy of neratinib vs placebo was consistent when analyzed by nodal status and schedule of trastuzumab administration (Figure 4).
- In the exploratory subset of patients with HR+ tumors who started treatment within 1 year of completing trastuzumab with no pCR after neoadjuvant therapy (n=295):
  - There was an absolute iDFS benefit of 4.6% with neratinib at 2 years [hazard ratio 0.64; 95% CI 0.30–1.29], and 7.4% with neratinib at 5 years [hazard ratio 0.60; 95% CI 0.33–1.07] (Figure 5). Baseline characteristics for this subgroup are described in Table 1.

Figure 3. Distant disease-free survival in patients with HR+ tumors and ≤1 year from last dose of trastuzumab to randomization (n=1334)

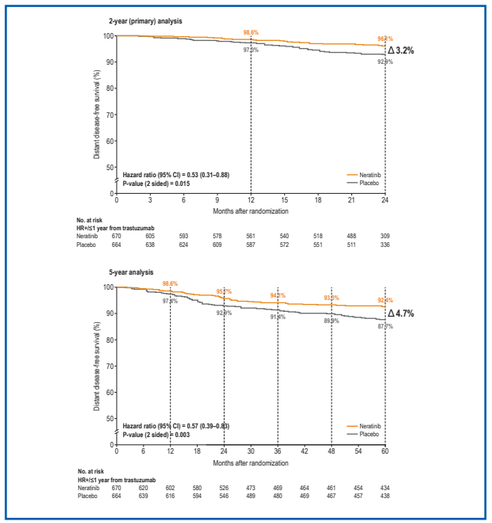


Figure 5. Invasive disease-free survival in patients with HR+ tumors who started treatment within 1 year of completing trastuzumab and who did not have a pCR after neoadjuvant therapy (exploratory subset) (n=295)

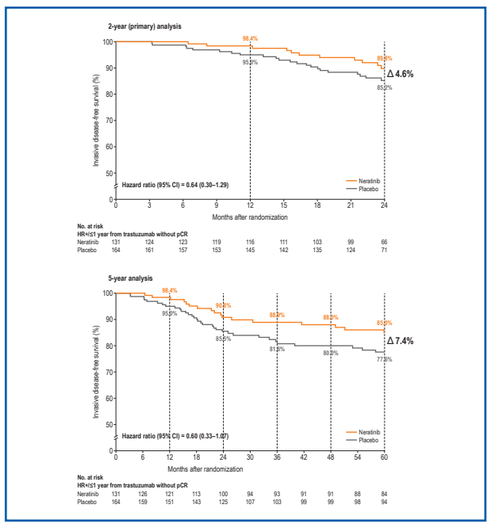
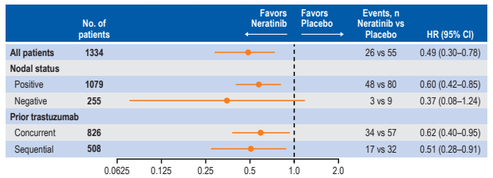


Figure 4. Subgroup analysis of invasive disease-free survival in patients with HR+ tumors and ≤1 year from last dose of trastuzumab to randomization at 5 years (n=1334)



Safety

- 1319 patients with HR+ tumors who started neratinib within 1 year of completing trastuzumab were included in the safety analysis (neratinib, n=662; placebo, n=657).
  - Median duration of treatment was 11.5 months in the neratinib group and 11.9 months in the placebo group.
  - The profile and frequency of treatment-emergent adverse events in this patient population were similar compared with the overall safety population.
    - The most common grade 3 treatment-emergent adverse events were diarrhea (neratinib, 39% vs placebo, 1%), nausea (1% vs <1%), and fatigue (2% vs <1%) [Reference rates in the overall safety population were diarrhea (neratinib, 40% [included one grade 4 event] vs placebo, 2%), nausea (2% vs <1%), and fatigue (2% vs <1%).]
  - Treatment-emergent adverse events led to dose reductions, dose holds and hospitalization in 203 (31%), 280 (42%) and 41 (6%) patients in the neratinib group, respectively, and 13 (2%), 75 (11%), and 35 (5%) patients in the placebo group.

Conclusions and discussion

- **The EC recently granted marketing authorization for neratinib to be used as extended adjuvant treatment in adult patients with early-stage HR+ HER2+ breast cancer who are less than 1 year from the completion of prior adjuvant trastuzumab-based therapy.[2]**
- In exploratory analyses of this patient population:
  - The 2-year absolute iDFS benefit of 4.5% (hazard ratio 0.49; 95% CI 0.30–0.78; p=0.002) was durable at 5 years and increased to 5.1% (hazard ratio 0.58; 95% CI 0.41–0.82; p=0.002).
  - In an exploratory analysis of patients with no pCR after neoadjuvant therapy (20–25% of patients), the absolute iDFS benefit at 5 years was 7.4% (hazard ratio 0.60; 95% CI 0.33–1.07).
  - The profile and frequency of treatment-emergent adverse events in this patient population were similar compared with the overall safety population, with diarrhea being the most common grade 3 adverse event.
  - Antidiarrheal prophylaxis reduced the incidence, severity and duration of neratinib associated diarrhea in early-stage HER2+ breast cancer in the phase II CONTROL study[6] compared with events observed in ExteNET, and is recommended as standard of care for the first 1–2 cycles of neratinib therapy.

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