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Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background ExteNET showed that 1 year of neratinib, an irreversible pan-HER tyrosine kinase inhibitor, significantly improves 2-year invasive disease-free survival after trastuzumab-based adjuvant therapy in women with HER2-positive breast cancer. We report updated efficacy outcomes from a protocol-defined 5-year follow-up sensitivity analysis and long-term toxicity findings.

Methods In this ongoing randomised, double-blind, placebo-controlled, phase 3 trial, eligible women aged 18 years or older (≥20 years in Japan) with stage 1–3c (modified to stage 2–3c in February, 2010) operable breast cancer, who had completed neoadjuvant and adjuvant chemotherapy plus trastuzumab with no evidence of disease recurrence or metastatic disease at study entry. Patients who were eligible patients were randomly assigned (1:1) via permuted blocks stratified according to hormone receptor status (hormone receptor-positive *vs* hormone receptor-negative), nodal status (0 *vs* 1–3 *vs* or ≥4 positive nodes), and trastuzumab adjuvant regimen (given sequentially *vs* concurrently with chemotherapy), then implemented centrally via an interactive voice and web-response system, to receive 1 year of oral neratinib 240 mg/day or matching placebo. Treatment was given continuously for 1 year, unless disease recurrence or new breast cancer, intolerable adverse events, or consent withdrawal occurred. Patients, investigators, and trial funder were masked to treatment allocation. The predefined endpoint of the 5-year analysis was invasive disease-free survival, analysed by intention to treat. ExteNET is registered with ClinicalTrials.gov, number NCT00878709, and is closed to new participants.

Findings Between July 9, 2009, and Oct 24, 2011, 2840 eligible women with early HER2-positive breast cancer were recruited from community-based and academic institutions in 40 countries and randomly assigned to receive neratinib (n=1420) or placebo (n=1420). After a median follow-up of 5·2 years (IQR 2·1–5·3), patients in the neratinib group had significantly fewer invasive disease-free survival events than those in the placebo group (116 *vs* 163 events; stratified hazard ratio 0·73, 95% CI 0·57–0·92, p=0·0083). The 5-year invasive disease-free survival was 90·2% (95% CI 88·3–91·8) in the neratinib group and 87·7% (85·7–89·4) in the placebo group. Without diarrhoea prophylaxis, the most common grade 3–4 adverse events in the neratinib group, compared with the placebo group, were diarrhoea (561 [40%] grade 3 and one [<1%] grade 4 with neratinib *vs* 23 [2%] grade 3 with placebo), vomiting (grade 3: 47 [3%] *vs* five [<1%]), and nausea (grade 3: 26 [2%] *vs* two [<1%]). Treatment-emergent serious adverse events occurred in 103 (7%) women in the neratinib group and 85 (6%) women in the placebo group. No evidence of increased risk of long-term toxicity or long-term adverse consequences of neratinib-associated diarrhoea were identified with neratinib compared with placebo.

Interpretation At the 5-year follow-up, 1 year of extended adjuvant therapy with neratinib, administered after chemotherapy and trastuzumab, significantly reduced the proportion of clinically relevant breast cancer relapses—ie, those that might lead to death, such as distant and locoregional relapses outside the preserved breast—without increasing the risk of long-term toxicity. An analysis of overall survival is planned after 248 events.

Funding Wyeth, Pfizer, and Puma Biotechnology.

Introduction

During the past decade, several large phase 3 randomised trials have established that the addition of 1 year of trastuzumab to chemotherapy for women with early-stage HER2-positive breast cancer significantly reduces disease recurrences and deaths.[1–3] Despite the proven benefits of trastuzumab in the adjuvant setting, data from long-term follow-up show that 15–24% of patients' breast cancers recur after a median of 8–11 years.[1,2] Furthermore, when analysed annually, the risk of relapse in patients with HER2-positive metastatic breast cancer is greatest during the first 12 months after completion of trastuzumab therapy.[4]

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Research in context

Evidence before this study

We searched PubMed from Jan 1, 2000, to June 30, 2017, using the search terms "HER2", "adjuvant", "breast", and "randomised". We identified three randomised trials of systemic adjuvant therapy in patients with early-stage HER2-positive breast cancer published in English that aimed to improve outcomes beyond current standard of care (ie, 1 year of trastuzumab). In HERA, 2 years of trastuzumab did not significantly improve disease-free survival compared with 1 year of trastuzumab after 8 years of follow-up. In ALTTO, lapatinib given concurrently with trastuzumab for 1 year, or sequentially for 8·5 months after 3 months of trastuzumab, did not significantly improve disease-free survival after a median follow-up of 4·5 years. In APHINITY, the addition of pertuzumab to trastuzumab for 1 year improved 3-year invasive disease-free survival (hazard ratio 0·81, 95% CI 0·66–1·00, p=0·045) compared with trastuzumab alone, after a median follow-up of 45·4 months.

Added value of this study

Long-term patient outcome data after a median follow-up of 5 years postrandomisation show that women with HER2-positive early-stage breast cancer who received neratinib for 1 year after trastuzumab-based adjuvant therapy had sustained and significant reductions in the risk of invasive disease-free survival compared with patients who received placebo.

Implications of all the available evidence

1 year of neratinib after chemotherapy and trastuzumab adjuvant therapy significantly reduces the likelihood of clinically relevant breast cancer relapse, without a significant risk of long-term toxicity in women with early-stage HER2-positive breast cancer. Extended adjuvant neratinib after chemotherapy and trastuzumab should be considered a new therapeutic option for this patient population. An analysis of overall survival is planned after 248 events.

Efforts to improve outcomes beyond those achieved with 1 year of trastuzumab in patients with early-stage HER2-positive breast cancer are ongoing. Several different approaches, including extending the duration of trastuzumab to 2 years (HERceptin Adjuvant [HERA] trial),[5] concurrent or sequential administration of lapatinib, a tyrosine kinase inhibitor, with trastuzumab (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation [ALTTO] trial),[6] and the addition of bevacizumab, an anti-angiogenic agent, to trastuzumab (Bevacizumab with Trastuzumab Adjuvant Therapy in HER2-Positive Breast Cancer [BETH] trial)[7] have all been unsuccessful, with no significant disease-free survival benefit compared with 1 year of trastuzumab. APHINITY (Adjuvant Pertuzumab and Herceptin in Initial Therapy in Breast Cancer) showed a significant improvement in invasive disease-free survival at 3 years from the addition of pertuzumab to trastuzumab-based adjuvant therapy;[8] however, the 3-year reduction in the percentage of patients with recurrence or death with pertuzumab was only 1% (pertuzumab group, 94%; placebo group, 93%).[8] Thus, the role of pertuzumab as adjuvant therapy in HER2-positive breast cancer is a matter of ongoing debate.[9] 1 year of trastuzumab added to adjuvant chemotherapy remains the standard of care for most patients with early-stage HER2-positive breast cancer;[10,11] however, other phase 3 trials addressing the same question are in progress.

Neratinib (Puma Biotechnology, Los Angeles, CA, USA) is an irreversible small-molecule tyrosine kinase inhibitor of HER1, HER2, and HER4,[12] with established single-agent efficacy in trastuzumab-pretreated HER2-positive metastatic breast cancer.[13,14] The international phase 3 Extended Adjuvant Treatment of Breast Cancer with Neratinib (ExteNET) trial was designed to evaluate whether or not 1 year of neratinib given after standard trastuzumab-based adjuvant therapy would improve outcomes in women with early-stage HER2-positive breast cancer. The primary analysis from ExteNET at the 2-year follow-up showed that neratinib significantly improved invasive disease-free survival compared with placebo (stratified hazard ratio [HR] 0·67, 95% CI 0·50–0·91, p=0·0091).[15] We report updated efficacy findings from a prespecified analysis of ExteNET, after a median follow-up of 5 years. Detailed health-related quality-of-life and biomarker data from the study will be reported separately.

Methods

Study design and participants

ExteNET is a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial designed to investigate extended adjuvant therapy with neratinib or placebo given for 1 year after standard locoregional treatment, trastuzumab, and chemotherapy; the trial design details are described in the primary 2-year analysis.[15] The final design of ExteNET comprised three discrete parts: the primary efficacy analysis at 2 years (July, 2014);[15] the sensitivity analysis of efficacy endpoints at 5 years (March, 2017), which is the focus of this paper; and the analysis of overall survival (to be done after 248 events).

During the trial, three different funders were involved, resulting in three global amendments to the study design.[15] Pertinent to this paper is global amendment 13 (January, 2014), which was implemented by the current funder to restore the original intention of the study—ie, to evaluate the long-term efficacy of neratinib in the intention-to-treat population. Because many patients had completed the study at 2 years post randomisation, re-consent was required from all patients to implement this amendment. Patients who were randomly assigned at

participating sites were asked to provide written informed consent to the retrospective collection of data concerning recurrent disease events from their medical records for an additional 3 years (ie, years 3–5 post randomisation) and to the collection of overall survival data.

Women aged 18 years or older (≥20 years in Japan) with histologically confirmed stage 2–3c (1–3c in original protocol, modified to stage 2–3c in February, 2010) HER2-positive operable breast cancer were eligible for inclusion. HER2 status was tested locally, but subsequently confirmed by central testing through the use of PathVysion HER2 DNA dual probe (Abbott Molecular, Des Plaines, IL, USA; ie, HER2:CEP17 ratio ≥2·2). Hormone receptor status had to be known before study entry and was determined locally; no protocol-specified threshold for defining hormone receptor status was set. We required clinical and radiological assessments to be negative for recurrences or metastatic disease at the time of study entry; assessments included CT, MRI, or ultrasound of the abdomen and chest if hepatic transaminases or alkaline phosphatase levels were at least twice the upper limit of normal, bone scan if symptoms of metastatic bone disease were present or alkaline phosphatase levels were at least twice the upper limit of normal, or a chest radiograph. Neoadjuvant and adjuvant trastuzumab was to be completed up to 1 year (2 years in original protocol) before randomisation. We required patients 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.

All patients provided written informed consent before any protocol-directed procedures were done, and patients who re-consented provided written informed consent on a new consent form to allow the further collection of information (as described earlier). The independent data monitoring committee was consistent throughout the trial to preserve the integrity of masking, and the infrastructure for study conduct and monitoring remained in place to preserve the operational consistency of the trial. The institutional ethics committee at participating sites approved the study protocol and all subsequent amendments.

Randomisation and masking

Patients were randomly assigned (1:1) to receive neratinib or matching placebo (visually identical). The randomisation sequence (1:1) was generated via permuted blocks and stratified according to 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 *vs* 1–3 *vs* ≥4 positive nodes), and trastuzumab adjuvant regimen (given sequentially *vs* concurrently with chemotherapy), and was implemented centrally via an interactive voice and web-response system. The study was done in a double-blind manner until the primary analysis (in July, 2014), at which time treatment allocation was unmasked to the Puma Biotechnology team responsible for this analysis. After the primary analysis, the funder established a firewall so that the team responsible for the collection of invasive disease-free survival and survival data remained masked to treatment allocation, thereby maintaining the integrity of the analyses. All investigators, study site personnel, and personnel from the funding body were masked to treatment allocation during the re-consent process.

See Online for appendix

Procedures

Patients were given 240 mg of neratinib orally, once per day, or matching placebo, in tablet form, continuously for 1 year, unless disease recurrence or new breast cancer, intolerable adverse events, or consent withdrawal occurred. No crossover was allowed in the trial. Drug compliance was monitored throughout the study. Neratinib dose reductions (to 200 mg, 160 mg, and 120 mg per day) were allowed for toxicity, with cessation of treatment if the lowest dose was not tolerated or if treatment was interrupted for more than 3 weeks. Dose reductions were recommended for persistent grade 2 diarrhoea, grade 3 diarrhoea, other grade 3 non-haematological events, and symptomatic grade 2 pneumonitis or interstitial lung disease. Adjuvant endocrine therapy for women with hormone receptor-positive disease confirmed by local assessment was allowed and recommended. Prophylaxis for the prevention of neratinib-associated diarrhoea was not mandated by the study protocol, but treatment with loperamide was advised at the earliest convenience.

Physical examinations were done at 1 month, every 3 months during year 1, and every 4 months during year 2. During years 1 and 2, mammograms were done annually, when appropriate, and CT or bone scans were done if clinically indicated. Liver function tests were done at months 1, 2, and 3, every 6 weeks thereafter, and as clinically indicated. Complete blood counts were done at months 1, 2, 3, 4·5, 6, 9, and 12, and as clinically indicated. During years 3–5, physical examination and mammogram schedules were based on the standard of care, defined by the treating physician. Details of recurrent disease events and deaths were obtained from the medical records of patients who re-consented by the treating institution.

Adverse events were monitored until 28 days after the last dose of study drug, and graded according to the National Cancer Institute Common Terminology Criteria, version 3.0. Thereafter, data on post-treatment serious adverse drug reactions were collected in the safety database on an ongoing basis; this will continue until the final analysis of overall survival is reported.

Outcomes

The primary endpoint was invasive disease-free survival at 2-year follow-up, defined as the time from randomisation

to first occurrence of invasive ipsilateral tumour recurrence, invasive contralateral breast cancer, local or regional invasive recurrence, distant recurrence, or death from any cause. This definition did not include second non-breast primary events based on feedback from the US Food and Drug Administration and European Medicines Agency's European Committee for Medicinal Products for Human Use; thus, it differs from the standardised efficacy endpoints (STEEP) system definition.[16] A global amendment (protocol amendment 13) was implemented in January, 2014, to evaluate the efficacy of neratinib in the intention-to-treat population with 5 years of follow-up data: the results of this analysis are reported here. Secondary efficacy endpoints were: disease-free survival including ductal carcinoma in situ (defined as time from randomisation to the first occurrence of a disease-free survival event or ductal carcinoma in situ event); time to distant recurrence (defined as time from randomisation to the date of the first distant recurrence or death from breast cancer); distant disease-free survival (defined as time from randomisation to the first occurrence of distant recurrence or death from any cause); cumulative incidence of CNS recurrences (defined as time from randomisation to CNS recurrence as first distant recurrence—either isolated CNS metastases or those diagnosed concurrently with other sites of metastatic disease), and overall survival (defined as time from randomisation to death). Safety was also a secondary endpoint. The primary safety analysis (data cutoff, July 7, 2014) is reported in our 2-year follow-up.[15] An analysis of long-term safety data, which included post-treatment serious adverse events reported after the last dose of study treatment plus 28 days until June 23, 2017, was also done, and is reported here.

Patient-reported health outcomes and biomarker analyses were exploratory objectives and are to be reported separately.

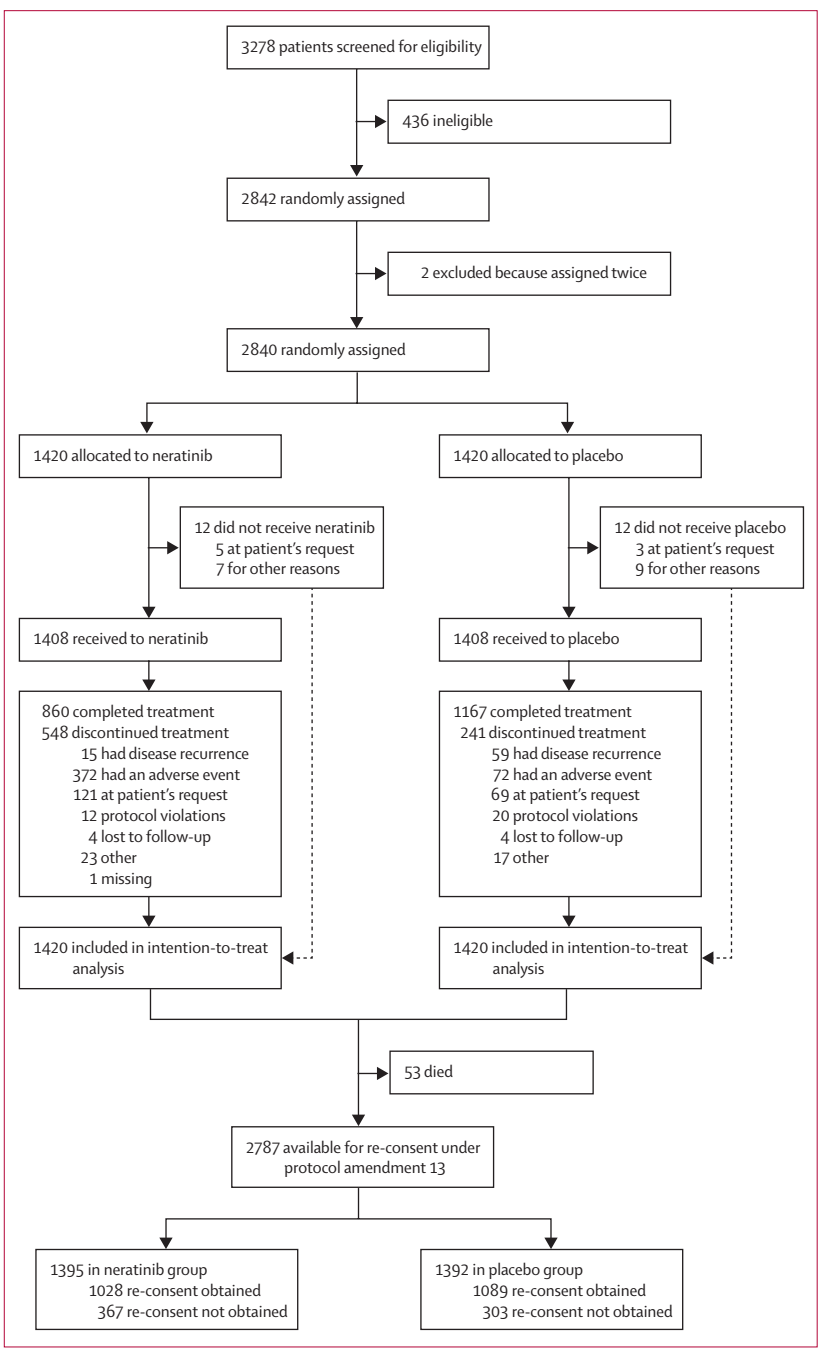

Figure 1: **ExteNET trial profile**

Statistical analysis

The study was originally designed to enrol 3850 patients with 90% power to detect an HR of 0·7 for invasive disease-free survival, at a two-sided 5% significance level. In October, 2011, enrolment was stopped after 2840 patients were randomly assigned and follow-up was truncated to 2 years. Consequently, the 2-year invasive disease-free survival analysis was considered the primary analysis and the power was projected to be 88%, assuming an HR of 0·667 at the two-sided 5% significance level. The 5-year analysis was prespecified in the study protocol as a sensitivity analysis to evaluate the durability of effect of neratinib therapy on efficacy endpoints related to recurrent disease—ie, all efficacy endpoints except for overall survival. Overall survival will be tested at a two-sided 5% significance level with 80% power to detect an HR of 0·7 when 248 deaths are reached; all deaths will be included in the analysis of overall survival, including publicly available death records for patients who did not re-consent in accordance with Good Clinical Practice guidelines and privacy laws.

We tested time-to-event endpoints with log-rank tests (two-sided p values), and used Cox proportional-hazards models to estimate HRs with 95% CIs. We used Kaplan-Meier methods to estimate annual event-free survival. We did analysis by intention to treat, and censored patients who did not re-consent for additional follow-up at the date of their last physical examination if disease

recurrence did not occur within the 2 years of follow-up. We censored patients without disease-free survival events at the date of their last physical examination that occurred within 5 years and 6 months post randomisation for all efficacy endpoints, and patients with invasive disease-free survival events after two missed assessments (a gap of 8 months during years 1 and 2, or 12 months during years 3–5) at the last available disease assessment, following guidance from the US Food and Drug Administration.[17] We did a cumulative incidence with competing risks analysis for CNS recurrences, and used Gray's test to compare the number of CNS recurrences between treatment groups. We stratified analyses in the intention-to-treat

	Intention-to-treat population (n=2840)		Re-consented patients (n=2117)	
	Neratinib (n=1420)	Placebo (n=1420)	Neratinib (n=1028)	Placebo (n=1089)
Age (years)	52 (45–59)	52 (45–60)	52 (45–59)	53 (45–60)
Region				
North America	519 (37%)	477 (34%)	326 (32%)	320 (29%)
Western Europe, Australia, New Zealand, and South Africa	487 (34%)	532 (37%)	369 (36%)	432 (40%)
Asia Pacific, eastern Europe, and South America	414 (29%)	411 (29%)	333 (32%)	337 (31%)
Menopausal status at diagnosis				
Premenopausal	663 (47%)	664 (47%)	486 (47%)	506 (46%)
Postmenopausal	757 (53%)	756 (53%)	542 (53%)	583 (54%)
Nodal status*				
Negative	335 (24%)	336 (24%)	216 (21%)	261 (24%)
1–3 positive nodes	664 (47%)	664 (47%)	506 (49%)	510 (47%)
≥4 positive nodes	421 (30%)	420 (30%)	306 (30%)	318 (29%)
Hormone receptor status*				
Positive (ER positive, PR positive, or both)	816 (57%)	815 (57%)	603 (59%)	615 (56%)
Negative (ER and PR negative)	604 (43%)	605 (43%)	425 (41%)	474 (44%)
Previous trastuzumab regimen*				
Concurrent	884 (62%)	886 (62%)	621 (60%)	671 (62%)
Sequential	536 (38%)	534 (38%)	407 (40%)	418 (38%)
T stage				
T1	440 (31%)	459 (32%)	315 (31%)	359 (33%)
T2	585 (41%)	555 (39%)	431 (42%)	421 (39%)
≥T3	144 (10%)	117 (8%)	104 (10%)	89 (8%)
Unknown	250 (18%)	288 (20%)	178 (17%)	220 (20%)
Missing	1 (<1%)	1 (<1%)	..	..
Histological grade of tumour				
Undifferentiated or poorly differentiated	670 (47%)	689 (49%)	495 (48%)	538 (49%)
Moderately differentiated	461 (32%)	416 (29%)	331 (32%)	311 (29%)
Well differentiated	76 (5%)	65 (5%)	57 (6%)	50 (5%)
Unknown	213 (15%)	241 (17%)	145 (14%)	190 (17%)
Previous surgery	..	..	..	..
Lumpectomy only	468 (33%)	511 (36%)	343 (33%)	392 (36%)
Mastectomy	951 (67%)	908 (64%)	684 (67%)	696 (64%)
Missing	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Previous radiotherapy				
Yes	1130 (80%)	1150 (81%)	830 (81%)	875 (80%)
No	290 (20%)	270 (19%)	198 (20%)	214 (20%)
Previous neoadjuvant or adjuvant therapy†				
Yes	1420 (100%)	1420 (100%)	1028 (100%)	1089 (100%)
Trastuzumab	1420 (100%)	1420 (100%)	1028 (100%)	1089 (100%)
Anthracycline only	136 (10%)	135 (10%)	102 (10%)	109 (10%)
Anthracycline plus taxane	962 (68%)	965 (68%)	725 (71%)	762 (70%)
Taxane only	318 (22%)	316 (22%)	198 (19%)	216 (20%)
Non-anthracycline or taxane	4 (<1%)	4 (<1%)	3 (<1%)	2 (<1%)

(Table 1 continues on next page)

	Intention-to-treat population (n=2840)		Re-consented patients (n=2117)	
	Neratinib (n=1420)	Placebo (n=1420)	Neratinib (n=1028)	Placebo (n=1089)
(Continued from previous page)				
Duration of previous adjuvant trastuzumab therapy (months)	11·5 (10·9–11·9); n=1413	11·4 (10·8–11·9); n=1416	11·5 (10·9–11·9); n=1023	11·4 (10·8–11·9); n=1086
Time from last dose of trastuzumab to randomisation (months)	4·4 (1·6–10·4)	4·6 (1·5–10·8)	4·5 (1·7–10·4)	4·3 (1·5–10·7)
Concomitant endocrine therapy for hormone receptor-positive tumours‡				
No	56 (7%)	51 (6%)	33 (6%)	28 (5%)
Yes	760 (93%)	764 (94%)	570 (95%)	587 (95%)
Anti-oestrogen only	375 (46%)	347 (43%)	294 (49%)	281 (46%)
Anti-oestrogen and aromatase inhibitor (sequential)	20 (3%)	34 (4%)	31 (5%)	31 (5%)
Aromatase inhibitor only	362 (44%)	379 (47%)	242 (40%)	272 (44%)
Neither anti-oestrogen nor aromatase inhibitor	3 (<1%)	4 (<1%)	3 (<1%)	3 (<1%)

Data are n (%) or median (IQR), unless otherwise specified. Because of rounding, not all percentages add up to 100. 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 taken at the time of initial diagnosis (for those who received adjuvant therapy) or surgery (for those who received neoadjuvant therapy). Patients with residual invasive disease in the breast, but node-negative or unknown nodal status in the axilla after neoadjuvant therapy, were included in the category of 1–3 positive nodes. †The proportion of patients who received neoadjuvant chemotherapy was 25% (n=247) in the neratinib group and 27% (n=282) in the placebo group. ‡Percentage is based on the number of patients with hormone receptor-positive tumours. 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 should be used.

Table 1: **Baseline demographics and disease characteristics for the intention-to-treat population and re-consented patients (5-year analysis)**

	Estimated event-free survival*		Hazard ratio (95% CI)†	p value‡
	Neratinib group (n=1420)	Placebo group (n=1420)		
Invasive disease-free survival	90·2% (88·3–91·8)	87·7% (85·7–89·4)	0·73 (0·57–0·92)	0·0083
Disease-free survival including ductal carcinoma in situ	89·7% (87·8–91·3)	86·8% (84·8–88·6)	0·71 (0·56–0·89)	0·0035
Distant disease-free survival	91·6% (89·8–93·1)	89·9% (88·1–91·5)	0·78 (0·60–1·01)	0·065
Time to distant recurrence	91·8% (90·1–93·3)	90·3% (88·5–91·8)	0·79 (0·60–1·03)	0·078
CNS recurrence	1·3% (0·8–2·1)	1·8% (1·2–2·7)	..	0·333

Data are % (95% CI), unless otherwise specified. *Event-free rates for all endpoints, except for CNS recurrence for which cumulative incidence is reported. †Stratified Cox proportional hazards model. ‡Stratified two-sided log-rank test for all endpoints, except for CNS recurrence for which Gray's method was used.

Table 2: **Efficacy endpoint analyses at 5 years post randomisation in the intention-to-treat population**

population by randomisation stratification factors, as specified in the statistical analysis plan.

We did protocol-defined sensitivity analyses of invasive disease-free survival in the amended intention-to-treat population, defined as all patients with node-positive disease and randomly assigned within 1 year of completion of previous trastuzumab therapy—ie, high risk patients. We also did subgroup analyses prespecified in the statistical analysis plan to examine the effects of stratification factors and other baseline factors of interest on treatment effect; we used tests for interaction to assess the homogeneity of treatment effects across different subgroups. We did safety analyses in the safety population, defined as all patients who received at least one dose of study drug, and included an analysis of mean grade of diarrhoea over time. This analysis was performed to better depict the timing, severity, and duration of diarrhoea—the primary toxicity associated with neratinib. We used SAS statistical software (version 9.2 or later) for all analyses. An independent data monitoring committee reviewed the data at least twice a year.

This study is registered at ClinicalTrials.gov, number NCT00878709.

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. The report was written 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 enrolled a total of 2840 eligible women from academic and community-based centres in 40 countries in Europe, North and South America, Asia, Australia, and New Zealand

(appendix pp 17–26) and randomly assigned them to receive neratinib (n=1420) or placebo (n=1420; **figure 1**). 2840 patients constituted the intention-to-treat population. 53 patients had died at the time of the primary analysis data snapshot (July 7, 2014), leaving 2787 patients available to re-consent to participation after protocol amendment 13 (January, 2014). At the cutoff date for the 5-year analysis (March 1, 2017), 2117 (75%) patients had re-consented to retrospective collection of data between years 2 and 5, and survival data beyond year 5 (1028 patients in the neratinib group and 1089 in the placebo group; figure 1). In these patients who re-consented, the median frequency of standard-of-care visits between years 3 and 5 was every 6 months (IQR 4–12) in both treatment groups. Baseline characteristics were well balanced between treatment groups in patients who re-consented, and were also similar in the intention-to-treat and re-consented populations (table 1). A summary of the baseline biomarker status of patients in each treatment group is shown in the appendix (p 11).

The median duration of treatment was 353 days (IQR 76–363) in the neratinib group and 360 days (350–365) in the placebo group. 760 (93%) of 816 patients with hormone receptor-positive breast cancer in the neratinib group and 764 (94%) of 815 patients in the placebo group were receiving concomitant endocrine therapy. After 5 years, an estimated 52% of patients in the neratinib group and 47% of those in the placebo group with hormone receptor-positive tumours were still receiving endocrine therapy (according to a Kaplan-Meier analysis of endocrine therapy duration); the small difference between the groups is probably due to more recurrences in the placebo group, after which endocrine therapy would have been discontinued and standard first-line therapy with a chemotherapy plus trastuzumab-containing regimen for metastatic disease initiated.

At the cutoff date (March 1, 2017), the median duration of follow-up was 5·2 years (IQR 2·1–5·3) in the intention-to-treat population (5·2 years [2·1–5·3] in the neratinib group; 5·3 years [2·2–5·3] in the placebo group). 885 (62%) patients in the neratinib group and 927 (65%) patients in the placebo group had at least 5 years of follow-up.

In the intention-to-treat population, at 5 years after randomisation, patients in the neratinib group had significantly fewer invasive disease-free survival events than patients in the placebo group (116 *vs* 163 events; stratified HR 0·73, 95% CI 0·57–0·92, p=0·0083; table 2). The 5-year invasive disease-free survival was 90·2% (95% CI 88·3–91·8) in the neratinib group and 87·7% (85·7–89·4) in the placebo group. The Kaplan-Meier curves for invasive disease-free survival separated after

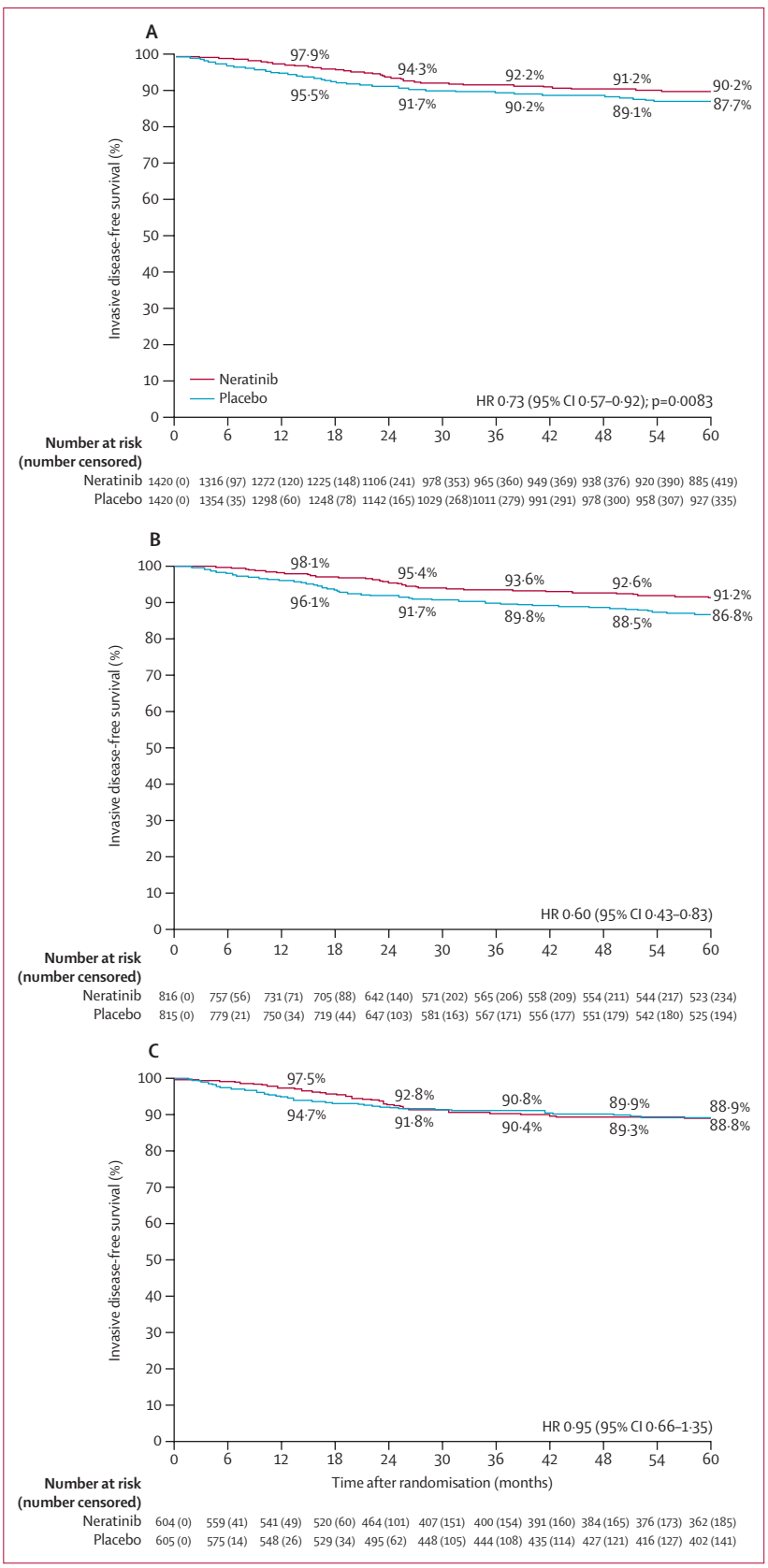

Figure 2: **Invasive disease-free survival in the intention-to-treat population (A), patients with hormone receptor-positive breast cancer (B), and patients with hormone receptor-negative breast cancer (C)**
HR=hazard ratio.

	Neratinib (n=1420)	Placebo (n=1420)
Any invasive disease-free survival event	116 (8%)	163 (11%)
Local or regional invasive recurrence	12 (1%)	35 (2%)
Invasive ipsilateral breast tumour recurrence	5 (<1%)	7 (1%)
Invasive contralateral breast cancer	4 (<1%)	11 (1%)
Distant recurrence*	91 (6%)	111 (8%)
Bone	31 (2%)	31 (2%)
Brain	15 (1%)	17 (1%)
Distant lymph node	11 (1%)	18 (1%)
Liver	24 (2%)	24 (2%)
Lung	14 (1%)	25 (2%)
Other	11 (1%)	6 (<1%)
Other abdominal viscera	0	2 (<1%)
Pleura	1 (<1%)	7 (1%)
Subcutaneous tissue	2 (<1%)	1 (<1%)
Unspecified	1 (<1%)	0
Death without previous recurrence	4 (<1%)	5 (<1%)

Data are n (%). *Event types are not mutually exclusive.

Table 3: **Site of first invasive disease-free survival event in the intention-to-treat population**

approximately 3 months and remained separated for the rest of the 5-year follow-up (figure 2). We censored patients without invasive-disease-free events at the time of the last disease assessment; the number of patients censored within 6 months of randomisation was 97 in the neratinib group and 35 in the placebo group. Invasive disease-free survival events by site of first occurrence are summarised in table 3. The reductions in distant recurrence and local and regional recurrence events in the neratinib group compared with the placebo group (91 [6·4%] *vs* 111 [7·8%] and 12 [0·8%] *vs* 35 [2·5%]) were of particular note. Information about the site of relapse (local *vs* regional) and pathohistological characteristics of recurrences was not collected. The proportional hazards assumption did not seem to hold, based on testing the cumulative sum of Martingale-based residuals,[18] so an exploratory analysis was done to estimate the difference in restricted mean invasive disease-free survival time over the 5-year period. The restricted mean invasive disease-free survival times were 56·5 months (95% CI 55·9–57·2) in the neratinib group (mean loss of 3·5 months from a total of 60 months) and 55·2 months (54·4–55·9) in the placebo group (mean loss of 4·8 months from a total of 60 months). The between-group difference was 1·3 months (95% CI 0·3–2·3, p=0·0085). The result was supportive of the main primary analysis with the log-rank test.

Disease-free survival, including ductal carcinoma in situ, was significantly improved in the neratinib group compared with the placebo group, whereas distant disease-free survival (appendix p 5) and time to distant recurrence were not (table 2). 16 (1%) of 1420 patients in the neratinib group and 23 (2%) of 1420 patients in the placebo group had CNS events as the first distant recurrence; the 5-year cumulative incidence of CNS events was 1·3% (95% CI 0·8–2.1) in the neratinib group and 1·8% (1·2–2·7). in the placebo group (p=0·333). Overall survival data are not yet mature (estimated maturation date: quarter 3, 2019).

According to predefined sensitivity analyses, the HR for the high-risk amended intention-to-treat population (those with node-positive disease and randomised within 1 year of previous trastuzumab therapy) was similar to that seen in the intention-to-treat population (HR 0·70, 95% CI 0·54–0·92, p=0·010; appendix p 6). In a separate post-hoc exploratory analysis of 2-year invasive disease-free survival in patients who re-consented only (n=2117 in total [n=1028 in the neratinib group and n=1089 in the placebo group]), the HR (unstratified) was 0·64 (0·39–1·02; appendix p 7), which was similar to that reported for the intention-to-treat population in the primary analysis (stratified HR 0·67, 95% CI 0·50–0·91).[15] The findings from an updated analysis of 2-year invasive disease-free survival, the primary study endpoint, are presented in the appendix (p 12).

A forest plot of the subgroup analysis in the intention-to-treat population is shown in figure 3. The findings were consistent with the intention-to-treat population for most patient subgroups (ie, point estimates were <1; figure 3). In the subgroup of 1631 patients with hormone receptor-positive disease, the HR for invasive disease-free survival in the neratinib group compared with the placebo group was 0·60 (95% CI 0·43–0·83; figure 2B), whereas in the 1209 patients with hormone receptor-negative disease, the HR for invasive disease-free survival was 0·95 (0·66–1·35; figure 2C).

We also compared invasive disease-free survival between the subgroup of patients who initiated neratinib within 1 year of completing adjuvant therapy with trastuzumab (n=2297; HR 0·70, 95% CI 0·54–0·90) versus those who initiated neratinib more than 1 year after completing trastuzumab (n=543, including 11 patients who initiated neratinib more than 2 years after completing trastuzumab; HR 1·00, 95% CI 0·51–1·94; figure 3, appendix p 8). A subgroup analysis in patients who initiated neratinib within 1 year of completing adjuvant therapy with trastuzumab is shown in the appendix (p 9).

The safety population included 2816 patients who received at least one dose of study treatment (1408 patients in each group). The primary safety analysis is reported in our 2-year follow-up.[15] In brief, the most common grade 3–4 adverse events at the 2-year follow-up in the neratinib group were diarrhoea (561 [40%] grade 3 and one [<1%] grade 4 with neratinib, *vs* 23 [2%] grade 3 with placebo), vomiting (grade 3: 47 [3%] *vs* five [<1%]), and nausea (grade 3: 26 [2%] *vs* two [<1%]; table 4). The mean daily grade of diarrhoea, according to the National Cancer Institute Common Terminology Criteria, in the neratinib group reached a

maximum of approximately 1·03 (SD 0·92) at day 4 of treatment, before decreasing steadily to less than 0·37 (SD 0·60) by the end of the 1-year treatment period. For the placebo group, the mean daily grade reached a maximum of 0·06 (SD 0·28) at day 3 of treatment. At the end of the 1-year treatment period, the average daily

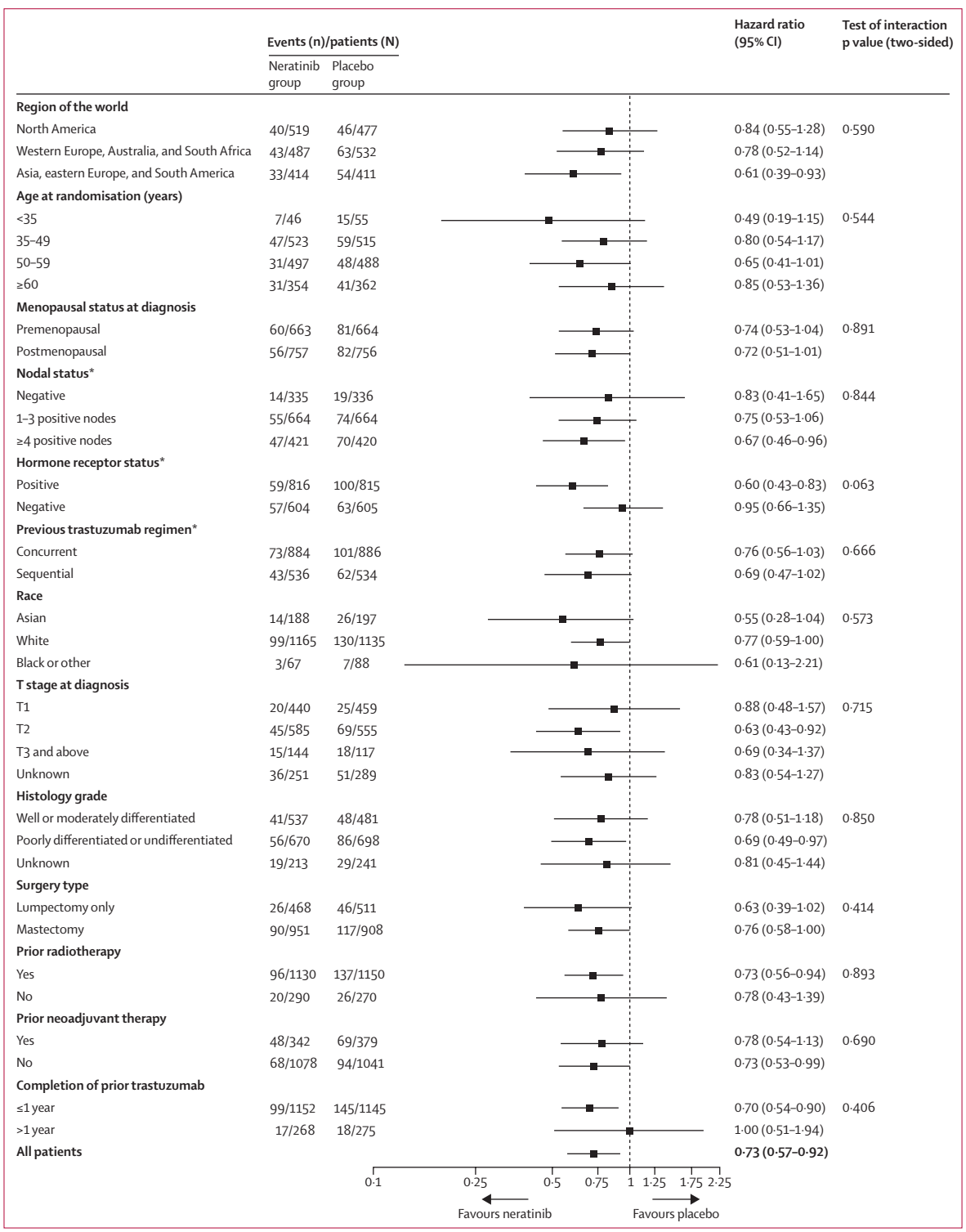

Figure 3: **Subgroup analysis of invasive disease-free survival in the intention-to-treat population**
The vertical dashed line indicates a hazard ratio of 1·00—the null hypothesis value. Error bars represent 95% CIs. *Stratification factor.

	Neratinib (n=1408)			Placebo (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 (%). The table shows grade 1–2 adverse events occurring in at least 10% patients in either group. Grade 5 events (deaths) were due to metastatic breast cancer, including metastases that had infiltrated the meninges (n=1), and acute myeloid leukaemia (n=1) in the neratinib group, and gastric cancer (n=1) in the placebo group.

Table 4: **Treatment-emergent adverse events**

grade in the placebo group was 0·04 (SD 0·21; appendix p 10). Dose reductions because of treatment-emergent adverse events were required in 440 (31%) patients in the neratinib group and 35 (2%) of patients in the placebo group, and treatment discontinuation because of treatment-emergent adverse events occurred in 388 (28%) patients in the neratinib group and 76 (5%) patients in the placebo group. 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 versus the placebo group were diarrhoea (22 with neratinib *vs* one with placebo), vomiting (12 *vs* one), and dehydration (nine *vs* one). Deaths reported as grade 5 adverse events were due to metastatic breast cancer, including metastases that had infiltrated the meninges (n=1), and acute myeloid leukaemia (n=1) in the neratinib group, and gastric cancer (n=1) in the placebo group. None of the deaths were attributed to study treatment in either group.

Reports of unsolicited serious adverse events occurring more than 28 days after the last dose of study treatment are presented in the appendix (pp 13–15). No evidence suggested increased long-term toxicity, specifically symptomatic cardiac toxicity, or second primary malignancies in the neratinib group compared with the placebo group.

At the time of the 5-year analysis, 121 deaths had been reported (in both treatment groups combined because overall survival data remained masked because the data have not yet reached maturity) due to disease progression (n=102) or other reasons (n=19; appendix p 16).

Discussion

After a median of 5 years of follow-up, 1 year of neratinib after standard trastuzumab-based adjuvant therapy significantly improved invasive disease-free survival in women with early-stage HER2-positive breast cancer. The 5-year analysis showed that the superior efficacy of neratinib, compared with placebo, was maintained every year after randomisation, with a significant reduction in the risk of an invasive disease-free survival event after 5 years of follow-up. The superiority of neratinib over placebo was mainly due to reductions of distant and local or regional relapses (excluding those in the ipsilateral breast). These locoregional recurrences were the first invasive disease-free events detected, and often preceded later spread to distant sites. Detailed information about the characteristics of recurrences was not collected and the reason for the particular pattern of distant relapses seen, mainly in the lung, pleura, and distant lymph nodes, is uncertain. Disease-free survival, including ductal carcinoma in situ, was also significantly improved with neratinib after 5 years of follow-up, although no significant differences were seen in other predefined secondary endpoints. Overall survival data are not yet mature.

Neratinib seemed to have a greater effect in patients with hormone receptor-positive breast cancer (most of whom were receiving concurrent hormone therapy) than in those with hormone receptor-negative disease. At 5 years post randomisation, an improvement in invasive disease-free survival with neratinib in the hormone receptor positive subgroup was identified, whereas in patients with hormone receptor-negative disease, neratinib elicited a transient effect that diminished after cessation of treatment. The apparent efficacy of neratinib in HER2-positive, hormone receptor-positive tumours, which is not evident with other HER2-directed agents in the adjuvant setting, could be attributable to bidirectional crosstalk between oestrogen receptor and HER2 receptor signalling.[19] Clinically, suppression of one pathway can lead to activation of the other,[20] and inhibition of both pathways might be necessary to achieve the best outcomes in this patient population. Neratinib is known to inhibit HER2 signalling,[12] and induce oestrogen receptor function in HER2-positive breast cancer cell lines.[21] In a model of oestrogen receptor-positive HER2-positive xenografts after tumour regrowth following treatment with trastuzumab and paclitaxel, mirroring the ExteNET population, treatment with neratinib and fulvestrant, compared with fulvestrant alone, showed prolonged complete responses in vivo and preserved sensitivity to endocrine therapy after recurrence.[22] Our observations in patients who were hormone receptor-positive, most of whom were receiving concomitant endocrine therapy, are consistent with this mechanism.

The dichotomous effect of neratinib by hormone receptor status differs from other HER2-directed agents (eg, trastuzumab, pertuzumab, and lapatinib) in the adjuvant setting, the effects of which seem to be independent of hormone receptor status or even numerically greater in hormone receptor-negative tumours.[1,2,6,8] This observation suggests either an

interaction between neratinib and hormones, or an absence of cross-resistance between trastuzumab and neratinib in the hormone receptor-positive population. The prolongation of HER2 suppression as an alternative explanation for the observed benefit is unlikely, given that 2 years of trastuzumab treatment was not superior to 1 year in the HERA trial.[5] Discrete patient subgroups seem to derive significantly less benefit from trastuzumab in the adjuvant setting (ie, HER2-positive with increased oestrogen receptor expression,[23,24] and oestrogen receptor-positive with low HER2 fluroescence in-situ hybridisation ratio[24]). Biomarker data from ExteNET might help to establish whether neratinib has particular activity in any of these subgroups, contributing to the overall better result in patients with hormone receptor-positive disease.

The effect of neratinib also seemed to be possibly greater in patients who initiated treatment within 1 year of completing trastuzumab-based adjuvant therapy than those who started neratinib later, although the number of events in the latter subgroup was small and the test of interaction was far from significant (p=0·406). The original study protocol stated that patients should receive neratinib within 2 years of their last dose of trastuzumab. The protocol was later modified, after the release of the NCCTGN9831/NSABP B31 joint analysis 4-year follow-up data showing that the risk of relapse was highest in the first 12 months after trastuzumab-based adjuvant therapy.[4] Consequently, enrolment into ExteNET was limited to patients at high risk, who had completed trastuzumab within the year before randomisation. In keeping with the rationale for the protocol change, patients who initiated neratinib within 1 year of their last dose of trastuzumab (81% of the intention-to-treat population) showed an improvement in invasive disease-free survival, whereas those who started neratinib later seemed to derive no significant benefit from neratinib therapy. Although this finding is not statistically compelling, and needs to be replicated in other studies, these observations suggest that neratinib can be initiated within the first year of completing adjuvant trastuzumab to prevent early recurrences. These findings are consistent with the relapse pattern of HER2-positive tumours treated with adjuvant trastuzumab, since the relapse rate increases soon after the end of trastuzumab therapy.[4]

Although the proportional hazards assumption did not seem to hold in the intention-to-treat population, the exploratory invasive disease-free survival analysis with restricted mean survival time provided evidence in support of the neratinib treatment effect. The prespecified analysis based on the log-rank test was robust to departure from the proportional hazards assumption, and is the valid test on which the study conclusion should be drawn. We suggest the findings from ExteNET are likely to be broadly generalisable to other populations of women with HER2-positive breast cancer. Furthermore, we acknowledge that the study was not powered to detect effects within subgroups, and that apparently striking results might be due to chance in multiple comparisons. Consequently, the results of the subgroup analyses need to be replicated in further studies. A central determination of hormone receptor status was not done and local criteria for receptor status were accepted to classify tumours, although the local standard criterion in most countries, including the USA and Europe, is a cutoff of 1% for both oestrogen and progesterone receptors. These facts could have led to the misclassification of a small proportion of tumours; however, since hormone receptor status was a stratification factor and any misclassified tumours were probably equally distributed between treatment groups, any consequential bias is unlikely.

Our review of unsolicited serious adverse events reported to the safety database provides reassurance that a 1-year course of neratinib is not associated with long-term toxicities, specifically increased symptomatic cardiac toxicity or second primary malignancies. Furthermore, no serious late-term consequences (eg, renal insufficiency or chronic intestinal disease) from neratinib-associated diarrhoea—the most common adverse event associated with neratinib—were evident. A structured prophylactic regimen of loperamide with neratinib for the first one to two cycles of therapy is being actively investigated in the phase 2 CONTROL study (NCT02400476),[25] and emerging data suggest that loperamide prophylaxis reduces the incidence, severity, and duration of neratinib-associated diarrhoea, as compared with events observed in ExteNET.

Other trials have investigated extended adjuvant therapy with HER2-directed agents without success. In HERA, trastuzumab given for 2 years seemed to improve disease-free survival for the first few years after randomisation, compared with 1 year of trastuzumab, but showed no benefit at or beyond 5 years.[5] TEACH, which compared lapatinib with placebo in patients who could not receive adjuvant trastuzumab for socioeconomic or logistic reasons, was also negative after a median follow-up of around 4 years, although the delay to onset of therapy (median time from diagnosis to treatment of 2·7 years) was notable.[26] So far, only one other trial—APHINITY—has shown marginal, but significant improvements in invasive disease-free survival compared with 1 year of trastuzumab in women with early-stage HER2-positive breast cancer. In APHINITY, the addition of pertuzumab to trastuzumab and chemotherapy for 1 year improved 3-year invasive disease-free survival (HR 0·81, 95% CI 0·66–1·00, p=0·045), the primary study endpoint, compared with trastuzumab plus chemotherapy;[8] the effect size was apparently smaller than that noted in ExteNET (HR 0.67, 95% CI 0·50–0·91; p=0·0091) after 2 years.[15] Furthermore, in APHINITY, the improvement in 3-year invasive disease-free survival in the hormone receptor-positive subgroup was less than 0·4%, compared with 1·6% in the hormone receptor-negative subgroup.[8] This

result suggests that neratinib might be more effective at partially reversing the anti-HER2 resistance caused by upregulation of the oestrogen receptor by trastuzumab, pertuzumab, and lapatinib,[20,27] and might be particularly effective in the hormone receptor-positive and HER2 receptor-positive driven subset. Follow-up to 10 years in APHINITY is planned; data from long-term analyses will hopefully provide a better understanding of how these findings should be applied in clinical practice.

The decision to restore the original long-term objective of ExteNET required the attempted re-consent of all patients who were randomly assigned—a large undertaking that required a coordinated effort across 40 countries. To this end, a comprehensive prospective monitoring and trial integrity plan was put in place to minimise bias during the re-consent process and to ensure that as much data as possible were captured. From these efforts, most patients re-consented to long-term follow-up, but we acknowledge that some uncertainty around the 5-year estimates remains because of missing data. During years 3–5 post randomisation, we recognise that the timing of follow-up visits was decided by the investigator, as per their regional standard of care, rather than by a protocol-defined schedule, although the median interval between visits (6 months) was consistent with the recommended standard of care by the American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Guidelines (ie, physical examinations every 6–12 months during years 3 and 4 after primary therapy, and annually thereafter).[28]

In conclusion, after a median follow-up of 5 years, a significant invasive disease-free survival benefit is evident with neratinib given for 1 year after completion of trastuzumab-based adjuvant therapy in women with early-stage HER2-positive breast cancer. These findings are consistent with the primary 2-year analysis, and support the durability of neratinib treatment effect in the intention-to-treat population. Prospectively defined subgroup analyses indicated greater benefit with neratinib in patients with hormone receptor-positive disease. No evidence of long-term toxicity with neratinib was identified.

Contributors

MM, FAH, BE, SD, BM, HI, GvM, SKLC, JM, CHB, MG, MB, AW, and ACh conceived and designed the study. All authors acquired the data. BY and FX analysed the data. All authors were involved in interpretation and critical review of the data, drafting or revising the report for important intellectual content, and approving the final version. 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

MM received grants and personal fees from Novartis, and Roche/Genentech, and personal fees from Amgen, AstraZeneca, Pfizer, Pharmamar, and Eli Lilly outside the submitted work. BE received grants from Novartis, Amgen, and Roche outside the submitted work. SD received grants from Puma during the conduct of the study. SD has received grants and personal fees from AstraZeneca, Novartis, Pfizer, Puma, Roche, and Sanofi outside the submitted work. HI 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. GvM received grants from Pfizer, Amgen, Roche, Teva, Novartis, AZ, Celgene, Myriad, AbbVie, and Vifor outside the submitted work. JM received grants and personal fees from 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 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. ND received grants from Puma Biotechnology during the conduct of the study. S-BK received grants from Novartis, Sanofi-Aventis, Kyowa-Kirin Inc, and Dongkook Pharma Co Ltd outside the submitted work. ACA received personal fees from Roche and Syndax Pharmaceuticals, and other fees from AstraZeneca, outside the submitted work. AAJ received fees from AstraZeneca, BMS, Eli Lilly, Novartis, Pfizer, Roche outside the submitted work. MB is an employee and stockholder of the International Drug Development Institute. ACh received personal fees for educational meetings from Pfizer, Amgen, and Eisai, and non-financial support from Puma Biotechnology outside the submitted work. RB, AW, SM, BY, FX and AA are employees of Puma Biotechnology Inc. All other authors declare no competing interests.

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