Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

Arlene Chan, Suzette Delaloge, Frankie A Holmes, Beverly Moy, Hiroji Iwata, Vernon J Harvey, Nicholas J Robert, Tajana Silovski, Erhan Gokmen, Gunter von Minckwitz, Bent Ejlertsen, Stephen K L Chia, Janine Mansi, Carlos H Barrios, Michael Gnant, Marc Buyse, Ira Gore, John Smith II, Graydon Harker, Norikazu Masuda, Katarina Petrakova, Angel Guerrero Zotano, Nicholas Iannotti, Gladys Rodriguez, Pierfrancesco Tassone, Alvin Wong, Richard Bryce, Yining Ye, Bin Yao, Miguel Martin, for the ExteNET Study Group

Summary

Background Neratinib, an irreversible tyrosine-kinase inhibitor of HER1, HER2, and HER4, has clinical activity in patients with HER2-positive metastatic breast cancer. We aimed to investigate the efficacy and safety of 12 months of neratinib after trastuzumab-based adjuvant therapy in patients with early-stage HER2-positive breast cancer.

Methods We did this multicentre, randomised, double-blind, placebo-controlled, phase 3 trial at 495 centres in Europe, Asia, Australia, New Zealand, and North and South America. Eligible women (aged ≥18 years, or ≥20 years in Japan) had stage 1–3 HER2-positive breast cancer and had completed neoadjuvant and adjuvant trastuzumab therapy up to 2 years before randomisation. Inclusion criteria were amended on Feb 25, 2010, to include patients with stage 2–3 HER2-positive breast cancer who had completed trastuzumab therapy up to 1 year previously. Patients were randomly assigned (1:1) to receive oral neratinib 240 mg per day or matching placebo. The randomisation sequence was generated with permuted blocks stratified by hormone receptor status (hormone receptor-positive [oestrogen or progesterone receptor-positive or both] *vs* hormone receptor-negative [oestrogen and progesterone receptor-negative]), nodal status (0, 1–3, or ≥4), and trastuzumab adjuvant regimen (sequentially *vs* concurrently with chemotherapy), then implemented centrally via an interactive voice and web-response system. Patients, investigators, and trial sponsors were masked to treatment allocation. The primary outcome was invasive disease-free survival, as defined in the original protocol, at 2 years after randomisation. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00878709.

Findings Between July 9, 2009, and Oct 24, 2011, we randomly assigned 2840 women to receive neratinib (n=1420) or placebo (n=1420). Median follow-up time was 24 months (IQR 20–25) in the neratinib group and 24 months (22–25) in the placebo group. At 2 year follow-up, 70 invasive disease-free survival events had occurred in patients in the neratinib group versus 109 events in those in the placebo group (stratified hazard ratio 0·67, 95% CI 0·50–0·91; p=0·0091). The 2-year invasive disease-free survival rate was 93·9% (95% CI 92·4–95·2) in the neratinib group and 91·6% (90·0–93·0) in the placebo group. The most common grade 3–4 adverse events in patients in the neratinib group were diarrhoea (grade 3, n=561 [40%] and grade 4, n=1 [<1%] *vs* grade 3, n=23 [2%] in the placebo group), vomiting (grade 3, n=47 [3%] *vs* n=5 [<1%]), and nausea (grade 3, n=26 [2%] *vs* n=2 [<1%]). QT prolongation occurred in 49 (3%) patients given neratinib and 93 (7%) patients given placebo, and decreases in left ventricular ejection fraction (≥grade 2) in 19 (1%) and 15 (1%) patients, respectively. We recorded serious adverse events in 103 (7%) patients in the neratinib group and 85 (6%) patients in the placebo group. Seven (<1%) deaths (four patients in the neratinib group and three patients in the placebo group) unrelated to disease progression occurred after study drug discontinuation. The causes of death in the neratinib group were unknown (n=2), a second primary brain tumour (n=1), and acute myeloid leukaemia (n=1), and in the placebo group were a brain haemorrhage (n=1), myocardial infarction (n=1), and gastric cancer (n=1). None of the deaths were attributed to study treatment in either group.

Interpretation Neratinib for 12 months significantly improved 2-year invasive disease-free survival when given after chemotherapy and trastuzumab-based adjuvant therapy to women with HER2-positive breast cancer. Longer follow-up is needed to ensure that the improvement in breast cancer outcome is maintained.

Funding Wyeth, Pfizer, Puma Biotechnology.

Introduction

Up to 20% of patients with breast cancer have HER2-amplified tumours, which were associated with a worse prognosis before the introduction of anti-HER2 therapy.[1] Pivotal trials,[2–4] reported in 2005, showed that addition of trastuzumab to standard chemotherapy in patients with HER2-positive early-stage breast cancer significantly improved their survival. However, up to

Lancet Oncol 2016

Published Online February 10, 2016 http://dx.doi.org/10.1016/S1470-2045(15)00551-3

See Online/Comment http://dx.doi.org/10.1016/S1470-2045(15)00623-3

Breast Cancer Research Centre-Western Australia and Curtin University, Perth, WA, Australia (Prof A Chan MD); **Institut Gustave Roussy, Villejuif, France** (S Delaloge MD); **Texas Oncology, Houston, TX, USA** (F A Holmes MD); **Massachusetts General Hospital Cancer Center, Boston, MA, USA** (B Moy MD); **Aichi Cancer Center, Chikusa-ku, Nagoya, Japan** (H Iwata MD); **Auckland Hospital, Auckland, New Zealand** (V J Harvey MD); **Virginia Cancer Specialists, The US Oncology Network, Fairfax, VA, USA** (N J Robert MD); **University Hospital For Tumors, University Hospital Center "Sestre Milosrdnice", Zagreb, Croatia** (T Silovski MD); **Ege University Faculty of Medicine, Izmir, Turkey** (E Gokmen MD); **Luisenkrankenhaus, German Breast Group Forschungs GmbH, Düsseldorf, Neu-Isenburg, Germany** (Prof G von Minckwitz MD); **Rigshospitalet, Copenhagen, Denmark** (B Ejlertsen MD); **BC Cancer Agency, Vancouver, BC, Canada** (S K L Chia MD); **Guy's and St Thomas' NHS Foundation Trust and Biomedical Research Centre, King's College London, London, UK** (J Mansi MD); **Pontifical Catholic University of Rio Grande do Sul School of Medicine, Porto Alegre, Brazil** (Prof C H Barrios MD); **Department of Surgery and**

Comprehensive Cancer Centre, Medical University of Vienna, Vienna, Austria (Prof M Gnant MD); **International Drug Development Institute (IDDI), Louvain-la-Neuve, Belgium** (M Buyse ScD); **Alabama Oncology, Birmingham, AL, USA** (I Gore MD); **Northwest Cancer Specialists, Vancouver, VA, USA** (J Smith II MD); **Utah Cancer Specialists, Salt Lake City, UT, USA** (G Harker MD); **National Hospital Organization Osaka National Hospital, Chuou-ku, Osaka, Japan** (N Masuda MD); **Masaryk Memorial Cancer Institute, Brno, Czech Republic** (K Petrakova MD); **Instituto Valenciano de Oncologia, València, Spain** (A G Zotano MD); **Hematology Oncology Associates of Treasure Coast, Port Saint Lucie, FL, USA** (N Iannotti MD); **South Texas Oncology and Hematology, San Antonio, TX, USA** (G Rodriguez MD); **Magna Graecia University, Catanzaro, Italy** (Prof P Tassone MD); **Puma Biotechnology, Los Angeles, CA, USA** (A Wong PharmD, R Bryce MBChB, Y Ye PhD, B Yao MS); **and Instituto de Investigación Sanitaria Gregorio Marañón, Universidad Complutense de Madrid, Madrid, Spain** (Prof M Martin MD)

Correspondence to:
Prof Arlene Chan, Breast Cancer Research Centre-Western Australia, Perth, WA 6005, Australia
arlenechan@me.com

See Online for appendix

Research in context

Evidence before this study

Addition of trastuzumab to standard chemotherapy significantly improves overall survival in women with early-stage HER2-positive breast cancer. However, 23–26% of women have breast cancer events after a median follow-up of 5·2–8·4 years despite adjuvant trastuzumab. Extended adjuvant treatment using a small-molecule pan-HER2 tyrosine-kinase inhibitor, such as neratinib, has been hypothesised to improve outcomes in this patient group. We searched PubMed between Jan 1, 2000, and Aug 31, 2015, with the search terms "HER2-positive", "adjuvant", and "randomized". To our knowledge, only one other trial (HERA) assessed the effect of 24 months of treatment with trastuzumab on improvement of outcomes beyond current standard of care—namely, 12 months of trastuzumab. In HERA, the longer duration of trastuzumab did not improve the primary study endpoint of disease-free survival (defined as invasive and in-situ breast cancer events) after 8 years of follow-up.

Added value of this study

In our study, 12 months of neratinib significantly improved 2-year invasive disease-free survival compared with placebo after trastuzumab-based adjuvant therapy in women with HER2-positive early-stage breast cancer.

Implications of all the available evidence

To our knowledge, neratinib taken for 12 months is the first therapeutic intervention to significantly improve invasive disease-free survival beyond trastuzumab-based adjuvant therapy in women with HER2-positive early-stage breast cancer. Longer follow-up is essential to ensure that the improvement in breast cancer outcome is maintained, and to identify patient subgroups who could benefit the most.

26% of patients will still develop recurrent disease despite this treatment.[2,4–6]

Neratinib is an oral, irreversible, tyrosine-kinase inhibitor of HER1, HER2, and HER4, with proven efficacy in trastuzumab-treated and trastuzumab-naive patients with HER2-positive metastatic breast cancer.[7,8] The potent inhibition of HER2 downstream phosphorylation by neratinib could render this drug effective despite development of trastuzumab resistance.[9] Phase 1 and 2 studies of neratinib in patients previously treated with anthracyclines, taxanes, and trastuzumab reported that up to 32% of patients achieved an objective response, and up to 44% of patients achieved a clinical benefit.[7,10] We designed the ExteNET study to evaluate the efficacy of extended adjuvant anti-HER2 treatment with neratinib after trastuzumab-based therapy in patients with HER2-positive breast cancer.

Methods

Study design and participants

We did this multicentre, randomised, double-blind, placebo-controlled, phase 3 trial at 495 community-based and academic institutions in Europe, Asia, Australia, New Zealand, and North and South America (appendix p 23). During the study, three different sponsors assumed responsibility, resulting in three global amendments with notable changes to study design (appendix p 5). In brief, at the time of study initiation, the primary study objective was to assess the effect of 12 months of neratinib versus placebo on invasive disease-free survival in women with early-stage HER2-positive breast cancer who had received trastuzumab and chemotherapy. Key inclusion criteria included stage 1–3 node-positive and node-negative (≥T1c) tumours in patients who were disease-free up to 2 years after completion of trastuzumab. In updated results of the NCCTG-N9831 trial (8·4 years of follow-up) and the BCIRG006 study (36·5 months of follow-up),[2,11,12] patients with node-negative tumours and those receiving concurrent trastuzumab-based chemotherapy had lower rates of recurrence than originally considered in the ExteNET design. A higher risk of recurrence was also reported closer to completion of trastuzumab therapy in these trials. On the basis of these findings, a global amendment on Feb 25, 2010 (amendment three), restricted recruitment to higher-risk patients, defined as those with node-positive disease who had completed trastuzumab therapy up to 1 year previously.

On Oct 14, 2011, two key changes were made by the sponsor at the time (amendment nine): cessation of enrolment and shortening of follow-up from 5 years to 2 years from randomisation. This decision was not made as a result of predefined futility boundaries having been met, any interim assessment of efficacy, or because of safety concerns. The study was continued with this design until January, 2014, when a global amendment by the current sponsor restored the primary endpoint of invasive disease-free survival to the intention-to-treat population, as defined in the original protocol, but with the primary analysis being done in all patients at 2 years of follow-up. Thus, all patients in the intention-to-treat population who had undergone protocol-specified treatment and follow-up to 24 months were included in this primary analysis report. Data collection for disease events and deaths from 2 years to 5 years after randomisation was resumed, with ongoing long-term survival follow-up for consenting patients. Treatment assignment remained masked before this primary analysis and the sponsor remains masked to treatment allocation for overall survival events. Despite the changes of study sponsors, independent statistical analysis to inform the Independent Data Monitoring Committee and the clinical research organisation responsible for data collection and site monitoring remained consistent throughout the trial.

Eligible women were aged 18 years or older (or ≥20 years in Japan, based on a Japan-specific protocol amendment [number one; Aug 3, 2009] introduced at the request of the Japanese regulatory authority) and had locally confirmed invasive HER2-positive breast cancer stage 1–3 (amended to 2–3 on Feb 25, 2010 [amendment three]; appendix p 5) without evidence of recurrence. HER2 status was subsequently confirmed centrally (HER2 amplification defined as a ratio of HER2 to CEP17 of ≥2·2 using PathVysion HER2 DNA dual probe [Abbott Molecular, Des Plaines, IL, USA]). A CT scan was done in the presence of clinical symptoms or elevated liver aminotransferase, and a bone scan was done in the presence of bone pain or elevated alkaline phosphatase. Neoadjuvant and adjuvant trastuzumab was completed up to 2 years (amended to 1 year) before randomisation. Concurrent adjuvant endocrine therapy for hormone receptor-positive disease was recommended. Patients had to have an Eastern Cooperative Oncology Group performance status of 0 or 1, normal organ function, and a left ventricular ejection fraction within normal institutional range. We excluded patients with clinically significant cardiac, gastrointestinal, or psychiatric comorbidities, and those who were unable to swallow oral medications. The study protocol was approved by the institutional ethics committee at participating sites and done in accordance with the 2008 Declaration of Helsinki. All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) to receive neratinib or matching placebo (visually identical). The randomisation sequence was generated with permuted blocks stratified by locally determined hormone receptor status (hormone receptor-positive [defined as either oestrogen or progesterone receptor-positive or both] *vs* hormone receptor-negative [defined as oestrogen and progesterone receptor-negative]), nodal status (0, 1–3, or ≥4), and trastuzumab adjuvant regimen (sequentially *vs* concurrently with chemotherapy), then implemented centrally via an interactive voice and web-response system. Patients, investigators, and trial sponsors were masked to treatment allocation.

Procedures

Placebo or neratinib (Puma Biotechnology, Los Angeles, CA, USA) 240 mg was taken orally, once daily continuously. Treatment was given for 12 months unless disease recurrence or new breast cancer, intolerable adverse events, or consent withdrawal occurred. Drug compliance was monitored throughout the study. Neratinib dose reductions (200 mg, 160 mg, and 120 mg per day) were allowed for toxicity, with treatment cessation if the lowest dose was not tolerated or if treatment was interrupted for more than 3 weeks. Dose reductions were mandated for grade 3 diarrhoea after resolution to grade 1 or lower within 3 weeks, if a second episode of grade 3 diarrhoea occurred despite optimum medical therapy, and in the event of symptomatic grade 2 pneumonitis or interstitial lung disease and other grade 3 non-haematological events after resolution to grade 1 or lower within 3 weeks. Antidiarrhoeal prophylaxis was not protocol specified, but treatment for diarrhoea was advised at its earliest occurrence.

Physical examinations were done at 1 month, every 3 months during year 1, and every 4 months during year 2. Mammograms were done annually, when appropriate, and CT or bone scans were done if clinically indicated. Recurrences were defined clinically, radiologically, and, when possible, pathologically. Assessments of left ventricular ejection fraction (by multigated acquisition scan or echocardiogram) and 12-lead electrocardiograms were done at baseline and months 1, 3, 6, 9, and 12. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria, version 3.0. We assessed patient-reported health-related

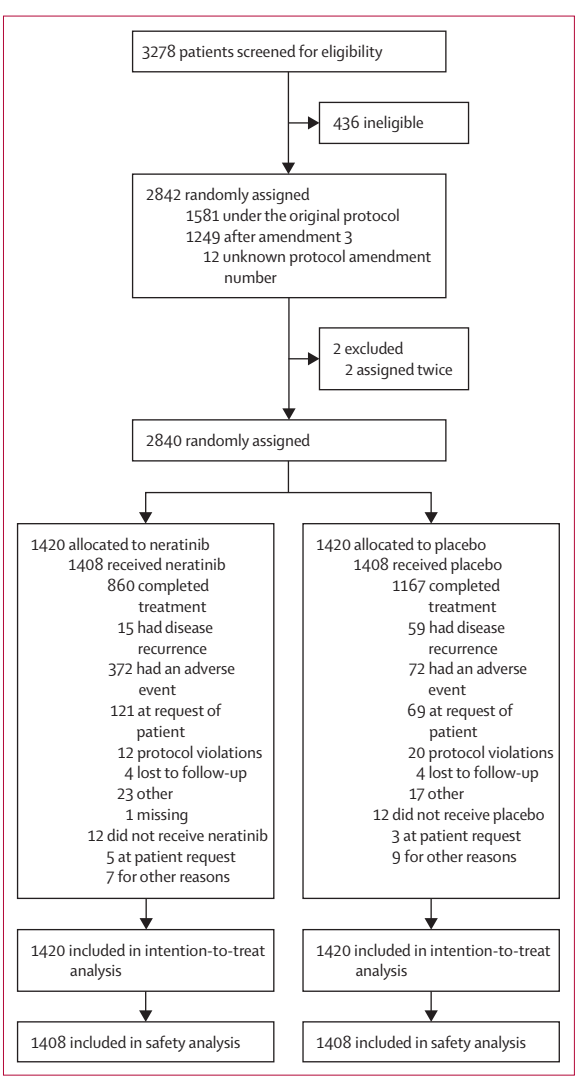

***Figure 1*: Trial profile**

quality of life with the EuroQol 5-Dimensions (EQ-5D) and Functional Assessment of Cancer Therapy–Breast (FACT-B), version 4, at baseline and months 1, 3, 6, 9, and 12 (end of treatment).

Outcomes

The primary endpoint was invasive disease-free survival at 2 years after randomisation where invasive disease was defined as invasive ipsilateral tumour recurrence, invasive contralateral breast cancer, local or regional invasive recurrence, distant recurrence, or death from any cause (appendix p 13). Patients were censored at the last assessment within 2 years plus 4 months from randomisation, allowing a window for assessments beyond the 2 years. Secondary endpoints were disease-free survival including ductal carcinoma in situ, time to distant recurrence, distant disease-free survival, cumulative incidence of CNS recurrences, overall survival, and safety. All time-to-event secondary endpoints were defined as from time of randomisation. Health-related quality of life was an exploratory endpoint. Secondary efficacy endpoints are defined in the appendix p 13.

Statistical analysis

The study was originally designed to enrol 3850 patients with 90% power to detect a hazard ratio (HR) of 0·7 for invasive disease-free survival, at a two-sided 5% significance level. In October, 2011, enrolment was stopped after 2842 patients were randomly assigned and follow-up truncated to 2 years. Consequently, the 2-year analysis of invasive disease-free survival was considered the primary analysis and the power was projected to be 88%, assuming an HR of 0·667 at a two-sided 5% significance level. No interim analyses were planned as a consequence of cessation of recruitment; the current primary analysis for invasive disease-free survival was not an event-driven analysis.

Efficacy analyses, including analyses of the primary and secondary endpoints, were done in the intention-to-treat population, defined as all randomly assigned patients. We tested time-to-event endpoints with two-sided log-rank tests stratified by randomisation factors. Although an unstratified analysis was stated in the protocol, it was revised to a stratified analysis in the statistical analysis plan before unmasking, so that the primary analysis was consistent with the stratified design of the trial. We used stratified Cox proportional-hazards models to estimate HRs with 95% CIs. We used Kaplan–Meier methods to estimate 2-year survival rates. Cumulative incidence in competing-risks analysis was done for CNS recurrences and Gray's test was used to compare treatments. Prespecified subgroup analyses, including the amended intention-to-treat subgroup of higher-risk patients (defined as all patients with node-positive disease and who were randomly assigned within 1 year of completing previous trastuzumab), were done using the same statistical methods as described above, with the analysis of the amended intention-to-treat subgroup considered a sensitivity analysis. Safety analyses were done in the safety population, defined as all patients who received at least one dose of study treatment. We compared changes from baseline in quality-of-life scores with ANCOVA, with baseline score as a covariate. Adjusted mean differences and 95% CIs were provided. An Independent Data Monitoring Committee reviewed the data semi-annually. We did analysis with SAS (version 9.2 or later). This trial is registered with ClinicalTrials.gov, number NCT00878709.

	Neratinib group (n=1420)	Placebo group (n=1420)
Region		
North America	519 (37%)	477 (34%)
Western Europe, Australia, New Zealand, and South Africa	487 (34%)	532 (37%)
Asia Pacific, eastern Europe, and South America	414 (29%)	411 (29%)
Race		
White	1165 (82%)	1135 (80%)
Black	27 (2%)	47 (3%)
Asian	188 (13%)	197 (14%)
Other	40 (3%)	41 (3%)
Age (years)	52 (45–59)	52 (45–60)
Age at randomisation (years)		
<35	46 (3%)	55 (4%)
35–49	523 (37%)	515 (36%)
50–59	497 (35%)	488 (34%)
≥60	354 (25%)	362 (25%)
Menopausal status at diagnosis		
Premenopausal	663 (47%)	664 (47%)
Postmenopausal	757 (53%)	756 (53%)

(Table 1 continues on next page)

Role of the funding source

The funders of the study designed the trial and were responsible for data collection, data integrity and analyses, and data interpretation, with oversight from the Academic Steering Committee (appendix p 4). The manuscript was written by the corresponding author, with input from all members of the Academic Steering Committee, and with review and input from the funders. The Academic Steering Committee was responsible for the final decision regarding manuscript contents and submission. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 9, 2009, and Oct 24, 2011, we randomly assigned 2842 patients to receive neratinib or placebo; two patients were allocated twice, thus 2840 patients (1420 per group) constituted the intention-to-treat population (figure 1). Baseline characteristics were

similar between groups (table 1). The median time from last trastuzumab dose to randomisation was 4·4 months (IQR 1·6–10·4) in the neratinib group and 4·6 months (1·5–10·8) in the placebo group (table 1). For patients recruited according to the original protocol (n=1580), the median interval between the last trastuzumab dose and randomisation was 7·1 months (IQR 2·6–14·7) in the neratinib group and 8·2 months (2·6–14·6) in the placebo group; for those recruited after the February, 2010 amendment (n=1248), the median interval was 2·5 months (1·3–5·8) and 2·6 months (1·2–5·7), respectively. The median duration of treatment was 353 days (range 1–406) in the neratinib group and 360 days (4–401) in the placebo group. Median relative dose intensity was 82% (range 0·3–105·5) in the neratinib group and 98% (1·1–108·5) in the placebo group. Median follow-up time was 24 months (IQR 20–25) in the neratinib group and 24 months (22–25) in the placebo group. The primary analysis was done in July, 2014.

2 years after randomisation, patients in the neratinib group had significantly fewer invasive disease-free survival events than did those in the placebo group (70 *vs* 109 events; stratified HR 0·67, 95% CI 0·50–0·91; p=0·0091; table 2, figure 2). The HR from unstratified analysis was 0·68 (95% CI 0·50–0·91; p=0·010). The 2-year invasive disease-free survival rate was 93·9% (95% CI 92·4–95·2) in the neratinib group and 91·6% (90·0–93·0) in the placebo group.

Disease-free survival including ductal carcinoma in situ was significantly improved in the neratinib group compared with the placebo group (93·9% [95% CI 92·4–95·2] *vs* 91·0 [89·3–92·5]; HR 0·63 [95% CI 0·46–0·84]; p=0·0017; figure 2). There was no significant difference between groups in either distant disease-free survival (HR 0·75 [95% CI 0·53–1·04]; p=0·089) or time to distant recurrence (0·71 [0·50–1·00]; p=0·054; appendix p 14); the 2-year rates for distant disease-free survival were 95·1% (95% CI 93·7–96·2) in the neratinib group versus 93·7% (92·2–94·9) in the placebo group, and for time to distant recurrence were 95·4% (94·1–96·5) versus 93·9% (92·4–95·0). The 2-year cumulative incidence of CNS recurrences was 0·91% (0·49–1·59) in the neratinib group and 1·25% (0·75–1·99) in the placebo group (p=0·44).

Prespecified subgroup analysis of invasive disease-free survival showed that neratinib provided greater benefit to patients with hormone receptor-positive breast cancer (HR 0·51, 95% CI 0·33–0·77; p=0·0013) than to those with hormone receptor-negative disease (0·93, 95% CI 0·60–1·43; p=0·74; $p_{interaction}$=0·054; figure 3). The appendix (p 8) shows Kaplan–Meier curves for both subgroups for invasive disease-free survival and for disease-free survival including ductal carcinoma in situ. HRs for the amended intention-to-treat population were similar to those for the intention-to-treat population (appendix p 9). At the

	Neratinib group (n=1420)	Placebo group (n=1420)
(Continued from previous page)		
Nodal status*		
Negative	335 (24%)	336 (24%)
1–3 positive nodes	664 (47%)	664 (47%)
≥4 positive nodes	421 (30%)	420 (30%)
Hormone receptor status*		
Positive (ER positive, PR positive, or both)	816 (57%)	815 (57%)
Negative (ER and PR negative)	604 (43%)	605 (43%)
Previous trastuzumab regimen*		
Concurrent	884 (62%)	886 (62%)
Sequential	536 (38%)	534 (38%)
T stage		
T1	440 (31%)	459 (32%)
T2	585 (41%)	555 (39%)
≥T3	144 (10%)	117 (8%)
Unknown	250 (18%)	288 (20%)
Missing	1 (<1%)	1 (<1%)
Histological grade of tumour		
Undifferentiated or poorly differentiated	670 (47%)	689 (49%)
Moderately differentiated	461 (32%)	416 (29%)
Well differentiated	76 (5%)	65 (5%)
Unknown	213 (15%)	241 (17%)
Previous surgery		
Lumpectomy only	468 (33%)	511 (36%)
Mastectomy	951 (67%)	908 (64%)
Missing	1 (<1%)	1 (<1%)
Previous radiotherapy		
Yes	1130 (80%)	1150 (81%)
No	290 (20%)	270 (19%)
Previous neoadjuvant or adjuvant therapy†		
Anthracycline only	136 (10%)	135 (10%)
Anthracycline plus taxane	962 (68%)	965 (68%)
Taxane only	318 (22%)	316 (22%)
Non-anthracycline or taxane	4 (<1%)	4 (<1%)
Duration of previous adjuvant trastuzumab therapy (months)‡	11·5 (10·9–11·9); n=1413	11·4 (10·8–11·9); n=1416
Time from last dose of trastuzumab to randomisation (months)	4·4 (1·6–10·4)	4·6 (1·5–10·8)
Concomitant endocrine therapy for hormone receptor-positive disease§		
Yes	760 (93%)	764 (94%)
Anti-oestrogen only	375 (46%)	347 (43%)
Anti-oestrogen and aromatase inhibitor (sequential)	20 (3%)	34 (4%)
Aromatase inhibitor only	362 (44%)	379 (47%)
Non-anti-oestrogen or aromatase inhibitor	3 (<1%)	4 (<1%)

Data are n (%), median (IQR), or median (IQR); n, unless otherwise specified. ER=oestrogen receptor. PR=progesterone receptor. *Stratification factor collected from the interactive voice and web-response system. For nodal status, the number of positive nodes was at the time of initial diagnosis (for patients who received adjuvant therapy) or surgery (for those who received neoadjuvant therapy). Patients with residual invasive disease in the breast, but node-negative disease or unknown nodal status in the axilla, after neoadjuvant therapy were included under 1–3 positive nodes. †The number of patients who received neoadjuvant chemotherapy was 342 (24%) in the neratinib group and 379 (27%) in the placebo group. ‡Patients with missing or partial dates of trastuzumab administration were not included in the analysis. §Percentage is based on the number of hormone receptor-positive patients. Tumours were assessed as being ER or PR positive on the basis of local pathology laboratory cutoffs. There was no protocol specification as to whether a 1% or 10% threshold be used.

Table 1: **Baseline characteristics of the intention-to-treat population**

	Neratinib group (n=1420)	Placebo group (n=1420)
Any event	70 (5%)	109 (8%)
Local or regional invasive recurrence	8 (1%)	25 (2%)
Invasive ipsilateral breast tumour recurrence	4 (<1%)	4 (<1%)
Invasive contralateral breast cancer	2 (<1%)	5 (<1%)
Distant recurrence*	52 (4%)	73 (5%)
Bone	21 (1%)	21 (1%)
Brain	11 (1%)	15 (1%)
Distant lymph node	6 (<1%)	10 (1%)
Liver	13 (1%)	21 (1%)
Lung	5 (<1%)	12 (1%)
Other	5 (<1%)	2 (<1%)
Other abdominal viscera	0	2 (<1%)
Pleura	1 (<1%)	3 (<1%)
Subcutaneous tissue	1 (<1%)	1 (<1%)
Unknown	1 (<1%)	0
Death without previous recurrence	4 (<1%)	2 (<1%)

Data are n (%). *Patients might have had more than one distant site of recurrence.

***Table 2*: Invasive disease-free survival events in the intention-to-treat population**

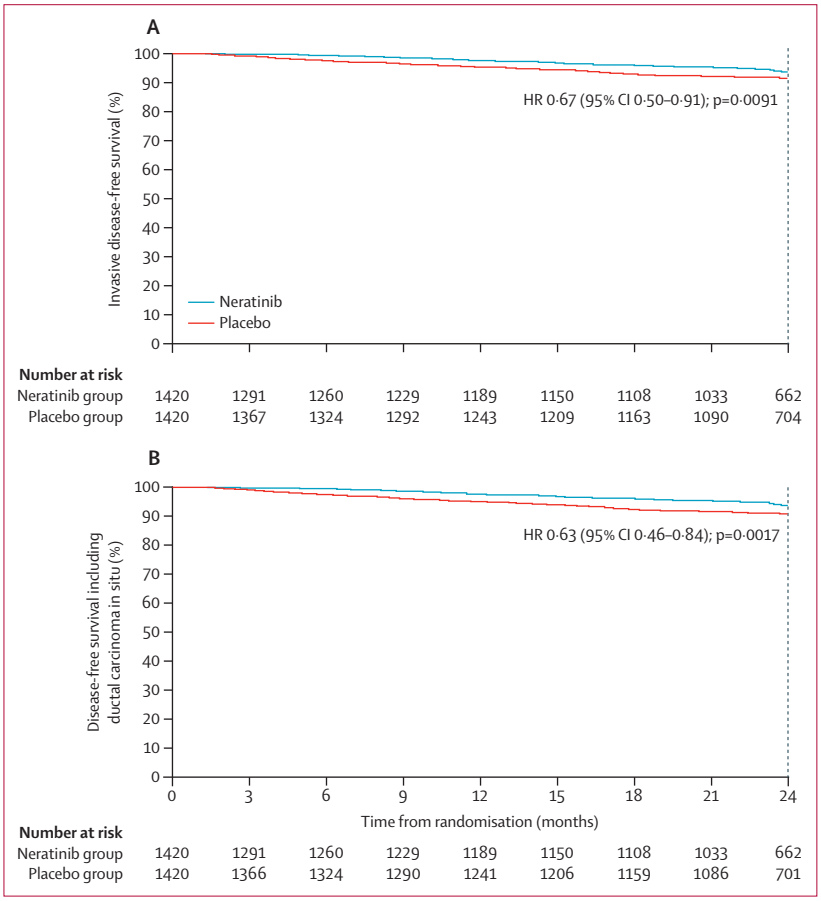

***Figure 2*: Kaplan–Meier curves for invasive disease-free survival (A) and disease-free survival including ductal carcinoma in situ (B) in the intention-to-treat population**

time of this report, 1705 (60%) of primary tumour specimens had undergone central HER2 testing. In a prespecified analysis of patients with centrally confirmed HER2-positive disease, invasive disease-free survival was significantly improved in patients in the neratinib group (n=741) compared with those in the placebo group (n=722; HR 0·51, 95% CI 0·33–0·77; p=0·0015; appendix p 10). The appendix (p 10) also shows Kaplan–Meier curves for invasive disease-free survival including ductal carcinoma in situ.

Overall survival data were not mature and there was no provision in the protocol for any analyses before the predetermined target number of events being reached. Overall survival will continue to be monitored by the Independent Data Monitoring Committee.

At least one dose of study treatment was received by 2816 patients (1408 patients in each group). Table 3 provides a summary of the most common treatment-emergent adverse events and appendix p 17 shows all events of grades 3–5. Diarrhoea was the most common treatment-emergent adverse event in the neratinib group (table 3). 458 (33%) patients had grade 2 diarrhoea, 561 (40%) patients had grade 3 diarrhoea, and one (<1%) patient had grade 4 diarrhoea. In the placebo group, 94 (7%) patients had 2 grade diarrhoea, 23 (2%) patients had grade 3, and no patients had grade 4 diarrhoea. All other grade 3–4 adverse events occurred in fewer than 4% of neratinib-treated patients, with similar incidence of non-gastrointestinal events in both groups (appendix). QT prolongation occurred in 49 (3%) patients given neratinib and 93 (7%) patients given placebo, and decreases in left ventricular ejection fraction (≥ grade 2) occurred in 19 (1%) and 15 (1%) patients, respectively. Incidence of interstitial lung disease (n=2 in the neratinib group *vs* n=1 in the placebo group), pneumonitis (n=1 *vs* n=1), and pulmonary fibrosis (n=1 *vs* n=2) were similar between groups. 11 (1%) patients in each group had second cancers (ie, neoplasms benign, malignant, and unspecified, including cysts and polyps). Serious treatment-emergent adverse events occurred in 103 (7%) patients in the neratinib group and 85 (6%) patients in the placebo group; the most common serious adverse events in the neratinib group were diarrhoea (n=22 *vs* n=1 in the placebo group), vomiting (n=12 *vs* n=1), and dehydration (n=9 *vs* n=1). Seven (<1%) deaths (four patients in the neratinib group and three patients in the placebo group) unrelated to disease progression occurred after study drug discontinuation. The causes of death in the neratinib group were unknown (n=2), a second primary brain tumour (n=1), and acute myeloid leukaemia (n=1), and in the placebo group were a brain haemorrhage (n=1), myocardial infarction (n=1), and gastric cancer (n=1). None of the deaths were attributed to study treatment in either group. In the neratinib group, grade 3 diarrhoea occurred after a median of 8 days (IQR 4–33) and lasted a median of 5 days (2–9) per patient (appendix p 22). Most grade 3 diarrhoea events

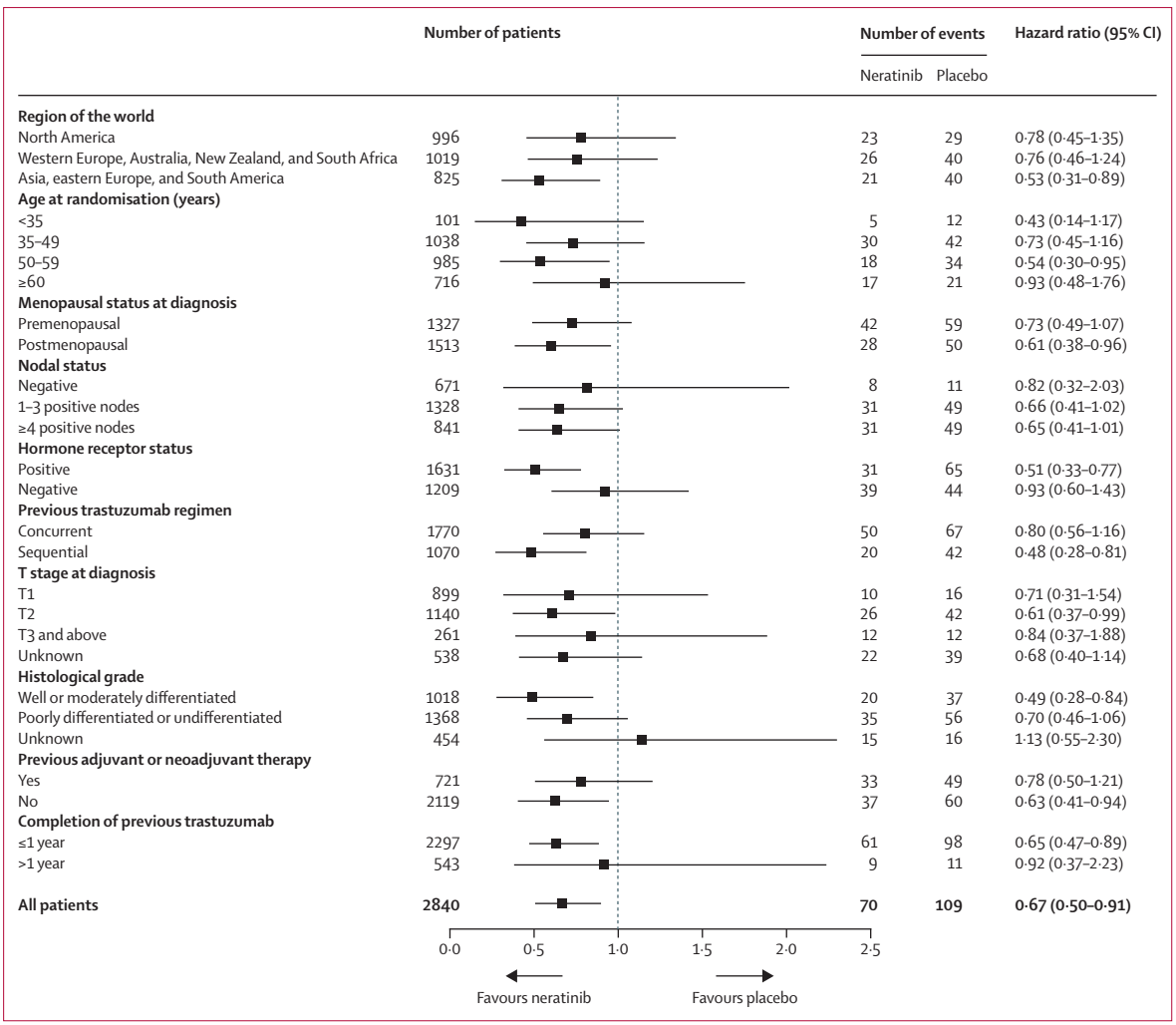

Figure 3: **Subgroup analyses of invasive disease-free survival in the intention-to-treat population**
The dashed line indicates a hazard ratio of 1·00—the null hypothesis value.

arose in the first month of treatment (appendix p 11). Diarrhoea led to neratinib dose reductions in 372 (26%) patients in the neratinib group and eight (1%) patients in the placebo group, hospital admission in 20 (1%) versus one (<1%) patient, and drug discontinuation in 237 (17%) patients (discontinued after a median of 20 days [IQR 9–56]) versus three (<1%) patients (discontinued after 241 days [147–305]; appendix p 22).

The adjusted mean difference of changes in quality of life between the neratinib and placebo groups was greatest at month 1 for both measures (FACT-B, –2·9 [95% CI –3·7 to –2·0]; EQ-5D, –2·7 [–3·7 to –1·7]). Neither difference was deemed clinically important for the respective measures. After the first month, the quality of life for patients in both groups recovered towards baseline levels and the difference between groups was less pronounced (appendix p 12).

There was a difference in attrition rate between the two groups, mainly because of early adverse events in

	Neratinib group (n=1408)			Placebo group (n=1408)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Diarrhoea	781 (55%)	561 (40%)	1 (<1%)	476 (34%)	23 (2%)	0
Nausea	579 (41%)	26 (2%)	0	301 (21%)	2 (<1%)	0
Fatigue	359 (25%)	23 (2%)	0	276 (20%)	6 (<1%)	0
Vomiting	322 (23%)	47 (3%)	0	107 (8%)	5 (<1%)	0
Abdominal pain	314 (22%)	24 (2%)	0	141 (10%)	3 (<1%)	0
Headache	269 (19%)	8 (1%)	0	269 (19%)	6 (<1%)	0
Upper abdominal pain	201 (14%)	11 (1%)	0	93 (7%)	3 (<1%)	0
Rash	205 (15%)	5 (<1%)	0	100 (7%)	0	0
Decreased appetite	166 (12%)	3 (<1%)	0	40 (3%)	0	0
Muscle spasms	157 (11%)	1 (<1%)	0	44 (3%)	1 (<1%)	0
Dizziness	143 (10%)	3 (<1%)	0	125 (9%)	3 (<1%)	0
Arthralgia	84 (6%)	2 (<1%)	0	158 (11%)	4 (<1%)	0

Data are n (%). Full adverse events are presented in the appendix (p 16).

Table 3: **Treatment-emergent adverse events occurring in at least 10% of patients in the safety population**

the neratinib group. A sensitivity analysis assessing the effect of early dropouts on invasive disease-free survival yielded results that were consistent with those of the primary analysis (appendix p 7). Baseline characteristics were similar in patients who dropped out before 3 months and those who continued beyond 3 months in both treatment groups (appendix p 15). Withdrawal of patient consent for any reason other than disease recurrence occurred at a rate of 0·4% (five of 1140 patients) to 4·0% (56 of 1409 patients) per study visit in the neratinib group, and 0·2% (three of 1343 patients) to 1·1% (15 of 1331 patients) per visit in the placebo group.

Discussion

Our findings show that 12 months of neratinib significantly improves invasive disease-free survival in trastuzumab-treated patients with early breast cancer. Disease-free survival including ductal carcinoma in situ was also significantly improved with neratinib compared with placebo after 2 years, although both distant disease-free survival and time to distant recurrence were similar in both groups.

The ability of neratinib to reduce the relapse rate after 1 year of trastuzumab is by contrast with data from the HERA study,[5] the only other published study that sought to improve outcome beyond current standard of care by administration of 24 months of trastuzumab. At a median follow-up of 8 years, findings from the HERA landmark analysis showed no improvement in the primary endpoint of disease-free survival (HR 0·99, 95% CI 0·85–1·14; p=0·86) with the extended duration of trastuzumab therapy.[5] Although there were similarities between the patient populations in HERA and our study, patients in HERA who remained disease free at 12 months of follow-up were immediately continued on trastuzumab, whereas more than 50% of patients in our study had an interval of greater than 4·5 months after completion of trastuzumab and before initiation of neratinib. The trials also differed in the proportion of patients enrolled with node-negative disease (about 32% in HERA and 24% in ExteNET). Importantly, all patients in HERA received trastuzumab sequentially after completion of chemotherapy, compared with only 38% of the patients in our study, with the remainder of our patients receiving trastuzumab concurrently with chemotherapy. Moreover, in the HERA study, 26% of patients received both an anthracycline and taxane as adjuvant chemotherapy, whereas 68% of patients received both an anthracycline and taxane as adjuvant chemotherapy in our study. The HERA results were not affected by hormone receptor status of the primary tumour, whereas we recorded an early separation favouring neratinib in hormone receptor-positive patients at 1 year, which persisted at 2 years. Thus, inherent differences in risk of relapse in each trial population, and the potentially greater effectiveness of neratinib in the hormone receptor-positive cohort might explain the differences in results between the two trials, and also underlies the importance of the longer follow-up of patients in our study.

A possible explanation of the improved outcome with neratinib might be the potent suppression of HER2 signalling through neratinib binding to the cysteine residue of the catalytic cleft of the HER2 receptor, leading to irreversible kinase inhibition.[7] HER2-positive breast cancer cells are an example of so-called oncogenic addiction to the HER2 pathway, and recurrence of HER2 breast cancer has been suggested to result from cells escaping the addiction by activation of alternative growth pathways.[13] However, both preclinical and clinical studies have shown that, in circumstances in which trastuzumab resistance has developed, tumour cells might still remain addicted to the HER2 pathway.[14–16] Findings from our study would suggest that recurrent tumours remain addicted to the HER2 pathway, whereby an anti-HER2 drug, which acts on a different target in the same growth signalling pathway, might result in cancer cell death, suggesting an absence of cross-resistance with trastuzumab.[17]

The finding of a greater benefit in patients with hormone receptor-positive breast cancer than in those with hormone receptor-negative disease (with a $p_{interaction}$ value of less than the 0·1 significance level generally used to test for interaction[18]) is of particular interest, because results from other trials, such as NSABP/N9831 and HERA, showed similar benefits irrespective of hormone receptor status (HR 0·61 for patients with hormone receptor-positive disease *vs* 0·62 for patients with hormone receptor-negative disease[2] and 0·68 *vs* 0·62,[19] respectively). Furthermore, three neoadjuvant trials of anti-HER2 therapy with chemotherapy[20–22] reported greater rates of pathological complete response and event-free survival in patients with hormone receptor-negative disease than in those with hormone receptor-positive disease.

Cross-talk between the oestrogen and HER2 receptors has been reported by several investigators, with HER2 over-amplification, resulting in resistance to oestrogen-deprivation therapies.[23–25] A possible explanation of the apparent benefit in patients with hormone receptor-positive disease in our study is that neratinib treatment might result in more effective HER2 blockade in a trastuzumab-treated environment compared with continuing with trastuzumab as a result of its different mechanism of action in irreversibly inhibiting intracellular HER2 downstream phosphorylation and potentially rendering cells more endocrine-responsive.[26] An alternative explanation is suggested from preclinical studies[27] in parental and anti-HER2-resistant derivatives. With use of HER2-positive, hormone receptor-positive cell lines (BT474) and xenograft models (UACC-812), the main mechanism for cellular proliferation in trastuzumab-resistant cells remained HER2 signalling, whereas in lapatinib-resistant cell lines, oestrogen-receptor activity was the dominant driver of growth. Thus, neratinib,

which can inhibit EGFR phosphorylation and EGFR and HER2 dimerisation (neither process being effectively suppressed by trastuzumab), has been postulated to preferentially provide more effective HER2-pathway inhibition in trastuzumab-resistant patients with hormone receptor-positive disease than does continuation of trastuzumab and endocrine treatment.[15] However, further studies are needed to confirm this theory.

Recurrences in the CNS following adjuvant trastuzumab remain an important area of clinical need, as shown in HERA (in which 47% of patients in the control group and 57% of those who received trastuzumab for 1 year who had a recurrence, died with CNS disease).[28] The significantly lower rates of CNS progression in the NEfERTT trial of patients with metastatic breast cancer given paclitaxel and neratinib[29] suggest that neratinib is an active drug in CNS disease. Although rates of CNS recurrence did not differ significantly between groups in our study, ongoing monitoring for CNS relapse with longer follow-up is an important goal of the ExteNET trial.

Diarrhoea was the most common side-effect in patients in the neratinib group, which typifies this class of drug, as has been reported in trials of neratinib in the metastatic setting.[8] Occurrences of diarrhoea were mostly self-limiting (ie, diminished in subsequent months without prophylactic antidiarrhoeal medication). The frequency of initiation of any antidiarrhoeal medications from months 2 to 12 in patients receiving neratinib was approximately 30–35% per month. This adverse event might be attributable to EGFR involvement in calcium-dependent chloride transport, such that EGFR inhibition might result in secretory diarrhoea—the postulated mechanism of neratinib's effect.[30] The severe diarrhoea (grade 3) in patients given neratinib tended to occur early in the course of treatment, with the highest incidence reported in cycle 1, after which point the incidence decreased substantially. The frequency of grade 3 diarrhoea in the first month of treatment is likely to be the reason for the worse quality-of-life scores during this time. In view of the early occurrence of severe diarrhoea, use of prophylactic loperamide for the first cycle (ie, 4 weeks) of treatment would be expected to effectively reduce the rates of severe diarrhoea and is supported by results of ongoing studies of neratinib with intensive loperamide prophylaxis (appendix p 22). Loperamide given during the first month of treatment with commencement of neratinib has been shown in several studies to effectively reduce rates of grade 3 diarrhoea to 0–17%,[31–33] and improve the overall tolerability of the drug. Notably, at the time of ExteNET study design, management of diarrhoea was instituted only after the development of symptoms. Routine use of intensive loperamide prophylaxis during the first month of neratinib administration is anticipated to abrogate the incidence and severity of diarrhoea, and is currently being assessed in an open-label, multicentre, prospective trial (ClinicalTrials.gov, number NCT02400476).

Another adverse event that has been noted with other anti-HER2 drugs is cardiac toxicity—namely, reductions in left ventricular ejection fraction and congestive heart failure. Cardiac toxicity with neratinib at the time of this analysis was minimal, although longer follow-up is essential to ensure that the improved breast cancer outcome reported in the study is not at the cost of serious cardiac toxicity. Patient quality of life deteriorated slightly during the first cycle of treatment with neratinib, although this decline was not clinically significant according to established minimally important differences in the two quality-of-life measures (FACT-B and EQ-5D).[34,35] Thereafter, quality-of-life scores were similar in both groups and returned towards baseline.

Despite the three global protocol amendments by the different sponsors, the 2-year analysis was prespecified with appropriate type I error control and, although the truncated follow-up led to a lower powered study, the HR and statistical significance reported remains accurate and valid. In particular, the primary analysis results would not have been changed by the decision to cease recruitment, because all patients underwent protocol-mandated follow-up until the 2-year point of analysis.

We recognise the limitations of the present analysis as providing an early assessment of treatment benefit. However, the early reporting of results in itself is not indicative of a likely loss of effect with longer follow-up. The clinically significant findings of the HERA, NSABP B-31/N9831, and MA17 trials were reported at years 1,[36] 2,[37] and 2·4 of follow-up,[38] respectively, although we clearly recognise that these studies had prespecified event-driven endpoints. The importance of long-term follow-up is recognised, and these results, together with those of the overall survival analysis, will be reported in accordance with the statistical plan.

In conclusion, neratinib taken for 12 months after trastuzumab-containing adjuvant therapy significantly improved invasive disease-free survival at 2 years in the intention-to-treat population. Thus, in patients considered to have a heightened risk of breast cancer relapse even after adjuvant chemotherapy and trastuzumab (eg, those with a heavy nodal burden, younger age, or locally advanced disease at diagnosis), neratinib could offer additional benefit. With longer follow-up and elucidation of the mechanism of benefit in hormone receptor-positive patients, patient subgroups might be identified who could benefit the most from extended adjuvant therapy with neratinib.

Contributors

CHB, AC, SKLC, SD, BE, MG, FAH, HI, JM, MM, BM, GvM, and MB conceived and designed the study. BE, VJH, and JS acquired the data. YY and BY analysed the data. All authors were involved in interpretation and critical review of the data, drafting or revising the manuscript for important intellectual content, and approving the final version of the manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests
AC has received personal fees for educational meetings from Pfizer, Amgen, and Eisai, and non-financial support from Puma Biotechnology outside the submitted work. SD has received grants and personal fees from Roche and Novartis, and personal fees from Pfizer outside the submitted work. HI has received grants and personal fees from AstraZeneca, personal fees from Eisai, and grants from GlaxoSmithKline, Novartis, Pfizer, Daiichi-Sankyo, Chugai, Lilly, and Nihon Kayaku outside the submitted work. BE has received grants from Novartis, Amgen, and Roche outside the submitted work. JM received institution support for infrastructure for patients enrolled in the study from Wyeth, Pfizer, and Puma Biotechnology during the conduct of the study. CHB has received grants and personal fees from GlaxoSmithKline, Roche, and Novartis outside the submitted work. MG has received grants from Sanofi-Aventis, Pfizer, and Smith Medical; grants and personal fees from Novartis, Roche, and GlaxoSmithKline; and personal fees from AstraZeneca, Nanostring Technologies, and Accelsiors outside the submitted work. MB is an employee and stockholder of the International Drug Development Institute (IDDI). IG has received grants from Puma Biotechnology during the study. NM has received personal fees from Chugai, AstraZeneca, Eisai, Kyowa-Hakko Kirin, and Sanofi outside the submitted work. MM has received grants and personal fees from Novartis, and personal fees from Roche, AstraZeneca, and Celgene outside the submitted work. RB, AW, BY, and YY are employees of Puma Biotechnology. All other authors declare no competing interests.

Acknowledgments
This study was funded by Wyeth, Pfizer, and Puma Biotechnology, who also provided the study drugs. Statistical analyses were done by, or with assistance from, Yining Ye, Bin Yao, Bo Zhang, and Janine Lu. Puma Biotechnology also funded the provision of editorial support provided by Lee Miller and Harriet Lamb of Miller Medical Communications. We would like to acknowledge the contribution of the Independent Data Monitoring Committee. We thank all the patients who contributed to this study, whose involvement made the reporting of these results possible. We also thank the investigators and members of the Academic Steering Committee (listed in the appendix). In memory of Zora Nešković-Konstantinović, we would like to recognise the important contribution she made to the ExteNET trial. She contributed many patients to the study and was involved in critical reviews of the manuscript.

References
1 Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987; **235:** 177–82.
2 Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol* 2014; **32:** 3744–52.
3 Gianni L, Dafni U, Gelber RD, et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. *Lancet Oncol* 2011; **12:** 236–44.
4 Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011; **365:** 1273–83.
5 Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, et al. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. *Lancet* 2013; **382:** 1021–28.
6 Joensuu H, Bono P, Kataja V, et al. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. *J Clin Oncol* 2009; **27:** 5685–92.
7 Wong KK, Fracasso PM, Bukowski RM, et al. A phase I study with neratinib (HKI-272), an irreversible pan ErbB receptor tyrosine kinase inhibitor, in patients with solid tumors. *Clin Cancer Res* 2009; **15:** 2552–58.
8 Burstein HJ, Sun Y, Dirix LY, et al. Neratinib, an irreversible ErbB receptor tyrosine kinase inhibitor, in patients with advanced ErbB2-positive breast cancer. *J Clin Oncol* 2010; **28:** 1301–07.
9 Nahta R, Esteva FJ. HER2 therapy: molecular mechanisms of trastuzumab resistance. *Breast Cancer Res* 2006; **8:** 215.
10 Martin M, Bonneterre J, Geyer CE Jr, et al. A phase two randomised trial of neratinib monotherapy versus lapatinib plus capecitabine combination therapy in patients with HER2+ advanced breast cancer. *Eur J Cancer* 2013; **49:** 3763–72.
11 Perez EA, Suman VJ, Davidson NE, et al. Sequential versus concurrent trastuzumab in adjuvant chemotherapy for breast cancer. *J Clin Oncol* 2011; **29:** 4491–97.
12 Slamon D, Eiermann W, Robert N, et al. BCIRG 006 Phase III trial comparing AC→T with AC→TH and with TCH in the adjuvant treatment of HER2-amplified early breast cancer patients: third planned efficacy analysis. 2009. http://bit.ly/1JTxDOr (accessed Jan 26, 2016).
13 Weinstein IB, Joe AK. Mechanisms of disease: oncogene addiction—a rationale for molecular targeting in cancer therapy. *Nat Clin Pract Oncol* 2006; **3:** 448–57.
14 Wang YC, Morrison G, Gillihan R, et al. Different mechanisms for resistance to trastuzumab versus lapatinib in HER2-positive breast cancers—role of estrogen receptor and HER2 reactivation. *Breast Cancer Res* 2011; **13:** R121.
15 von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a German Breast Group 26/Breast International Group 03-05 study. *J Clin Oncol* 2009; **27:** 1999–2006.
16 Blackwell KL, Burstein HJ, Storniolo AM, et al. Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *J Clin Oncol* 2010; **28:** 1124–30.
17 Weinstein IB, Joe A. Oncogene addiction. *Cancer Res* 2008; **68:** 3077–80.
18 Fleiss JL. Analysis of data from multiclinic trials. *Control Clin Trials* 1986; **7:** 267–75.
19 Untch M, Gelber RD, Jackisch C, et al. Estimating the magnitude of trastuzumab effects within patient subgroups in the HERA trial. *Ann Oncol* 2008; **19:** 1090–96.
20 Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2 negative cohort. *Lancet* 2010; **375:** 377–84.
21 Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012; **13:** 25–32.
22 de Azambuja E, Holmes AP, Piccart-Gebhart M, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. *Lancet Oncol* 2014; **15:** 1137–46.
23 De Laurentiis M, Arpino G, Massarelli E, et al. A meta-analysis on the interaction between HER-2 expression and response to endocrine treatment in advanced breast cancer. *Clin Cancer Res* 2005; **11:** 4741–48.
24 Dowsett M, Harper-Wynne C, Boeddinghaus I, et al. HER-2 amplification impedes the antiproliferative effects of hormone therapy in estrogen receptor-positive primary breast cancer. *Cancer Res* 2001; **61:** 8452–58.
25 Nahta R, O'Regan RM. Therapeutic implications of estrogen receptor signaling in HER2-positive breast cancers. *Breast Cancer Res Treat* 2012; **135:** 39–48.
26 Kurokawa H, Lenferink AE, Simpson JF, et al. Inhibition of HER2/neu (erbB-2) and mitogen-activated protein kinases enhances tamoxifen action against HER2-overexpressing, tamoxifen-resistant breast cancer cells. *Cancer Res* 2000; **60:** 5887–94.
27 Canonici A, Gijsen M, Mullooly M, et al. Neratinib overcomes trastuzumab resistance in HER2 amplified breast cancer. *Oncotarget* 2013; **4:** 1592–605.
28 Pestalozzi BC, Holmes E, de Azambuja E, et al. CNS relapses in patients with HER2-positive early breast cancer who have and have not received adjuvant trastuzumab: a retrospective substudy of the HERA trial (BIG 1-01). *Lancet Oncol* 2013; **14:** 244–48.
29 Awada A, Colomer R, Inoue K, et al. Neratinib plus paclitaxel vs trastuzumab plus paclitaxel in previously untreated metastatic HER2-positive breast cancer: the NEfERT-T randomized clinical trial. *JAMA Oncol* (in press).

30 Andreyev J, Ross P, Donnellan C, et al. Guidance on the management of diarrhoea during cancer chemotherapy. *Lancet Oncol* 2014; **15:** e447–60.

31 Besse B, Soria J, Yao B, et al. Neratinib with or without temsirolimus in patients with non-small cell lung cancer (NSCLC) carrying *HER2* somatic mutations: an international randomized phase II study. *Ann Oncol* 2014; **25:** 1–41 (A39 abstr).

32 Gajria D, Modi S, Saura C, et al. A phase I/II study of neratinib plus temsirolimus in HER2+ metastatic breast cancer reveals ongoing HER2 pathway dependence in many patients despite several lines of HER2 targeted therapy. *Cancer Res* 2015; **75** (suppl 9)**:** P5-19-04.

33 Jankowitz RC, Abraham J, Tan AR, et al. Safety and efficacy of neratinib in combination with weekly paclitaxel and trastuzumab in women with metastatic HER2-positive breast cancer: an NSABP Foundation Research Program phase I study. *Cancer Chemother Pharmacol* 2013; **72:** 1205–12.

34 Eton DT, Cella D, Yost KJ, et al. A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. *J Clin Epidemiol* 2004; **57:** 898–910.

35 Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes* 2007; **5:** 70.

36 Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005; **353:** 1659–72.

37 Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005; **353:** 1673–84.

38 Mann BS, Johnson JR, Kelly R, Sridhara R, Williams G, Pazdur R. Letrozole in the extended adjuvant treatment of postmenopausal women with history of early-stage breast cancer who have completed 5 years of adjuvant tamoxifen. *Clin Cancer Res* 2005; **11:** 5671–77.