Journal Pre-proof

Final efficacy results of neratinib in HER2-positive hormone receptor-positive early-stage breast cancer from the phase III ExteNET trial

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ORIGINAL ARTICLE

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Neratinib for Early-Stage HER2-Positive Breast Cancer

International, Randomized, Phase 3 ExteNET Trial

Intention-to-treat population

2840 patients

HER2+ early-stage breast cancer after prior trastuzumab

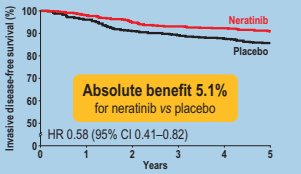
*According to labelling in the European Union and other countries

HER2+/HR+ early-stage breast cancer within 1 year of prior trastuzumab*

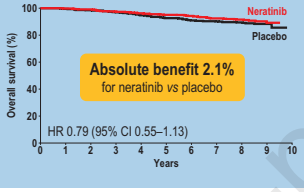
1334 patients

HER2+/HR+ early-stage breast cancer within 1 year of prior trastuzumab

Invasive disease-free survival 5 years' follow-up



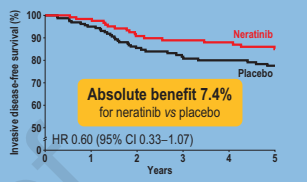
Overall survival 8 years' follow-up

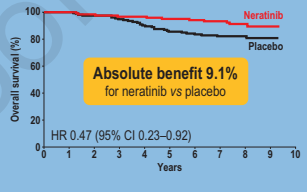


Patients with residual disease after neoadjuvant therapy

295 patients

HER2+/HR+ early-stage breast cancer within 1 year of prior trastuzumab with residual disease after neoadjuvant therapy





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Abbreviations[1]

[1] CI, confidence interval; CONSORT, Consolidated Standards of Reporting Trials; CNS, central nervous system; CNS-DFS, central nervous system disease-free survival; DDFS, distant disease-free survival; DFS-DCIS, disease free survival including ductal carcinoma in situ; eBC, early breast cancer; EMA, European Medicines Agency; FDA, Food and Drug Administration; HER2+, human epidermal growth factor receptor 2-positive; HR+, hormone receptor-positive; HR–, hormone receptor-negative; iDFS, invasive disease-free survival; ITT, intention-to-treat; OS, overall survival; pCR, pathologic complete response; SD, standard deviation; TDR, time to distant recurrence; TEAE, treatment-emergent adverse event.

Conflicts of interest

Declarations of interest: none (Arlene Chan, Janine Mansi, Isil Somali, Noelia Martinez, Mirta Garcia Alonso, John S. Link, Søren Cold, Serafin Morales Murillo, Francis Senecal, and Debra Patt).

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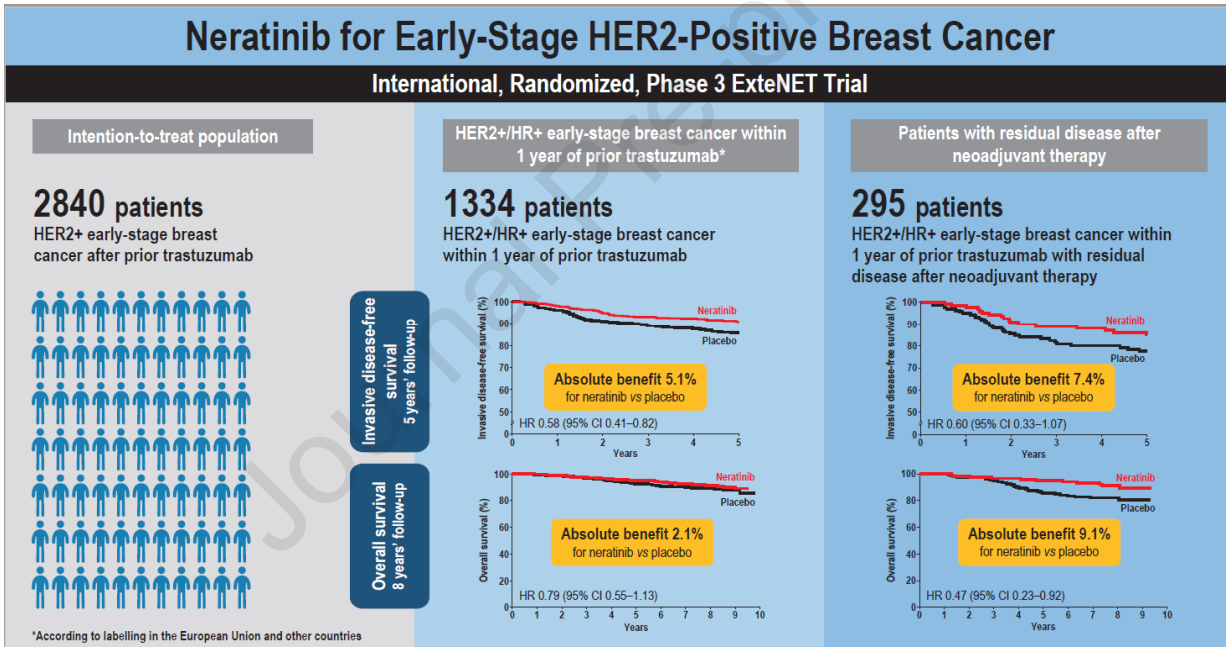
Novartis, OBI, Odonate, Seattle Genetics, and Sermonix, and personal fees from AstraZeneca and Samsung outside the submitted work. Stephen R.D. Johnston reports grants and personal fees from Puma Biotechnology Inc. during the conduct of the study, grants and personal fees from AstraZeneca, Eisai, Eli Lilly, Novartis, Pfizer, and Roche/Genentech outside the submitted work. Richard Bryce, Bo Zhang, Feng Xu, and Alvin Wong are employees of Puma Biotechnology Inc., and own stock in Puma Biotechnology Inc. Miguel Martin reports grants and personal fees from Novartis and Roche/Genentech, and personal fees from Amgen, AstraZeneca, Lilly, Pfizer, Pharmamar, and Puma Biotechnology Inc. outside the submitted work.

MicroAbstract

In the patient population with early-stage HER2+/HR+ breast cancer who initiate neratinib within 1 year of trastuzumab-based therapy, the absolute 5-year invasive disease-free survival benefit versus placebo is 5.1%, and absolute 8-year overall survival benefit is 2.1%. Among those with residual disease after neoadjuvant therapy (non-pathologic complete response), absolute gains with neratinib are 7.4% and 9.1%, respectively.

Word count: 58 words (allowance: 60 words)

Graphical Abstract



Structured Abstract

Background

The ExteNET trial demonstrated improved invasive disease-free survival (iDFS) with neratinib, an irreversible pan-HER tyrosine kinase inhibitor, versus placebo in patients with HER2+ hormone receptor-positive (HR+) early-stage breast cancer (eBC).

Patients and methods

ExteNET was a multicenter, randomized, double-blind, phase III trial of 2840 HER2+ eBC patients after neoadjuvant/adjuvant trastuzumab-based therapy. Patients were stratified by HR status and randomly assigned 1-year oral neratinib 240 mg/day or placebo. Primary endpoint was iDFS. Descriptive analyses were performed in patients with HR+ eBC who initiated treatment ≤1 year (HR+/≤1-year) and >1 year (HR+/>1-year) post-trastuzumab.

Results

HR+/≤1-year and HR+/>1-year populations comprised 1334 (neratinib, *n*=670; placebo, *n*=664) and 297 (neratinib, *n*=146; placebo, *n*=151) patients, respectively. Absolute iDFS benefits at 5 years were 5.1% in HR+/≤1-year (HR=0.58, 95% CI 0.41–0.82) and 1.3% in HR+/>1-year (HR=0.74; 95% CI 0.29–1.84). In HR+/≤1-year, neratinib was associated with a numerical improvement in overall survival (OS) at 8 years (absolute benefit, 2.1%; HR=0.79, 95% CI 0.55–1.13). Of 354 HR+/≤1-year patients who received neoadjuvant therapy, 295 had residual disease and results showed absolute benefits of 7.4% at 5-year iDFS (HR=0.60; 95% CI 0.33–1.07) and 9.1% at 8-year OS (HR=0.47; 95% CI 0.23–0.92). There were fewer CNS events with neratinib. Adverse events were similar to previously reported.

Conclusion

Neratinib significantly improved iDFS in the HER2+/HR+/≤1-year population, and a similar trend was observed in patients with residual disease following neoadjuvant treatment. Numerical improvements in CNS events and OS were consistent with iDFS benefits and suggest long-term benefit for neratinib in this population.

Trial registration: Clinicaltrials.gov identifier: NCT00878709.

Word count: 250 words (allowance: 250 words)

Key words: Adjuvant therapy; Breast cancer; Disease-free survival; Distant disease-free survival; Hormone receptor-positive; HER2-positive; Neoadjuvant therapy; Neratinib; Overall survival

Introduction

Trastuzumab, the first monoclonal antibody to target the human epidermal growth factor receptor 2 (HER2), markedly reduces the risk of disease recurrences and death among patients with HER2-positive (HER2+) early breast cancer (eBC) when added to adjuvant chemotherapy.[1-3] After the initial trials of trastuzumab, several subsequent adjuvant strategies designed to further improve outcomes were unsuccessful, i.e. extending the duration of adjuvant trastuzumab from 1 to 2 years,[4] concurrent or sequential use of lapatinib with trastuzumab,[5] or by adding bevacizumab to trastuzumab.[6] However, significant disease-free survival gains compared with 1 year of trastuzumab have since been reported with other approaches. These include the addition of pertuzumab to trastuzumab,[7,8] targeted use of the anti-HER2 antibody-drug conjugate trastuzumab emtansine in patients with residual disease after neoadjuvant therapy,[9] and extending the duration of adjuvant HER2-based therapy with neratinib, an irreversible pan-HER tyrosine kinase inhibitor, given for 1 year after completion of trastuzumab.[10,11]

Extended adjuvant therapy with neratinib after trastuzumab-based therapy was investigated in the phase III ExteNET trial, in which 1 year of neratinib was shown to significantly improve invasive disease-free survival (iDFS) compared with placebo at the planned primary analysis time-point of 2 years (hazard ratio 0.66; 95% confidence interval [CI] 0.49–0.90; p=0.008).[12] The efficacy of neratinib was confirmed at the 5-year analysis (hazard ratio 0.73; 95% CI 0.57–0.92; p=0.008).[11] A consistent finding at both time-points was that the benefit of neratinib was more marked in predefined subgroups including patients who initiated treatment within 1 year of completing prior trastuzumab compared to those who started treatment later, and among patients with hormone receptor-positive (HR+) versus hormone receptor-negative (HR–) disease.[10,11] The greater efficacy of neratinib in the ExteNET HR+ population (most of whom were receiving concurrent endocrine therapy) may be attributed to the effective inhibition of cross-talk between HER2 and estrogen receptors, a known mechanism of resistance in HER2+/HR+ tumors.[13] Patients with HR+/HER2+ cancers, as for HR+/HER2-negative cancers, are at continuous risk of late recurrences,[14] and the benefit of neratinib as extended adjuvant therapy in this population is biologically sound.

Based on the findings from ExteNET, neratinib was approved by the Food and Drug Administration (FDA) as extended adjuvant therapy in the intention-to-treat (ITT) patient population, which included patients with HR+ and HR– tumors.[12] The European Medicines Agency (EMA) approved neratinib in patients with HER2+/HR+ early-stage breast cancer who initiate treatment within 1 year of completing trastuzumab-based therapy.[15]

We describe clinically relevant breast cancer events in patients with HR+ breast cancer from ExteNET. As the magnitude and durability of iDFS benefit with neratinib was notable in patients with HR+ tumors who initiated treatment within a year of completing trastuzumab, referred to hereafter as the HR+/≤1-year population, we report additional descriptive analyses for this population, including estimates of overall survival (OS). We also report iDFS and OS in a subset of patients considered to be at higher risk of relapse – patients with HR+ tumors with residual disease after neoadjuvant therapy (non-pathologic complete response [non-pCR] subgroup).

Methods

Study design and patients

ExteNET was a multicenter, randomized, double-blind, placebo-controlled phase III trial designed to investigate extended adjuvant therapy with 1 year of neratinib or placebo after standard locoregional treatment, and neoadjuvant and/or adjuvant therapy with chemotherapy and trastuzumab (*n*=2840).[7] The study was initiated in April 2009 and conducted in 40 countries worldwide. The study design comprised 3 parts: Part A, the primary efficacy analysis at 2 years;[10] Part B, a sensitivity analysis of efficacy at 5 years;[11] and Part C, a definitive analysis of OS when 248 deaths had occurred in the ITT population.[12] Randomization was stratified by locally determined HR status, schedule of trastuzumab administration (sequential *vs* concurrent administration with chemotherapy), and nodal status (0, 1–3 or 4+ positive nodes). A detailed description of the study design is provided by Chan et al.[10]

Women aged 18 years or older with stage 1–3c HER2+ primary breast cancer who received standard locoregional treatment and completed neoadjuvant or adjuvant chemotherapy (anthracycline and/or a taxane or non-taxane regimen) plus trastuzumab within 2 years of randomization were eligible. Clinical and radiologic assessments were required to be negative for recurrences or metastatic disease at study entry. Initially all patients who completed neoadjuvant therapy were eligible irrespective of outcome at surgery (pCR and non-pCR patients). Recruitment was restricted in February 2010 (protocol amendment 3) to higher risk patients with stage 2–3c disease and completion of trastuzumab within 1 year of randomization. With this amendment, patients who completed neoadjuvant therapy were eligible only if residual invasive cancer in the breast and/or axilla was present after completing a year of adjuvant trastuzumab. Patients were excluded if they achieved a pCR in breast and/or axilla (if axillary status was known), or if they had only residual in situ disease in breast and/or axilla (if axillary status was known).

The study protocol and subsequent amendments were approved by institutional ethics committees at participating sites. Patients provided written informed consent.

Treatment

Patients were randomized (1:1 ratio) to neratinib 240 mg orally once daily or matching placebo for 1 year or until disease recurrence, new breast cancer, intolerable adverse events or consent withdrawal. Adjuvant endocrine therapy for women with HR+ disease was recommended according to local guidelines. Primary prophylaxis for diarrhea was not protocol-specified, but treatment for diarrhea with loperamide was recommended once symptoms became apparent. Neratinib dose

reductions (200, 160 and 120 mg/day) or dose interruptions were allowed to manage treatment-emergent toxicities; treatment was stopped if neratinib 120 mg was not tolerated or if treatment was interrupted for more than 3 weeks.

Endpoints

The primary endpoint was iDFS, defined as the 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 endpoints were disease-free survival including ductal carcinoma in situ (DFS-DCIS), distant disease-free survival (DDFS), time to distant recurrence (TDR), cumulative incidence of first occurrence of central nervous system (CNS) recurrences, OS, and safety. Definitions for efficacy endpoints are provided in Appendix Table A.1. The composite endpoint of CNS disease-free survival (CNS-DFS), defined as time from randomization to any CNS recurrence or death from any cause, was also evaluated on an exploratory basis. Treatment-emergent adverse events (TEAE) were monitored until 28 days after the last dose of study drug and graded according to National Cancer Institute Common Terminology Criteria, version 3.0.

Statistical analysis

Analyses of protocol-defined 2-year (cut-off date, July 2014), 5-year (cut-off date, March 2017), and OS (cut-off date, July 2019) datasets were performed. Time-to-event endpoints were tested with a 2-sided log-rank test, and hazard ratios with 95% CI were estimated using a Cox proportional hazards model. Kaplan-Meier methods were used to estimate event-free survival rates. Cumulative incidence of CNS recurrence was analyzed by competing risks analysis and tested via Gray's method. All analyses are descriptive and *p*-values presented are without multiplicity adjustments. Safety analyses included all patients who received at least one dose of study treatment. SAS statistical software (version 9.2 or later) was used for all analyses.

Results

Patients

Between July 2009 and October 2011, 2840 patients were randomly assigned to study treatment and constituted the ITT population (1420 per group), of whom 1631 patients (57%) had HR+ disease (neratinib, *n*=816; placebo, *n*=815). Among patients with HR+ tumors, 1334 patients (82%) had initiated study treatment within 1 year of prior trastuzumab – HR+/≤1-year population (neratinib, *n*=670; placebo, *n*=664) – and 297 patients (18%) had initiated study treatment 1 year or more after prior trastuzumab – HR+/>1-year population (neratinib, *n*=146; placebo, *n*=151) [see Appendix Figure A.1 for CONSORT flowchart]. Baseline characteristics in the HR+/≤1-year population, the focus of this manuscript, were balanced between treatment groups and were similar to the ITT population [Appendix Table A.2]. In the HR+/≤1-year population, the median interval from last dose of trastuzumab to randomization was 3.1 (range, 0.2–12.0) months in the neratinib group and 3.3 (range, 0.3–12.0) months in the placebo group, and median duration of trastuzumab therapy was 11.4 (range, 1.4–29.1) months and 11.4 (range, 1.4–24.0) months, respectively.

Within the HR+/≤1-year population, 354 patients (27%) had received neoadjuvant therapy, of whom 295 patients had residual invasive disease (non-pCR) at study entry. The baseline characteristics of this patient subgroup are presented in Appendix Table A.2.

Treatment exposure

In the HR+/≤1-year population, the median duration of study treatment was 11.5 (range, 0.0–13.3) months in the neratinib group and 11.9 (range, 0.1–12.9) months in the placebo group, with mean actual dose intensities of 210.4 mg/day (standard deviation [SD], 43.9) and 235.9 mg/day (SD, 11.0), respectively. Most patients (neratinib, 93%; placebo, 95%) were receiving concomitant endocrine therapy at baseline; the most frequently used therapies were an anti-estrogen only, which was largely tamoxifen (neratinib, 52%; placebo, 47%), or aromatase inhibitor only (44% and 48%, respectively) [Appendix Table A.3].

Efficacy

The iDFS benefits at 2 and 5 years were evaluated in both the HR+/≤1-year and HR+/>1-year populations.

In the 2-year analysis of the HR+/≤1-year population, iDFS rates were 95.3% (95% CI 93.1–96.7) with neratinib and 90.8% (95% CI 88.2–92.9) with placebo, corresponding to an absolute benefit of 4.5% with neratinib (hazard ratio 0.49; 95% CI 0.30–0.78) [Figure 1A]. In the HR+/>1-year population, 2-year iDFS rates were 97.4% (95% CI 92.1–99.2) with neratinib and 94.4% (95% CI 89.0–97.1) with

placebo, corresponding to an absolute benefit of 3.0% with neratinib (hazard ratio 0.43; 95% CI 0.09–1.47) [Appendix Figure A.2A].

In the 5-year analysis of the HR+/≤1-year population, iDFS rates were 90.8% (95% CI 88.1–93.0) in the neratinib group and 85.7% (95% CI 82.6–88.3) in the placebo group, corresponding to a durable absolute benefit of 5.1% (hazard ratio 0.58; 95% CI 0.41–0.82) [Figure 1B]. In the HR+/>1yr population, 5-year iDFS rates were 93.0% (95% CI 86.5–96.5) in the neratinib group and 91.7% (95% CI 85.4–95.4) in the placebo group, corresponding to an absolute benefit of 1.3% (hazard ratio 0.74; 95% CI 0.29–1.84) [Appendix Figure A.2B].

Evaluation of the Kaplan-Meier curves for iDFS in the HR+/≤1-year group revealed that they separated early (3 months) and continued to separate for the duration of follow-up (Figure 1); this was in contrast to the HR+/>1-year group where an early benefit for the neratinib group was not maintained (Appendix Figure A.2).

Most of the reduction in invasive recurrent events seen in patients who received neratinib was at distant sites. The 5-year DDFS rates were 92.4% (95% CI 89.9–94.4) with neratinib and 87.7% (95% CI 84.8–90.1) with placebo, corresponding with an absolute benefit of 4.7% (hazard ratio 0.57; 95% CI 0.39–0.83) [Figure 1C], and confirmed the results from the primary 2-year analysis [Figure 2; Appendix Figure A.3]. The cumulative incidence of first CNS recurrences at 5 years was 0.7% with neratinib and 2.1% with placebo (Table 1). At 5 years, 98.4% (95% CI 96.8–99.1) of patients in the neratinib group and 95.7% (95% CI 93.6–97.2) of patients in the placebo group were alive and did not report a CNS recurrence (hazard ratio for CNS-DFS 0.41; 95% CI 0.18–0.85) [Table 2]. In the OS analysis after a median follow-up of 8.0 (range, 0–9.8) years, 53 of 670 patients (7.9%) in the neratinib group and 68 of 664 patients (10.2%) in the placebo group of the HR+/≤1-year population had died. The hazard ratio (95% CI) of OS was 0.79 (0.55–1.13) and the estimated 8-year OS rates were 91.5% (95% CI 88.9–93.5) in the neratinib group and 89.4% (95% CI 86.6–91.6) in the placebo group of the HR+/≤1-year population, giving an absolute between-group difference of 2.1% (Figure 1D).

Subgroup analyses in HR+/≤1-year population including subgroups of clinical interest

A subgroup analysis of the HR+/≤1-year population according to randomization stratification factors showed that iDFS, DDFS and CNS endpoints at 5 years for neratinib compared with placebo were consistent when analyzed by nodal status and schedule of administration of prior trastuzumab with chemotherapy, and that OS showed a small but consistent numerical benefit with neratinib across patient subgroups (Figure 3; Tables 1 and 2).

Of the 354 patients (27%) in HR+/≤1-year population who had received neoadjuvant therapy, 295 (83%) patients had residual invasive disease (non-pCR), 38 (11%) patients achieved a pCR, and 21 (6%) patients had no outcome reported. Analyses of these subgroups of clinical interest are presented in Figure 4, and their baseline characteristics are shown in Appendix Table A.2. In patients with no pCR (*n*=295), the absolute benefits in iDFS and DDFS were 7.4% (hazard ratio 0.60; 95% CI 0.33–1.07) and 7.0% (hazard ratio 0.61; 95% CI 0.32–1.11), respectively, and 8-year OS rates demonstrated a 9.1% absolute benefit (hazard ratio 0.47; 95% CI 0.23–0.92) [Figure 4]. Kaplan-Meier curves for iDFS, DDFS and OS in this subgroup are shown in Figure 5. In patients with no evidence of invasive residual disease (pCR) after neoadjuvant therapy (*n*=38), the absolute 5-year iDFS benefit was 9.8% (hazard ratio 0.44; 95% CI 0.06–1.89), and the absolute 8-year OS benefit was 19.6% (hazard ratio 0.40; 95% CI 0.06–1.88) [Figure 4]. In both subgroups, the cumulative incidence of CNS recurrences and CNS-DFS at 5 years were improved with neratinib versus placebo (Tables 1 and 2).

Safety

A total of 1319 patients in the HR+/≤1-year population were included in the safety analysis (neratinib, *n*=662; placebo, *n*=657). The most common TEAE with neratinib in the HR+/≤1-year population was diarrhea (no mandatory anti-diarrheal prophylaxis given); grade 1, 2 and 3 events were reported in 23%, 32%, and 39% of patients in the neratinib group, respectively, and in 26%, 7% and 1% of patients in the placebo group, respectively; no grade 4 diarrhea was reported (Appendix Table A.4). In cases of grade 3 diarrhea, most episodes with neratinib occurred in the first month of treatment with a median time to onset of 8 days versus 240 days in the placebo group. The median cumulative duration of grade 3 diarrhea, defined as the sum of the durations of all grade 3 episodes, was 5 days with neratinib versus 1 day with placebo.

All other grade 3 adverse events in the neratinib group were each reported in 4% of patients or less. Grade 4 or greater TEAE occurred in 8 (1%) patients in the neratinib group (neutropenia, *n*=1; elevated aminotransferases, *n*=1; anemia, *n*=1; rectal cancer, *n*=1; increased blood creatinine and hypokalemia, *n*=1; increased blood creatine, *n*=1; dehydration, *n*=1; glioma, *n*=1) and 2 (<1%) patients in the placebo group (vertigo, *n*=1; septic shock, *n*=1). One fatal (grade 5) TEAE occurred with neratinib (acute myeloid leukemia). There was no evidence of hematopoietic, pulmonary or cardiac toxicity with neratinib, and no evidence of increased risk for second malignancies. TEAE led to dose reductions, dose interruptions and hospitalization in 203 (31%), 280 (42%), and 41 (6%) patients in the neratinib group, respectively, and in 13 (2%), 75 (11%), and 35 (5%) patients in the placebo group (Appendix Table A.5).

Discussion

Approximately 25% of patients with HER2+ breast cancer who receive trastuzumab-based adjuvant therapy will experience disease recurrences within 8 to 10 years of completing therapy,[4,16,17] highlighting an unmet need for new treatment options beyond trastuzumab-based adjuvant treatment alone. The ExteNET trial demonstrated that neratinib given for 1 year following trastuzumab-based therapy significantly improved iDFS in patients with HER2+ breast cancer, with the greatest efficacy seen in patients who initiated treatment within one year of prior trastuzumab and in those with HR+ disease. After 5 years of follow-up, the absolute iDFS benefit with neratinib compared with placebo was 5.1% in the HR+/≤1-year population and 1.3% in the HR+/>1-year population, suggesting a more pronounced and durable response among patients who initiated neratinib shortly after completing trastuzumab-based therapy, consistent with the current use of neratinib in clinical practice. In the HR+/≤1-year population, an important clinical endpoint achieved was the 4.7% absolute DDFS benefit. The OS analysis in the HR+/≤1-year population confirmed the value of neratinib.

Patients who do not attain a pCR after neoadjuvant treatment experience significantly worse outcomes.[18] While trastuzumab emtansine is now used in clinical practice in patients with residual invasive disease after neoadjuvant therapy based on findings from the KATHERINE trial,[9] the study further reinforced the poor prognosis of this patient population despite a hazard ratio for iDFS of 0.50.[9] In an exploratory subset analysis, we were able to show that patients with residual invasive disease after neoadjuvant therapy showed clinically meaningful improvements with neratinib, with absolute benefits at 5-year iDFS of 7.4% and 8-year OS of 9.1%. Clinically meaningful improvements were also evident with neratinib in those attaining a pCR (absolute benefits at 5-year iDFS of 9.8% and 8-year OS of 19.6%). The prognosis of patients who are HER2+/HR+ and who achieve a pCR has been unclear, with several studies suggesting that clinical outcomes in these patients may not be appreciably better than patients without a pCR.[19-21] Similarly in ExteNET, 5-year iDFS rates in patients with or without a pCR were similar, i.e. 84% and 85% in the neratinib arm, respectively, and 74% and 78% in the placebo arm, respectively. This highlights an unmet need in patients with HER2+/HR+ breast cancer who receive neoadjuvant therapy, and evaluation of additional treatment strategies in this patient group is needed.

Between 35 to 55% of first distant recurrences after HER2-directed adjuvant therapies occur in the CNS,[7-9] and our results suggest that neratinib may be effective in controlling CNS events in the HR+/≤1-year population as well as in patients who received neratinib following neoadjuvant therapy. Benefits of neratinib in the prevention[22,23] and treatment[24] of CNS metastases in HER2+ breast cancer have been reported in other phase II and III studies, supporting a recommendation in current

treatment guidelines for the use of neratinib-based therapy in brain metastases.[25] In the randomized NEfERT-T trial of patients with metastatic HER2-positive breast cancer treated in the first-line setting, the incidence of symptomatic or progressive CNS events was significantly reduced with neratinib plus paclitaxel versus trastuzumab plus paclitaxel (p=0.002).[22] Further support for the role of neratinib in CNS disease was shown in the phase III NALA trial.[23] In this trial of 621 patients, neratinib plus capecitabine significantly reduced the cumulative incidence of therapeutic interventions for CNS disease compared with lapatinib plus capecitabine after 2 or more HER2-directed therapies for metastatic disease (p=0.043).[23]

In the HR+/≤1-year population, adverse events associated with neratinib were generally transient and manageable with dose modifications and/or conventional treatment, as has been reported for the ITT population. Diarrhea, a known class effect of tyrosine kinase inhibitors,[26] was common with neratinib in the absence of proactive antidiarrheal prophylaxis (grade 3, 39%), although most grade 3 events occurred in the first month of treatment (median time to onset, 8 days) and had a short cumulative duration (median, 5 days). Antidiarrheal prophylaxis or neratinib dose escalation (escalating from 160mg to 240mg over two weeks) have since been shown to reduce the incidence, severity and duration of neratinib-associated grade ≥3 diarrhea in the phase II CONTROL study as compared with ExteNET.[27] The greatest benefits were seen in the dose-escalation cohort of CONTROL, where the rate of grade 3 diarrhea was 15% (*vs* 40% in ExteNET), the median cumulative duration of grade 3 diarrhea was 2 days (5 days in ExteNET), and the rate of discontinuation due to diarrhea was 3% (17% in ExteNET).[27] Tolerability is also improved with pre-emptive prophylaxis or dose escalation,[27] allowing many patients to complete the full year of neratinib treatment.

Current clinical practice in some countries may involve the use of two additional HER2-directed agents (pertuzumab[7] and trastuzumab emtansine[9]) prior to receiving extended adjuvant therapy with neratinib, which differs from the patient population in ExteNET. While the precise implications of changing clinical practice on the findings from ExteNET are not known, several studies have demonstrated the efficacy and safety of neratinib-based regimens after pertuzumab and/or trastuzumab emtansine,[23,24,27] or neratinib in combination with trastuzumab emtansine.[28] Moreover, due to the mechanism of action of neratinib, which differs from the above therapies — namely inhibition of the intracellular component of the HER2 pathway — neratinib represents a potentially non-cross–resistant therapy. Furthermore, the demonstrated synergy of concurrent anti-estrogen receptor therapy and HER2 inhibition is an additional benefit.[29,30] These factors suggest that extended adjuvant use of neratinib remains an appropriate agent for managing patients with HER2-positive/HR+ eBC.

While subgroup analyses based on HR status and the interval between completion of prior trastuzumab and randomization were defined by two prespecified factors and were the basis for the EMA approval of neratinib, the analyses described herein are exploratory. We provided conventional 95% confidence intervals to help quantify the variability associated with effect estimates. Some confidence intervals for the hazard ratios crossed one and some did not. However, the study was not powered for subgroup findings and no multiplicity adjustments were performed. The patient numbers in some subgroups, notably those with a pCR after neoadjuvant therapy, were small. The CNS-DFS endpoint was not prespecified, and disease recurrences beyond the first recurrence might not have been collected consistently during the study. These limitations should be considered when evaluating our findings. The present analyses focus on the HR+ population from ExteNET; although greater benefits with neratinib were also documented in the HR– population when treatment was initiated within six months of prior trastuzumab rather than later,[31] the conclusions described here for the HR+ group cannot be extended to the HR– population.

Conclusion

Extended adjuvant treatment with neratinib after trastuzumab-based therapy significantly reduces the risk of invasive recurrence and prolongs distant disease-free survival. Our exploratory analyses demonstrate consistent benefit in patients with HR+ disease who initiate neratinib within 1 year of trastuzumab-based therapy. In particular, there was consistent numerical benefit seen in iDFS, OS, and CNS events in patients with residual disease following neoadjuvant treatment, who would be considered at heightened risk of disease recurrence. The rate and severity of diarrhea seen in the HR+ population was identical to that of the entire ExteNET population, although recent data show that the tolerability of neratinib can be improved by various treatment modalities, including anti-diarrheal prophylaxis or neratinib dose escalation.

Clinical Practice Points

- Approximately 25% of patients with HER2+ breast cancer who receive trastuzumab-based adjuvant therapy experience disease recurrences within 8–10 years of completing therapy, highlighting a need for improved treatment options in the extended adjuvant setting.
- Neratinib, an irreversible pan-HER tyrosine kinase inhibitor, is the first HER2-targeted agent approved for extended adjuvant therapy in patients with HER2+ early-stage breast cancer after trastuzumab-based therapy based on the phase III ExteNET trial.
- In the ExteNET trial, greater and more durable efficacy was observed in the subgroup with HR+ disease who initiated treatment within 1 year of completing trastuzumab, referred to as the HR+/≤1-year population.
- In analyses of the HR+/≤1-year population from ExteNET, the absolute invasive disease-free survival (iDFS) benefit of neratinib versus placebo at 5 years was 5.1%, and the absolute overall survival (OS) benefit at 8 years was 2.1%.
- Greater benefits were apparent in subgroups of clinical interest, including patients with residual disease after neoadjuvant therapy (absolute benefits, 5-year iDFS 7.4%; 8-year OS 9.1%).
- Notably, 5-year iDFS rates were similar in patients with and without residual disease (neratinib, 85.0% *vs* 84.0%; placebo, 77.6% *vs* 74.2%, respectively), supporting continued HER2 suppression after neoadjuvant therapy and the lesser prognostic value of no residual disease in HR+ breast cancer.
- In HR+/≤1-year and patient subgroups of clinical interest, there were fewer CNS events with neratinib versus placebo.
- Neratinib significantly improves iDFS in the HR+/≤1-year population. Descriptive analyses suggest benefit with neratinib in patients at higher risk, including patients with residual disease following neoadjuvant treatment.

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Data statement

The authors declare that the data supporting the findings of this study are available within the article. The authors may be contacted for further data sharing.

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Table 1. Cumulative incidence of CNS recurrences as first site of metastases at 5 years in the HR+/≤1-year population (*n*=1334) and subgroups

Population or subgroup	CNS events (no. of patients)		Cumulative incidence of CNS recurrences at 5 years (95% CI), %	
	Neratinib	Placebo	Neratinib	Placebo
HR+/≤1-year population	4 (670)	12 (664)	0.7 (0.2–1.7)	2.1 (1.1–3.5)
Nodal status				
Positive	4 (540)	10 (539)	0.8 (0.3–2.0)	2.2 (1.1–3.8)
Negative	0 (130)	2 (125)	0 (NE–NE)	1.9 (0.4–6.0)
Prior trastuzumab regimen				
Concurrent	2 (411)	8 (415)	0.6 (0.1–1.9)	2.3 (1.1–4.3)
Sequential	2 (259)	4 (249)	0.9 (0.2–3.0)	1.8 (0.6–4.3)
Adjuvant or neoadjuvant therapy				
Adjuvant	3 (508)	6 (472)	0.7 (0.2–2.0)	1.5 (0.6–3.0)
Neoadjuvant	1 (162)	6 (192)	0.7 (0.1–3.3)	3.7 (1.5–7.4)
pCR status[a]				
No	1 (131)	5 (164)	0.8 (0.1–4.0)	3.6 (1.3–7.8)
Yes	0 (17)	1 (21)	0 (NE)	5.0 (0.3–21.2)

[a]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.

CI, confidence interval; CNS, central nervous system; NE, not estimable; pCR, pathologic complete response.

Table 2. CNS disease-free survival at 5 years in the HR+/≤1-year population (*n*=1334) and subgroups

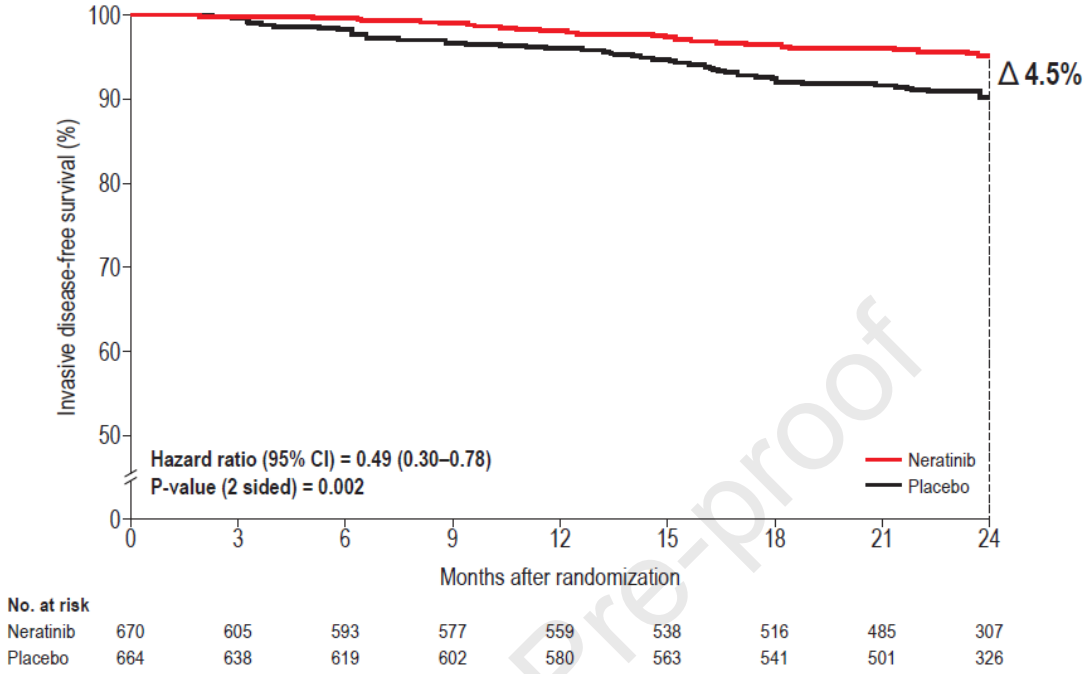
Population or subgroup	Events (no. of patients)		Kaplan-Meier estimate at 5 years (95% CI), %		Hazard ratio (95% CI)
	Neratinib	Placebo	Neratinib	Placebo	
HR+/≤1-year population	9 (670)	23 (664)	98.4 (96.8–99.1)	95.7 (93.6–97.2)	0.41 (0.18–0.85)
Nodal status					
Positive	8 (540)	20 (539)	98.2 (96.4–99.1)	95.4 (92.9–97.0)	0.41 (0.17–0.89)
Negative	1 (130)	3 (125)	99.1 (93.9–99.9)	97.2 (91.4–99.1)	0.37 (0.02–2.87)
Prior trastuzumab regimen					
Concurrent	6 (411)	16 (415)	98.1 (95.8–99.2)	95.3 (92.3–97.1)	0.40 (0.15, 0.98)
Sequential	3 (259)	7 (249)	98.7 (95.9–99.6)	96.5 (92.8–98.4)	0.42 (0.09–1.50)
Adjuvant or neoadjuvant therapy					
Adjuvant	7 (508)	10 (472)	98.2 (96.3–99.2)	97.5 (95.3–98.6)	0.70 (0.25–1.82)
Neoadjuvant	2 (162)	13 (192)	98.7 (94.8–99.7)	91.2 (85.1–94.8)	0.18 (0.03–0.63)
pCR status[a]					
No	2 (131)	10 (164)	98.4 (93.6–99.6)	92.0 (85.6–95.7)	0.24 (0.04–0.92)
Yes	0 (17)	3 (21)	100.0 (100.0–100.0)	81.9 (53.1–93.9)	0 (NE, 1.08)

[a]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.

CI, confidence interval; CNS, central nervous system; NE, not estimable; pCR, pathologic complete response.

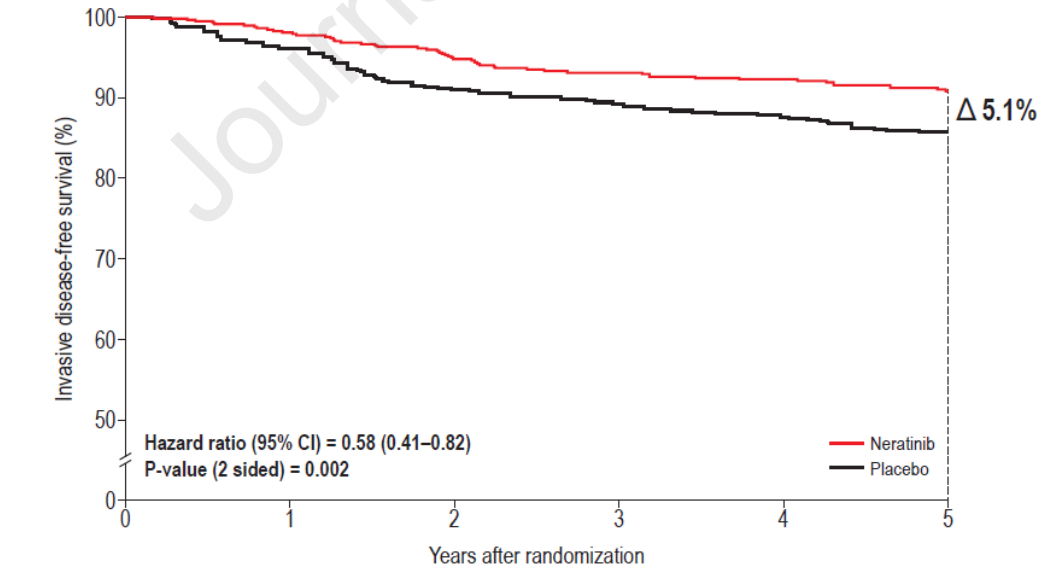
Figure 1. Invasive disease-free survival at 2 years (Panel A) and 5 years (Panel B), distant disease-free survival at 5 years (Panel C), and overall survival (Panel D) in the HR+/≤1-year population (*n*=1334)

A) Invasive disease-free survival at 2 years



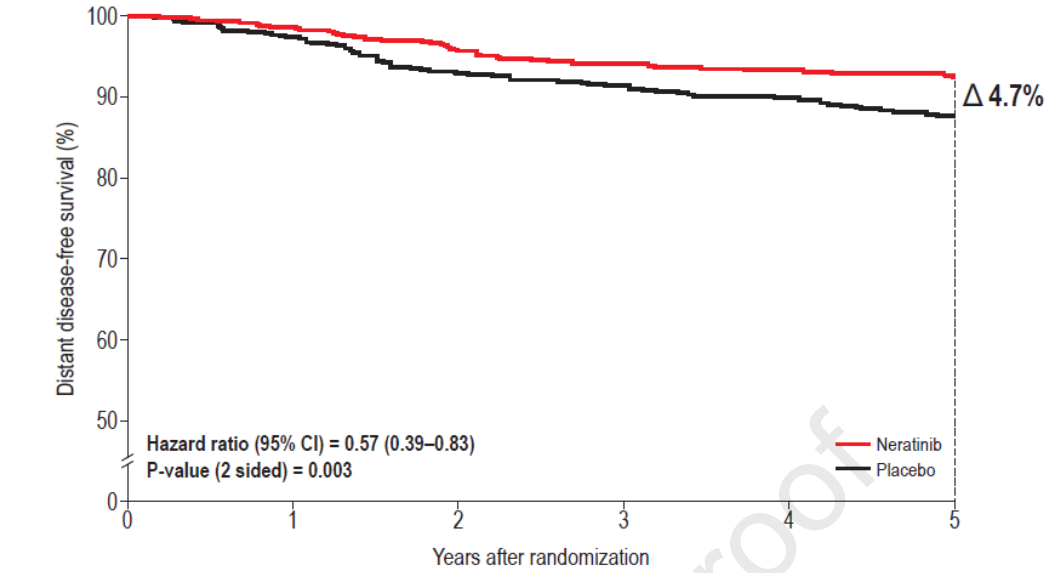
No. at risk									
Neratinib	670	605	593	577	559	538	516	485	307
Placebo	664	638	619	602	580	563	541	501	326

B) Invasive disease-free survival at 5 years



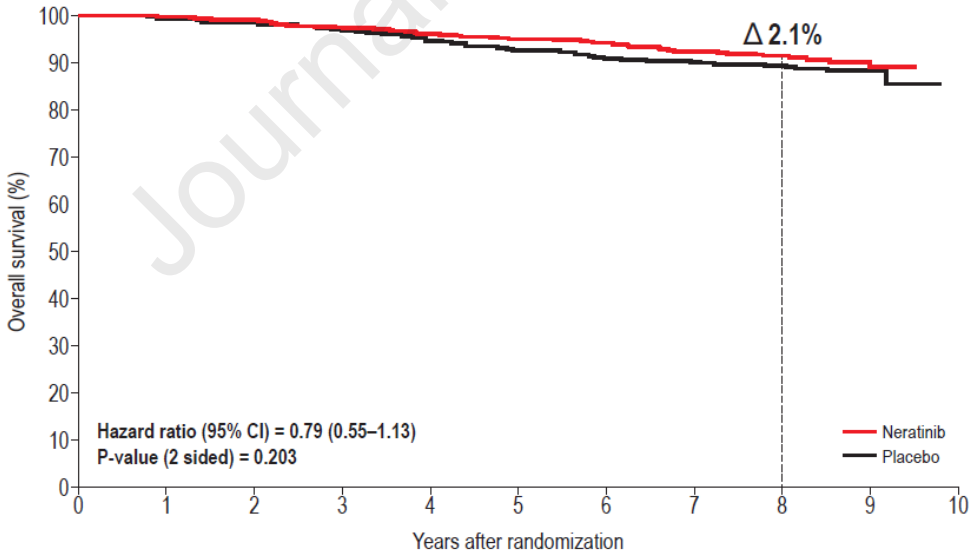
No. at risk											
Neratinib	670	620	599	577	523	469	465	460	457	448	428
Placebo	664	634	609	583	535	481	471	462	458	450	433

C) Distant disease-free survival



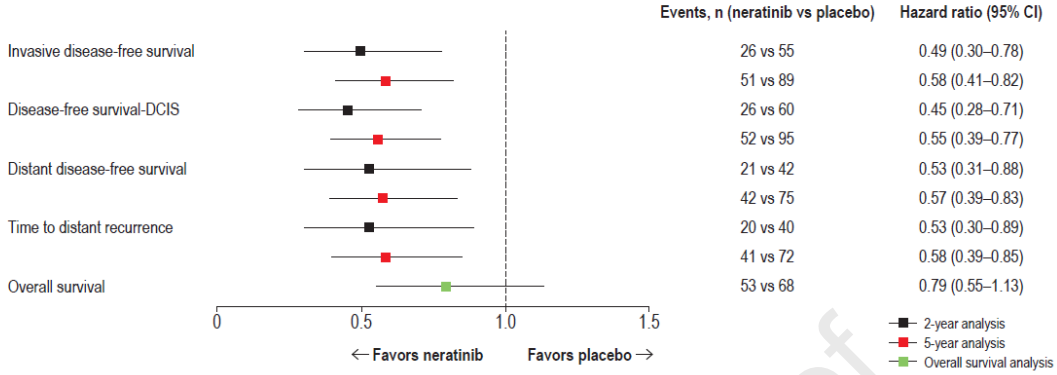
No. at risk											
Neratinib	670	620	602	580	526	473	469	464	461	454	434
Placebo	664	639	616	594	546	489	480	469	467	457	438

D) Overall survival



No. at risk											
Neratinib	670	640	620	578	567	556	534	490	315	78	0
Placebo	664	645	630	589	574	560	537	497	335	78	0

Figure 2. Two-year, 5-year and overall survival analyses in the HR+/≤1-year population (*n*=1334)



Note: Definitions for efficacy endpoints provided in Table A.1.

CI, confidence interval; disease-free survival-DCIS, disease-free survival including ductal carcinoma in situ.

Figure 3. Subgroup analyses of invasive disease-free survival and disease-free survival at 5 years, and overall survival according to randomization stratification factors in the HR+/≤1-year population (*n*=1334)

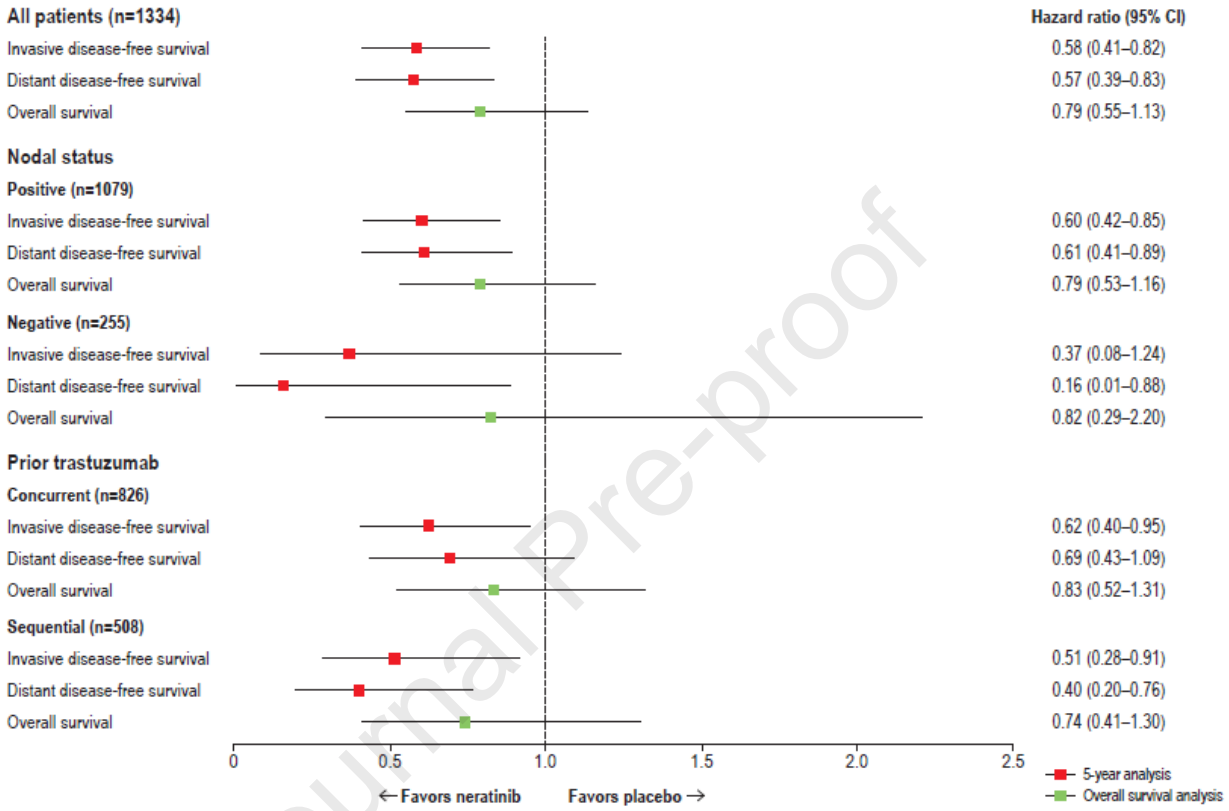
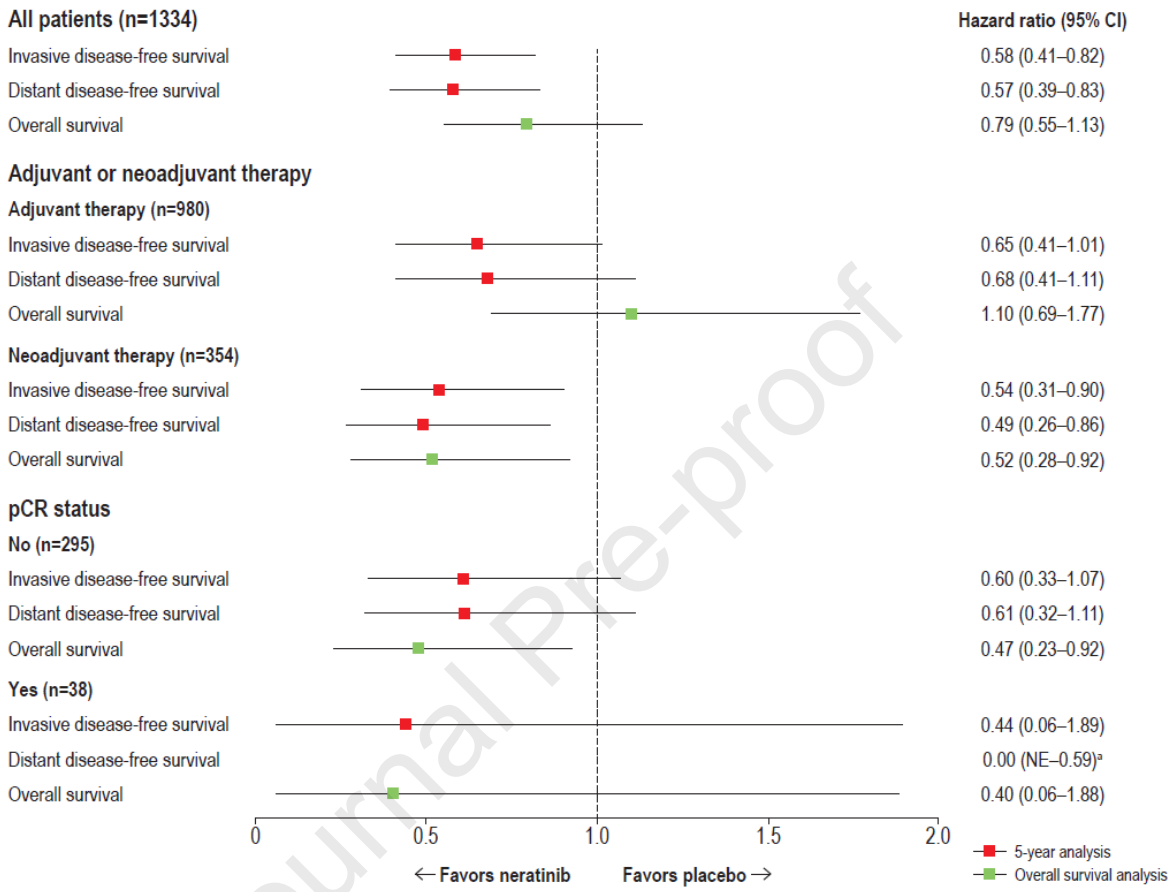


Figure 4. Subgroup analyses of 5-year invasive disease-free and distant disease-free survival at 5 years, and overall survival in subgroups of clinical interest in the HR+/≤1-year population (*n*=1334)



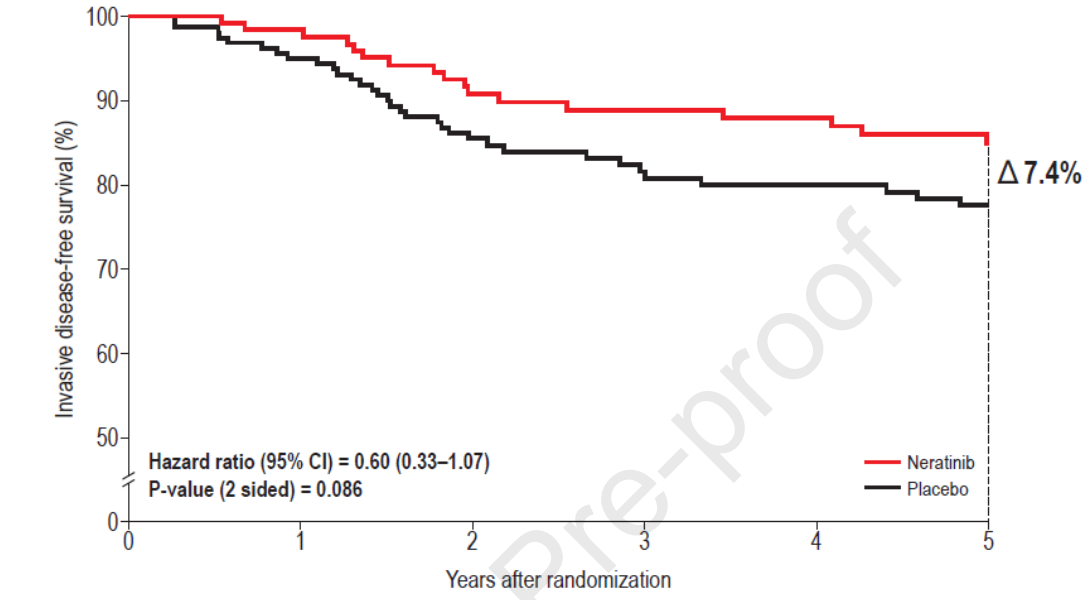
Note: Among 354 patients who had received neoadjuvant therapy, 295 patients had no pCR, 38 patients achieved a pCR, and 21 patients had no outcome reported.

[a]Distant disease-free survival results for the pCR (yes) subgroup are not displayed because there were no events in the neratinib group, and it was therefore not possible to estimate the confidence boundary for the hazard ratio.

CI, confidence interval; NE, not estimable; pCR, pathologic complete response.

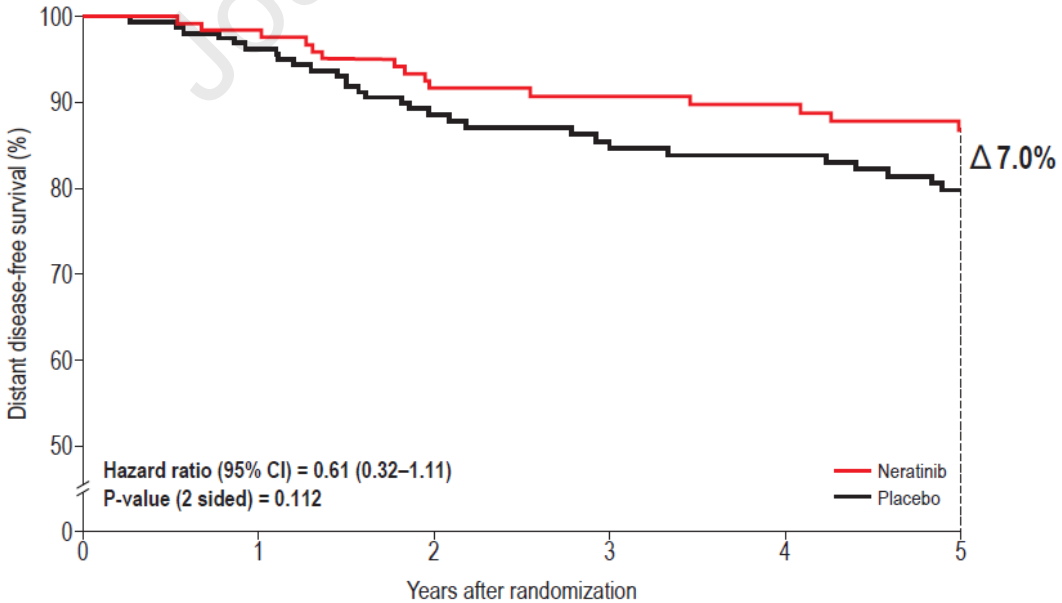
Figure 5. Invasive disease-free survival (Panel A) and distant disease-free survival at 5 years (Panel B), and overall survival (Panel C) in the HR+/≤1-year population with no pCR after neoadjuvant therapy (*n*=295)

A) Invasive disease-free survival



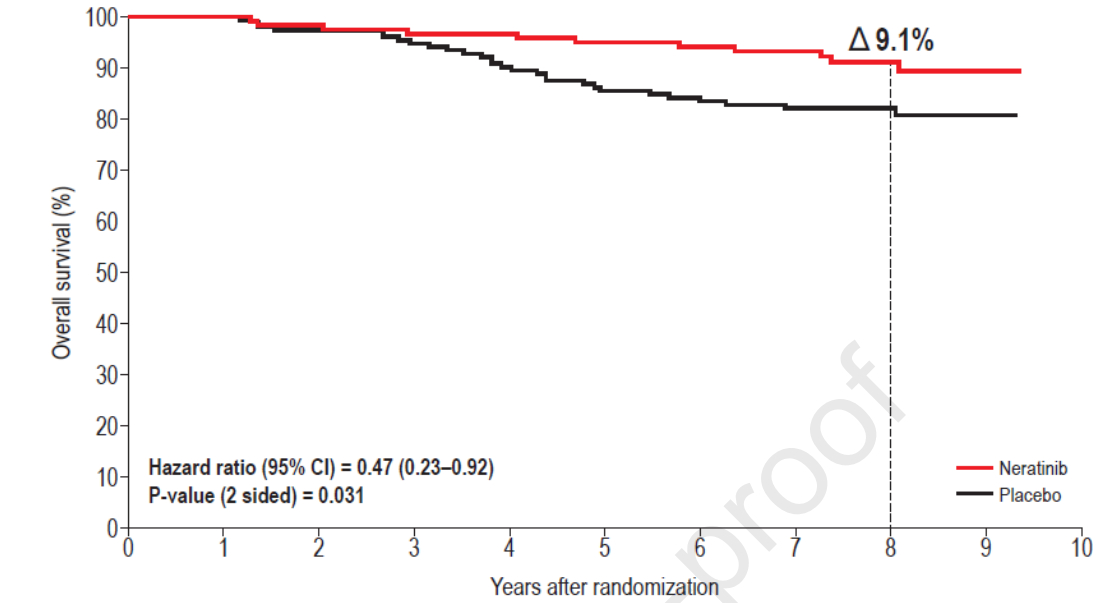
No. at risk											
Neratinib	131	126	121	113	100	94	93	91	91	88	84
Placebo	164	159	151	143	125	107	103	99	99	98	94

B) Distant disease-free survival



No. at risk											
Neratinib	131	126	121	113	101	96	95	93	93	90	86
Placebo	164	160	153	147	130	110	107	103	103	101	95

C) Overall survival



No. at risk											
Neratinib	131	126	121	116	113	110	106	100	60	14	0
Placebo	164	161	156	143	135	129	123	115	65	12	0

MicroAbstract

In the patient population with early-stage HER2+/HR+ breast cancer who initiate neratinib within 1 year of trastuzumab-based therapy, the absolute 5-year invasive disease-free survival benefit versus placebo is 5.1%, and absolute 8-year overall survival benefit is 2.1%. Among those with residual disease after neoadjuvant therapy (non-pathologic complete response), absolute gains with neratinib are 7.4% and 9.1%, respectively.

Clinical Practice Points

- Approximately 25% of patients with HER2+ breast cancer who receive trastuzumab-based adjuvant therapy experience disease recurrences within 8–10 years of completing therapy, highlighting a need for improved treatment options in the extended adjuvant setting.
- Neratinib, an irreversible pan-HER tyrosine kinase inhibitor, is the first HER2-targeted agent approved for extended adjuvant therapy in patients with HER2+ early-stage breast cancer after trastuzumab-based therapy based on the phase III ExteNET trial.
- In the ExteNET trial, greater and more durable efficacy was observed in the subgroup with HR+ disease who initiated treatment within 1 year of completing trastuzumab, referred to as the HR+/≤1-year population.
- In analyses of the HR+/≤1-year population from ExteNET, the absolute invasive disease-free survival (iDFS) benefit of neratinib versus placebo at 5 years was 5.1%, and the absolute overall survival (OS) benefit at 8 years was 2.1%.
- Greater benefits were apparent in subgroups of clinical interest, including patients with residual disease after neoadjuvant therapy (absolute benefits, 5-year iDFS 7.4%; 8-year OS 9.1%).
- Notably, 5-year iDFS rates were similar in patients with and without residual disease (neratinib, 85.0% *vs* 84.0%; placebo, 77.6% *vs* 74.2%, respectively), supporting continued HER2 suppression after neoadjuvant therapy and the lesser prognostic value of no residual disease in HR+ breast cancer.
- In HR+/≤1-year and patient subgroups of clinical interest, there were fewer CNS events with neratinib versus placebo.
- Neratinib significantly improves iDFS in the HR+/≤1-year population. Descriptive analyses suggest benefit with neratinib in patients at higher risk, including patients with residual disease following neoadjuvant treatment.