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Original Research

Overall survival with neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): A randomised, double-blind, placebo-controlled, phase 3 trial

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Abstract ***Background:*** ExteNET showed that neratinib, an irreversible pan-HER tyrosine kinase inhibitor, given for 1 year after trastuzumab-based therapy significantly improved invasive disease-free survival in women with early-stage HER2-positive breast cancer. We report the final analysis of overall survival in ExteNET.
Methods: In this international, randomised, double-blind, placebo-controlled, phase 3 trial, women aged 18 years or older with stage 1–3c (amended to stage 2–3c) HER2-positive breast cancer who had completed neoadjuvant and adjuvant chemotherapy plus trastuzumab were eligible. Patients were randomly assigned to oral neratinib 240 mg/day or placebo for 1 year. Randomisation was stratified according to hormone receptor (HR) status (HR-positive vs. HR-negative), nodal status (0, 1–3 or 4+), and trastuzumab regimen (sequentially vs. concurrently with chemotherapy). Overall survival was analysed by intention to treat. ExteNET is registered (Clinicaltrials.gov: NCT00878709) and is complete.
Results: Between July 9, 2009, and October 24, 2011, 2840 women received neratinib (n = 1420) or placebo (n = 1420). After a median follow-up of 8.1 (IQR, 7.0–8.8) years, 127 patients (8.9%) in the neratinib group and 137 patients (9.6%) in the placebo group in the intention-to-treat population had died. Eight-year overall survival rates were 90.1% (95% CI 88.3–91.6) with neratinib and 90.2% (95% CI 88.4–91.7) with placebo (stratified hazard ratio 0.95; 95% CI 0.75–1.21; p = 0.6914).
Conclusions: Overall survival in the extended adjuvant setting was comparable for neratinib and placebo after a median follow-up of 8.1 years in women with early-stage HER2-positive breast cancer.

1. Introduction

Trastuzumab added to adjuvant chemotherapy for 1 year significantly reduces the risk of disease recurrences and mortality in early-stage human epidermal growth factor receptor 2 (HER2)-positive breast cancer [1–3]. While there is a reduction in recurrences and a survival advantage after trastuzumab, there remains an unmet clinical need for further improvement in outcomes due to ongoing recurrences. Long-term follow-up data indicate that 23–30% of patients experience disease recurrences or die within 8–10 years despite the use of trastuzumab as adjuvant therapy [3–5]. A more recent trial investigating HER2-directed adjuvant therapy in a potentially lower risk population (node-negative disease, 38% of study population vs. 29–32% in trials of trastuzumab [3–5]) reported that 12% of patients had disease recurrences or had died at 8.4 years [6].

Extending the duration of HER2-directed adjuvant therapy with an additional year of trastuzumab did not improve disease-free survival [7]. In contrast, significant disease-free survival benefits were observed after receipt of an irreversible pan-HER tyrosine kinase inhibitor, neratinib (Nerlynx®) for 1 year after trastuzumab-based adjuvant therapy in the phase 3 ExteNET trial [8]. Invasive disease-free survival rates were 94.2% with neratinib vs. 91.9% with placebo after 2 years (hazard ratio 0.66; 95% confidence intervals [CI] 0.49–0.90; $p = 0.008$) [9], and 90.2% vs. 87.7%, respectively, after 5 years of follow-up (hazard ratio 0.73; 95% CI 0.57–0.92; $p = 0.008$) [10]. Further data on invasive disease-free survival were not collected after 5 years. Based on the findings from ExteNET, neratinib was approved by the Food and Drug Administration (FDA) as extended adjuvant therapy in the intention-to-treat patient population [9], whereas the European Medicines Agency (EMA) approved neratinib in patients with HER2-positive, hormone receptor-positive early-stage breast cancer who initiate treatment within 1 year of completing trastuzumab-based therapy [11].

We report here the final protocol-defined analysis of overall survival from the ExteNET trial in the intention-

to-treat population. The findings from this analysis were added to the United States prescribing information in 2020 [9]. Overall survival data for the patient subset for which neratinib is approved by the EMA have been published separately [12]. The primary safety analysis at 2 years [8] and an analysis of long-term safety data including post-treatment serious adverse events [10] from ExteNET have also been previously reported.

2. Methods

2.1. Study design and participants

ExteNET (Extended Adjuvant Treatment of Breast Cancer with Neratinib) was an international, multicentre, randomised, double-blind, parallel, placebo-controlled phase 3 trial designed to investigate extended adjuvant therapy with neratinib or placebo given for 1 year after standard locoregional treatment, chemotherapy and neoadjuvant or adjuvant therapy with trastuzumab. Prior to the unblinding of ExteNET for the primary analysis, the final design comprised three discrete parts: Part A, the primary efficacy analysis at 2 years, which was completed in July 2014 [8]; Part B, a sensitivity analysis at 5 years of all efficacy endpoints, except for overall survival, which was completed in March 2017 [10]; and Part C, an event-driven analysis of overall survival, the focus of the present paper which was completed in July 2019. Details of the study design, settings, and protocol amendments have been described with the 2-year primary analysis [8]. Of relevance to the overall survival analysis is global amendment 13 (January 2014), which restored the original intention of the study 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, reconsent was required from all patients to implement this amendment and to allow the retrospective collection of overall survival data.

The study population included women aged 18 years or older with stage 1–3c HER2-positive primary breast cancer who received standard locoregional treatment and completed neoadjuvant or adjuvant chemotherapy and trastuzumab within 2 years of randomisation. HER2 status was tested locally, but subsequently confirmed by central testing (ie, HER2:CEP17 ratio $\geq$2.2; PathVysion HER2 DNA dual probe; Abbott Molecular, Des Plaines, IL, USA). Clinical and radiologic assessments were required to be negative for recurrences or metastatic disease at study entry. Recruitment was restricted in February 2010 (protocol amendment 3) to higher risk patients with stage 2–3c disease and completion of neoadjuvant or adjuvant trastuzumab within 1 year of randomisation. Patients who completed neoadjuvant therapy were eligible only if residual invasive cancer in the breast and/or axilla was present after completing 1 year of adjuvant trastuzumab (no pathologic complete response). Patients were also required 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. Patients provided written informed consent prior to study entry, and patients who re-consented to allow the collection of long-term information provided written informed consent on a new consent form.

2.2. Randomisation and masking

Patients were randomly assigned (1:1 ratio) to receive neratinib or matching placebo. The randomisation sequence was generated via permuted blocks and stratified by hormone receptor status (hormone receptor-positive [oestrogen or progesterone receptor-positive or both] vs. hormone receptor-negative [oestrogen and progesterone receptor-negative] determined locally by local criteria, schedule of adjuvant trastuzumab administration (sequential vs. concurrent administration with chemotherapy), and nodal status (0, 1–3 or 4+ positive nodes). The randomisation sequence was then implemented centrally via an interactive voice and web-response system. The study was performed in a double-blind manner until the primary analysis at 2 years. Access to both data and the results of Part A were restricted from study personnel directly involved in the operations of Parts B and C. Investigators, study site and sponsor personnel were blinded to overall survival data until time of analysis.

2.3. Procedures

Patients were assigned to neratinib 240 mg orally once daily or matching placebo continuously for 1 year or until disease recurrence, new breast cancer, intolerable adverse events or consent withdrawal. No crossover was permitted in the study. Neratinib dose reductions (200, 160 and 120 mg/day) were allowed to manage treatment-emergent toxicity; treatment was stopped if neratinib 120 mg was not tolerated or if treatment was interrupted for more than 3 weeks. Antidiarrhoeal prophylaxis was not mandated; loperamide use was recommended as treatment if diarrhoea occurred. Adjuvant endocrine therapy for women with hormone receptor-positive disease was recommended.

During years 1 and 2 post-randomisation, survival information was collected every 6 months. From year 2 onwards, survival data were actively collected or gathered from patient medical records or publicly available death records in accordance with Good Clinical Practice guidelines and privacy laws. The search of public records was also used to obtain the last date a patient was known to be alive. Details of anti-cancer medications prescribed during the follow-up period were also

collected; for Part A, all new anti-cancer medications were documented, whereas for Parts B and C, only the first anticancer treatment was required.

2.4. Outcomes

The primary endpoint was invasive disease-free survival, and secondary endpoints were disease-free survival including ductal carcinoma in situ, time to distant recurrence, distant disease-free survival, cumulative incidence of central nervous system recurrences, overall survival, and safety. Data for all efficacy endpoints, except for overall survival, were collected until 5 years of follow-up and have been previously reported [8,10]. Safety data at 2 years [8] and 5 years [10] have also been previously reported. The present paper reports the only analysis of overall survival, which was defined as time from randomisation to death.

2.5. Statistical analysis

Overall survival was tested when 248 deaths had occurred at a 2-sided 5% significance level with 80% power to detect a hazard ratio of 0.70 in the intention-to-treat population. In addition, one interim analysis at 50% information fraction (relative to the target 248 events) was planned with the Lan-DeMets alpha-spending function approximating the O'Brien Fleming boundary (data not presented). Overall survival was defined as the time from date of randomisation to date of death, censored at the last date the patient was known to be alive. All deaths, including those identified from the study clinical database (RAVE), long-term safety database (ARGUS), and publicly available death records, were included in the analysis. The cutoff date for this analysis was July 10, 2019.

Analyses were performed in the intention-to-treat population, defined as all randomised patients, and in the predefined centrally confirmed HER2-positive population, defined as all randomised patients who were confirmed by central testing to be HER2-positive. Overall survival was tested with a 2-sided log-rank test, and hazard ratios with 95% CI for neratinib versus placebo were estimated using a Cox proportional hazards regression. Analyses in the intention-to-treat population were stratified by randomisation stratification factors (hormone receptor status, schedule of trastuzumab administration, and nodal status) as specified in the statistical analysis plan. Kaplan–Meier methods were used to estimate survival rates. Subgroup analyses prespecified in the statistical analysis plan were also performed to examine the effects of stratification factors, other subsets of interest (i.e., patients who completed trastuzumab within or more than 1 year from randomisation), and other baseline factors of interest on treatment effect. Analyses in the centrally confirmed HER2-positive population and all subgroup analyses were unstratified. Anticancer medications started after the completion of study drug were summarised; aromatase inhibitors (anastrozole, exemestane, etc.) and steroids (dexamethasone, prednisone, methylprednisolone, etc.) were excluded from the analysis. Exploratory analyses of time to first post-treatment anticancer medication, defined as time from randomisation to the beginning of the first subsequent anticancer medication, and post-treatment anticancer medication-free survival, defined as time from randomisation to first subsequent anticancer medication or death, were also performed. SAS statistical software (version 9.2 or later) was used for all analyses. An Independent Data Monitoring Committee reviewed the overall survival data on a regular basis. This study is registered at ClinicalTrials.gov, number NCT00878709.

2.6. Role of the funding source

The funders of the study designed the trial, were responsible for data collection, data integrity and analyses, and interpretation of the data with oversight by the Academic Steering Committee. The manuscript was written with input from all members of the Academic Steering Committee, and with review and input from the sponsor. 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.

3. Results

Between July 9, 2009, and October 24, 2011, 2840 eligible patients were randomly assigned to study treatment (1420 per group) and constituted the intention-to-treat population. A CONSORT flowchart with details of patient follow-up is presented in Fig. 1. Patient baseline characteristics and demographics are presented in Table A.1 and were similar between treatment groups.

Full details of treatment exposure have been described previously [8]. In brief, the median duration of study treatment in the intention-to-treat population was 11.6 (IQR, 2.5–11.9) months in the neratinib group and 11.8 (IQR, 11.5–12.0) months in the placebo group, with median relative actual dose intensities of 98% (IQR, 81–100) and 100% (IQR, 99–100), respectively.

At the cutoff date for this analysis (July 10, 2019), the median duration of follow-up was 8.0 (IQR, 6.9–8.8) years in the neratinib group and 8.1 (IQR, 7.1–8.9) years in the placebo group. A total of 743 patients (52.3%) and 796 patients (56.1%), respectively, completed 8 years or more of follow-up (Fig. 1). There were 712 patients (25.1%; neratinib, $n = 391$; placebo, $n = 321$) who did not consent to long-term follow-up ($n = 659$) or who died ($n = 53$) prior to the reconsent

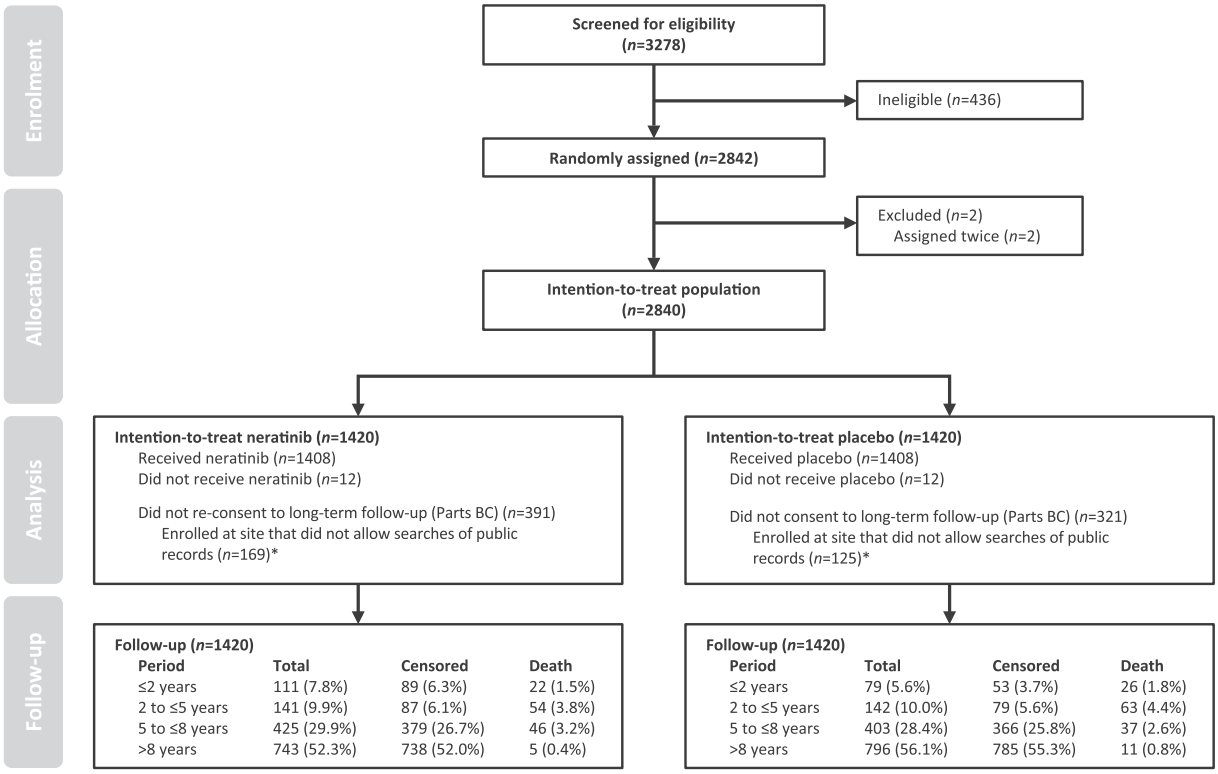

Fig. 1. ExteNET trial profile and follow-up. *Subset of patients who did not consent to long-term follow-up.

process, and of the 712 patients, 294 were enrolled at sites that did not allow access to public records (neratinib, $n = 169$; placebo, $n = 125$).

In the intention-to-treat population, 127 of 1420 patients (8.9%) in the neratinib group and 137 of 1420 patients (9.6%) in the placebo group had died at the time of analysis. Sixty-five of the deaths in the neratinib group and 75 of the deaths in the placebo group were in patients that did not reconsent to long-term follow-up. The 8-year overall survival rates were 90.1% (95% CI 88.3–91.6) in the neratinib group and 90.2% (95% CI 88.4–91.7) in the placebo group (stratified hazard ratio 0.95; 95% CI 0.75–1.21; $p = 0.6914$) [Fig. 2a].

Primary tumour specimens from 2160 patients (76.1%) underwent central HER2 testing, 1796 of which were HER2-positive. In the centrally confirmed HER2-positive population ($n = 1796$), 73 of 917 patients (8.0%) in the neratinib group and 82 of 879 patients (9.3%) in the placebo group died. The 8-year overall survival rates were 91.2% (95% CI 89.0–93.0) in the neratinib group and 90.8% (95% CI 88.5–92.6) in the placebo group (hazard ratio 0.86; 95% CI 0.63–1.19) [Fig. 2b].

The subgroup analysis of predefined subgroups in the intention-to-treat population is presented in Fig. 3. When analysed by hormone receptor status, in the hormone receptor-positive cohort ($n = 1631$), 8-year overall survival rates were 91.6% in the neratinib group and 90.1% in the placebo group (hazard ratio 0.80; 95% CI 0.58–1.11) (Fig. 4a). In the hormone receptor-negative cohort ($n = 1209$), 8-year overall survival rates were 88.1% in the neratinib group and 90.3% in the placebo group (hazard ratio 1.18; 95% CI 0.83–1.69) (Fig. 4b). Considering overall survival by nodal status, in node-negative patients ($n = 671$), 8-year overall survival rates were 94.9% in the neratinib group and 94.8% in the placebo group (hazard ratio 0.78; 95% CI 0.40–1.48), in patients with 1–3 positive nodes ($n = 1328$), 8-year overall survival rates were 91.8% and 90.6%, respectively (hazard ratio 0.81; 95% CI 0.55–1.18), and in patients with 4 or more positive nodes ($n = 841$), 8-year overall survival rates were 83.8% and 85.9%, respectively (hazard ratio 1.17; 95% CI 0.82–1.69) [Figure A.1].

A subgroup analysis of the centrally confirmed HER2-positive population is presented in Figure A.2. In the hormone receptor-positive cohort from the centrally confirmed HER2-positive population ($n = 951$), 8-year overall survival rates were 93.2% in the neratinib group and 90.4% in the placebo group (hazard ratio 0.65; 95% CI 0.41–1.03), and in the hormone receptor-negative cohort ($n = 845$), the 8-year overall survival rates were 89.0% in the neratinib group and 91.2% in the placebo group (hazard ratio 1.13; 95% CI 0.73–1.76).

Of the 264 deaths documented in the intention-to-treat-population, 184 (neratinib, $n = 85$, 6.0%; placebo, $n = 99$, 7.0%) were because of disease progression, and 80 (neratinib, $n = 42$, 3.0%; placebo, $n = 38$, 2.7%) were from other causes including cardiovascular events (e.g. cardiogenic shock, myocardial infarction), and

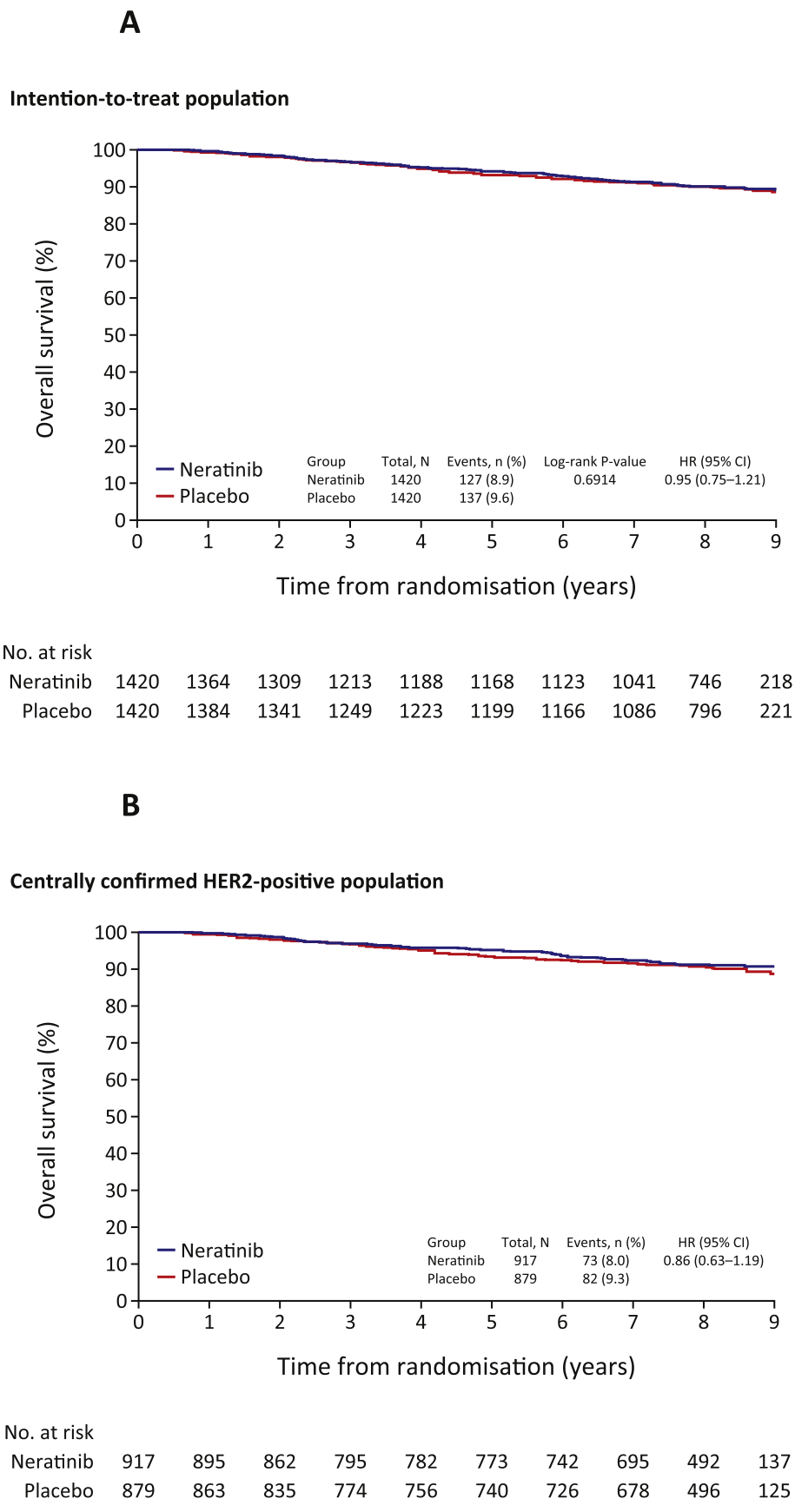

Fig. 2. Kaplan–Meier curves for overall survival in the (A) intention-to-treat population, and (B) centrally confirmed HER2-positive population.

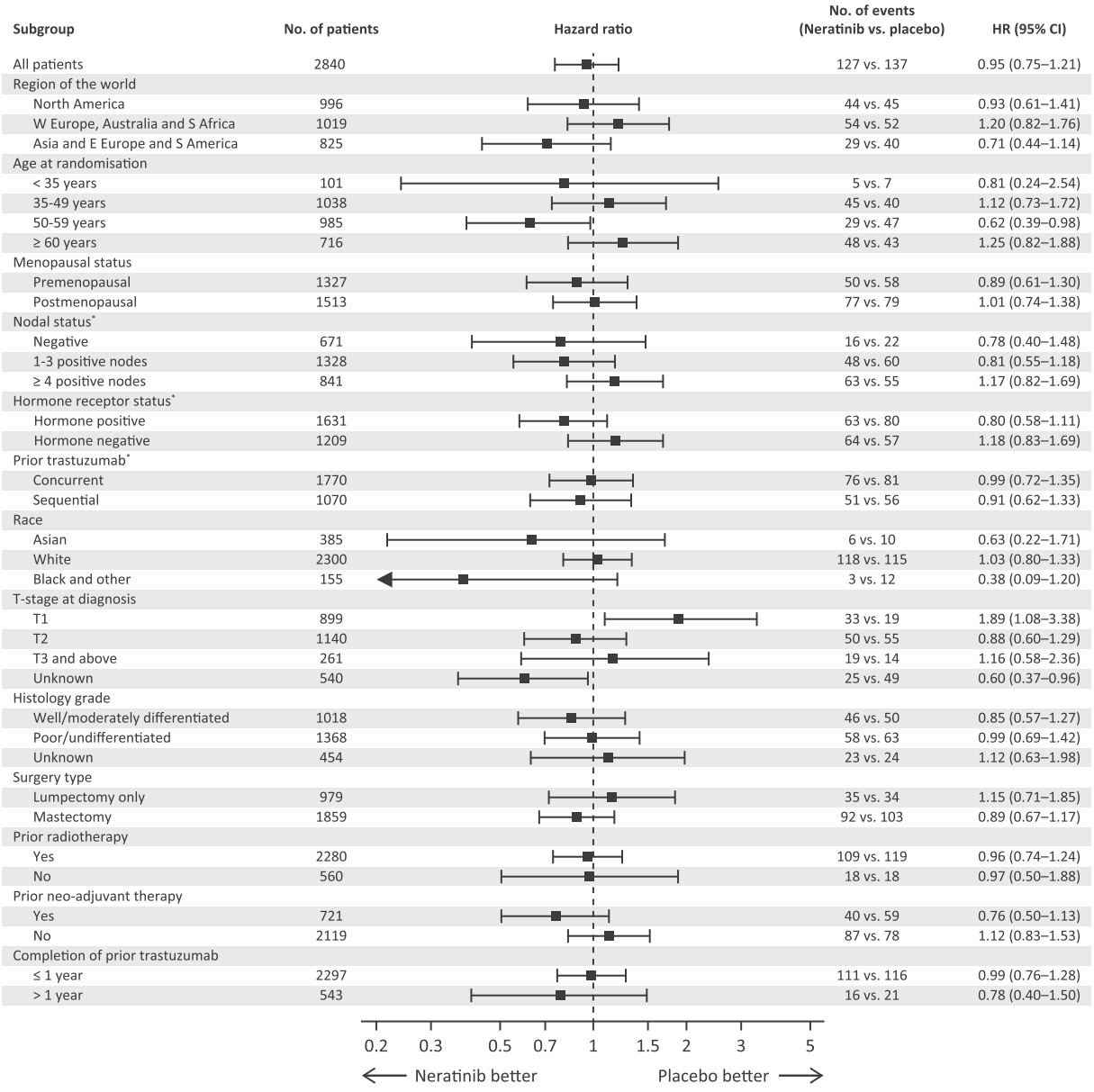

Fig. 3. Subgroup analyses of overall survival in the intention-to-treat population. The vertical dashed line indicates a hazard ratio of 1.0, the null hypothesis value.* Stratification factor.

secondary cancers (e.g. metastatic colorectal cancer, non-small cell lung cancer).

Anticancer medications initiated after completion of study treatment were similar in the neratinib and placebo groups (Table 1). Medications included HER2-directed agents (e.g. trastuzumab, lapatinib, pertuzumab, trastuzumab emtansine), antineoplastic agents (e.g. capecitabine, paclitaxel, docetaxel), and bone-targeted agents (e.g. zoledronic acid, denosumab). There was a slight imbalance between groups in the usage of trastuzumab (neratinib, $n = 74$, 5.2%; placebo, $n = 98$, 6.9%). Exploratory analyses showed that anticancer medication-free survival (hazard ratio 0.79; 95% CI 0.64–0.98) and time to first subsequent anticancer medication (hazard ratio 0.74; 95% CI 0.58–0.94) were longer in the neratinib group than in the placebo group (Figure A.3).

4. Discussion

In this final protocol-defined analysis of the ExteNET trial, despite significant invasive disease-free survival benefits with neratinib compared with placebo at 2 years [8] and 5 years [10], there was no statistically significant improvement with neratinib on mortality in the intention-to-treat population after 8 years' follow-up (hazard ratio, 0.95; 95% CI 0.75–1.21). These findings are consistent with those of other contemporary trials of HER2-directed agents in the adjuvant setting (pertuzumab and trastuzumab emtansine) that have not reported overall survival benefits (APHINITY 8.4-year analysis: hazard ratio, 0.83; 95% CI 0.68–1.02 [6]; KATHERINE 3-year analysis: hazard ratio, 0.70; 95% CI 0.47–1.05 [13]) despite significant disease-free survival gains.

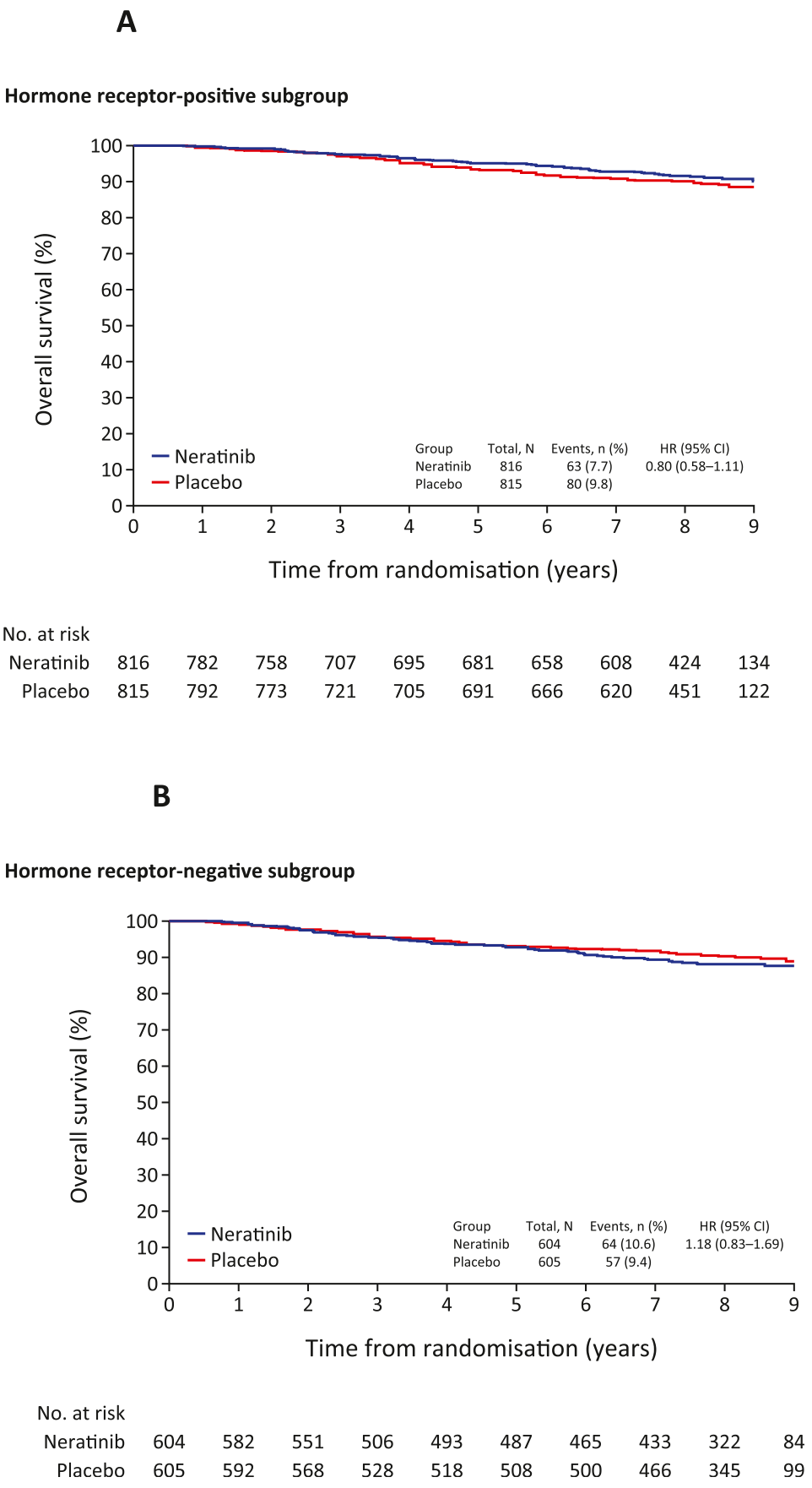

Fig. 4. Kaplan–Meier curves for overall survival in (A) patients with hormone receptor-positive breast cancer, and (B) patients with hormone receptor-negative breast cancer.

Table 1
Anticancer medications initiated after completion of study treatment in the intention-to-treat population.

Medication	Intention-to-treat population (n = 2840)	
	Neratinib (n = 1420)	Placebo (n = 1420)
HER2-directed agents	88 (6.2)	117 (8.2)
Trastuzumab	74 (5.2)	98 (6.9)
Lapatinib	28 (2.0)	32 (2.3)
Pertuzumab	17 (1.2)	22 (1.5)
Trastuzumab emtansine	16 (1.1)	16 (1.1)
Antineoplastic agents	88 (6.2)	134 (9.2)
Capecitabine	35 (2.5)	40 (2.8)
Paclitaxel	30 (2.1)	43 (3.0)
Docetaxel	23 (1.6)	35 (2.5)
Vinorelbine	15 (1.1)	30 (2.1)
Carboplatin	13 (0.9)	14 (1.0)
Cyclophosphamide	5 (0.4)	17 (1.2)
Gemcitabine	5 (0.4)	7 (0.5)
Doxorubicin	4 (0.3)	10 (0.7)
Bone-targeted agents	13 (0.9)	18 (1.3)
Zoledronic acid	9 (0.6)	10 (0.7)
Denosumab	2 (0.1)	6 (0.4)
Gonadotrophins	10 (0.7)	4 (0.3)
Goserelin	7 (0.5)	3 (0.2)

Data are n (%). Table shows individual agents used in ≥5 patients in either treatment group. For each patient, medications that began after completion of study drug are included. Endocrine treatments (letrozole, anastrozole, tamoxifen, exemestane, fulvestrant, toremifene) which may have been changed during the follow-up period because of side effects rather than disease recurrence, and medications administered for reasons other than disease recurrence, i.e. corticosteroids (dexamethasone, prednisone, methylprednisolone, etc.), were excluded from the analysis.

Overall survival results in the higher risk population for which neratinib is approved in Europe (i.e., hormone receptor-positive disease who initiated treatment within 1 year of completing trastuzumab-based therapy) trended in favour of neratinib (hazard ratio, 0.79; 95% CI 0.55–1.13) as reported previously [12].

A key observation in earlier subgroup analyses of ExteNET was that patients with hormone receptor-positive disease had greater invasive disease-free survival improvements than patients with hormone receptor-negative tumours [8,10]. Patients with hormone receptor-positive disease typically have longer post-progression survival [2], reinforcing the need for a longer duration of follow-up in these patients. Trends in overall survival observed at 2 and 5 years in ExteNET relating to the hormone receptor subgroups were also apparent in the overall survival analysis at 8 years. The improved invasive disease-free survival of neratinib in patients with hormone receptor-positive tumours in ExteNET, most of whom were receiving concomitant endocrine therapy, has been attributed to the successful inhibition of both oestrogen and HER2 receptors to overcome compensatory reciprocal crosstalk between the signalling pathways. This proposed mechanism has since been supported by preclinical models [14,15] and other clinical trials of neratinib in patients with hormone receptor-positive, HER2-positive breast cancer [16].

A number of potential confounding factors should be considered when interpreting the findings from this analysis. During the follow-up period, patients in both treatment groups went on to receive a range of effective post-protocol treatments, including HER2-based therapies (trastuzumab, pertuzumab, trastuzumab emtansine) and chemotherapeutic agents, which were administered at the discretion of the treating physician rather than controlled by protocol. While we recognise that the data on these anticancer medications may have been collected less reliably than other data and showed regional variability, there is no reason to suspect data collection was biased in favour or against either of the randomised treatment groups. The fact that the overall survival hazard ratio was 0.95 in favour of neratinib, despite some observed imbalances in post-protocol therapies (Table 1), suggests that neratinib did not cause detriment to patients. Another observation is that 30.3% of deaths in the intention-to-treat population were due to causes other than progression of breast cancer (i.e., cardiovascular events and secondary cancers) against which neratinib would not be anticipated to have efficacy.

The safety profile of neratinib is characterised by adverse events, predominantly gastrointestinal in nature, that are generally transient and manageable with dose modifications and/or conventional treatments [8], and which do not lead to long-lasting morbidities [10]. Improvements in diarrhoea control using neratinib dose escalation have been described recently in the phase 2 CONTROL trial [17] and added to the US prescribing information [9]. With 91% of patients in the neratinib group alive after a median follow-up of 8.1 years in ExteNET and no detrimental effect versus placebo on overall survival, this final analysis with no new safety signals observed provides further confirmation of the long-term safety of neratinib.

This final analysis of the intention-to-treat population of the ExteNET trial did not demonstrate an overall survival benefit with extended adjuvant neratinib therapy versus placebo after a median follow-up of 8 years for women with early-stage HER2-positive breast cancer. The long-term survival of both the neratinib and placebo arms remained very high, with more than 90% of patients alive at 8 years.

Author contributions

FAH, BM, SD, SKLC, BE, JM, HI, MG, MB, CHB, AW, MM, and ACh conceived and designed the study. BZ analysed the data. All authors were involved in interpretation of data for the work, drafting or revising the report critically for important intellectual content, and final approval of the version to be published. 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.

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Data sharing

The authors declare that the data supporting the findings of this study are available within the article. Qualified researchers and study participants may submit requests for other study documentation and clinical trial data to clinicaltrials@pumabiotechnology.com for consideration.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **SD** declares institutional grants from Puma Biotechnology Inc. during the conduct of the study, institutional grants from Pfizer, Novartis, AstraZeneca, Roche Genentech, Lilly, Myriad, Orion, Amgen, Sanofi, Genomic Health, GE, Servier, MSD, Bristol Myers Squibb, Pierre Fabre, Seagen, Exact Sciences, Rappta, Besins, European Commission, French Government, Fondation ARC, Taiho, and Elsan, and non-financial support from Pfizer, AstraZeneca, and Roche Genentech outside the submitted work.

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Appendix A. Supplementary data

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