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Neratinib Plus Paclitaxel vs Trastuzumab Plus Paclitaxel in Previously Untreated Metastatic ERBB2-Positive Breast Cancer

The NEfERT-T Randomized Clinical Trial

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IMPORTANCE Efficacious ERBB2 (formerly HER2 or HER2/neu)-directed treatments, in addition to trastuzumab and lapatinib, are needed.

OBJECTIVE To determine whether neratinib, an irreversible pan-ERBB tyrosine kinase inhibitor, plus paclitaxel improves progression-free survival compared with trastuzumab plus paclitaxel in the first-line treatment of recurrent and/or metastatic ERBB2-positive breast cancer.

DESIGN, SETTING, AND PARTICIPANTS In the randomized, controlled, open-label NEfERT-T trial conducted from August 2009 to December 2014 at 188 centers in 34 countries in Europe, Asia, Africa, and North America, 479 women with previously untreated recurrent and/or metastatic ERBB2-positive breast cancer were randomized to 1 of 2 treatment arms (neratinib-paclitaxel [n = 242] or trastuzumab-paclitaxel [n = 237]). Women with asymptomatic central nervous system metastases were eligible, and randomization was stratified by prior trastuzumab and lapatinib exposure, hormone-receptor status, and region.

INTERVENTIONS Women received neratinib (240 mg/d orally) or trastuzumab (4 mg/kg then 2 mg/kg weekly), each combined with paclitaxel (80 mg/m^2 on days 1, 8, and 15 every 28 days). Primary prophylaxis for diarrhea was not mandatory.

MAIN OUTCOME AND MEASURES The primary outcome was progression-free survival. Secondary end points were response rate, clinical benefit rate, duration of response, frequency, and time to symptomatic and/or progressive central nervous system lesions, and safety.

RESULTS The intent-to-treat population comprised 479 women 18 years or older (neratinib-paclitaxel, n = 242; trastuzumab-paclitaxel, n = 237) randomized and stratified in their respective treatment arms by prior trastuzumab and lapatinib exposure, hormone-receptor status, and region. Median progression-free survival was 12.9 months (95% CI, 11.1-14.9) with neratinib-paclitaxel and 12.9 months (95% CI, 11.1-14.8) with trastuzumab-paclitaxel (hazard ratio [HR], 1.02; 95% CI, 0.81-1.27; *P* =.89). With neratinib-paclitaxel, the incidence of central nervous system recurrences was lower (relative risk, 0.48; 95% CI, 0.29-0.79; *P* = .002) and time to central nervous system metastases delayed (HR, 0.45; 95% CI, 0.26-0.78; *P* = .004). Common grade 3 to 4 adverse events were diarrhea (73 of 240 patients [30.4%] with neratinib-paclitaxel and 9 of 234 patients [3.8%] with trastuzumab-paclitaxel), neutropenia (31 patients [12.9%] vs 34 patients [14.5%]) and leukopenia (19 patients [7.9%] vs 25 patients [10.7%]); no grade 4 diarrhea was observed.

CONCLUSIONS AND RELEVANCE In first-line ERBB2-positive metastatic breast cancer, neratinib-paclitaxel was not superior to trastuzumab-paclitaxel in terms of progression-free survival. In spite of similar overall efficacy, neratinib-paclitaxel may delay the onset and reduce the frequency of central nervous system progression, a finding that requires a larger study to confirm.

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Over the past 15 years, therapies directed against human epidermal growth factor receptor 2 (ERBB2 [formerly HER2 or HER2/neu]) have improved overall survival in patients with early-stage[1,2] and metastatic ERBB2-positive breast cancers.[3,4] However, patients with stage IV disease still die on average 2 to 5 years after relapse.[4-6] Metastatic ERBB2-positive breast cancer has a characteristic pattern of spread, with over 75% of patients developing liver metastases,[7] and approximately half with poor-prognosis central nervous system (CNS) involvement.[8] Recent studies suggest that small-molecule ERBB2 kinase inhibitors may be effective in patients with ERBB2-positive metastatic breast cancer and CNS metastases.[9,10]

Neratinib (Puma Biotechnology Inc) is an oral small-molecule tyrosine kinase inhibitor of ERBB1, ERBB2, and ERBB4[11] that binds irreversibly to the intracellular domain of ERBB receptors, leading to sustained inhibition of signal transduction.[12] Neratinib has demonstrated clinical activity in patients with ERBB2-positive metastatic breast cancer both as a single agent[13] and in combination with various chemotherapeutic agents, including paclitaxel.[14] Diarrhea is the most common toxic effect associated with neratinib[13] and is now managed with intensive primary antidiarrheal prophylaxis administered with the first cycle of neratinib.[15,16]

Study 3144A2-3005-WW (NEfERT-T) evaluated the efficacy and safety of first-line neratinib plus paclitaxel compared with trastuzumab plus paclitaxel in women with locally recurrent or metastatic ERBB2-positive breast cancer, including those with asymptomatic CNS metastases. We report here the efficacy and safety analyses from this phase 2 randomized study.

Key Points

Question Does neratinib plus paclitaxel improve progression-free survival compared with trastuzumab plus paclitaxel as first-line therapy in recurrent and/or metastatic ERBB2-positive breast cancer?

Findings In this randomized clinical trial that included 479 women, median progression-free survival was 12.9 months with neratinib-paclitaxel and 12.9 months with trastuzumab-paclitaxel with no statistically significant difference between groups. The incidence of central nervous system (CNS) recurrences was significantly lower and time to CNS metastases significantly delayed with neratinib-paclitaxel.

Meaning Neratinib-paclitaxel is not superior to trastuzumab-paclitaxel in terms of progression-free survival in previously untreated women with ERBB2-positive metastatic breast cancer, and the CNS findings warrant further clinical investigation.

Methods

Study Design

NEfERT-T was initiated in 2009 as a multinational, open-label, randomized phase 3 trial to determine whether neratinib-paclitaxel was superior to trastuzumab-paclitaxel as first-line treatment for women with metastatic ERBB2-positive breast cancer (Trial Protocol is available in Supplement 1). In June 2011, the study goals and statistical parameters were revised after neratinib was passed from Wyeth to Pfizer and after it became evident that the estimate of progression-free survival (PFS) used to determine the sample size (control arm, 9 months) was shorter than in the CHAT[17] and HERNATA[18] studies (approximately 12 months) which were reported at that time. The study objective was revised to gain a preliminary understanding of the safety and efficacy of neratinib-paclitaxel in the context of a randomized study. The accrual goal was reduced from 1200 to 480 patients, and subsequently the study was no longer powered as a randomized phase 3 study. This decision was not related to any safety issue and was made without any knowledge of the efficacy data.

Approval of the protocol was obtained at participating sites from an institutional review board and/or independent ethics committee. All patients provided written informed consent.

Study Population

Women 18 years and older with measurable histologically and/or cytologically confirmed inoperable locally recurrent or metastatic breast cancer were eligible. Documentation of *ERBB2*-amplification (fluorescence in situ hybridization [FISH] score >2.2 or chromogenic in situ hybridization [CISH] according to manufacturer instructions) or ERBB2-overexpression (immunohistochemistry score 3+ or 2+ with FISH or CISH confirmation) at a local or central laboratory was required. Prior systemic therapy for metastatic disease, excluding endocrine therapy, and prior treatment with an ERBB2 inhibitor, excluding trastuzumab and/or lapatinib in the (neo)adjuvant setting, was not allowed. Women with newly detected asymptomatic CNS metastases, a history of CNS metastases, or spinal involvement with cord compression were eligible provided that they were asymptomatic, had been treated definitively with surgery and/or radiation therapy, and had not received anticonvulsants or steroids within 4 weeks prior to study treatment. Patients had adequate organ and hematological function.

Randomization and Masking

A centralized permuted block randomization procedure through an interactive voice response system was used to assign patients to each treatment group (1:1 ratio). Randomization was stratified by prior trastuzumab exposure (yes/no), prior lapatinib exposure (yes/no), estrogen receptor (ER)/progesterone receptor (PgR) status (ER-positive and/or PgR-positive/ER-negative and PgR-negative), and region. Neither participants nor investigators were masked to treatment allocation.

Treatment

Eligible patients were randomly assigned (1:1) to treatment with either neratinib (240 mg orally once daily) plus paclitaxel (80 mg/m^2 intravenously on days 1, 8, and 15 every 28 days) or trastuzumab (4 mg/kg loading dose intravenously then 2 mg/kg on days 1, 8, 15, and 22 every 28 days) plus paclitaxel (80 mg/m^2 intravenously on days 1, 8, and 15 every 28 days). Treatment was initiated within 2 days of randomization and continued

until disease progression, symptomatic deterioration, unacceptable toxic effects, death, or withdrawal of consent. Neratinib compliance was monitored using tablet counts and drug inventory records. Toxic effect–related dose reductions for neratinib (first dose reduction: 160 mg/d; second: 120 mg/d) and paclitaxel (first dose reduction: 70 mg/m^2; second: 60 mg/m^2) were permitted. Patients discontinued neratinib and/or paclitaxel if more than 2 dose reductions were required or if treatment was delayed more than 3 weeks. Primary prophylaxis and management for diarrhea with low-dose loperamide (2 mg with each neratinib dose) was recommended but not mandatory.

Assessments

At baseline, information regarding demography (including race [Asian, black/African American, white, other] classified by the investigator) and cancer history were collected. Tumor assessments (contrast-enhanced computed tomography [CT] or magnetic resonance imaging [MRI] of the chest, abdomen, and liver) were performed at baseline and every 8 weeks thereafter until objective disease progression. For patients without documented objective disease progression at treatment discontinuation, scans continued every 8 weeks until objective disease progression, initiation of new anticancer treatment, or death. Additional imaging (ie, bone scans, contrast-enhanced CT or MRI of the brain or other sites) was performed at baseline and repeated every 8 weeks if disease was present and/or if clinically indicated. In March 2012, after enrolment was complete, the frequency of tumor assessments was changed to every 12 weeks to alleviate patient burden and be in line with clinical practice. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Patient-reported health-related quality of life (QoL) was assessed with Functional Assessment of Cancer Therapy–Breast (FACT-B), version 4, and EuroQol 5-Dimensions visual analogue scale (EQ-5D-VAS) completed at baseline, cycle 2, and every 2 cycles thereafter until treatment discontinuation. Health-related QoL data were not collected after June 2011.

Outcomes

The primary end point was PFS. Secondary end points were objective response rate, duration of response, clinical benefit rate, frequency of and time to symptomatic or progressive CNS lesions, and safety. Health-related QoL was an exploratory endpoint. All tumor-based efficacy end points were assessed by investigators and are defined in eTable 1 in Supplement 2.

Statistical Analysis

The study was to enroll 480 patients to detect a 30% improvement in median PFS (based on assumptions in the original protocol that the median PFS would be 11.7 months in the experimental arm of neratinib-paclitaxel and 9 months in the control arm of trastuzumab-paclitaxel) with 80% power at a 1-sided significance level of .075. The study was event driven; a total of 304 PFS events were needed. No interim analysis was planned. As the requisite number of PFS events were reached for the primary analysis in accordance with the protocol, the trial ended as planned, and this report describes the first and final analysis from this study. The cut-off date for this analysis was December 16, 2014.

Efficacy analyses were based on the intent-to-treat population (ie, all randomized patients). Time-to-event end points were analyzed using a Cox proportional hazards regression model stratified for randomization factors and presented as hazard ratios with 95% confidence intervals (CI). Median values were estimated using the Kaplan-Meier method, and treatment groups were compared using a log-rank test stratified for randomization factors. Response rates and frequency of CNS lesions were compared using the Cochran Mantel-Haenszel test adjusted for randomization factors. Cumulative incidence with competing risks analysis was performed for CNS lesions, where progression events occurring at extracranial sites and deaths were considered competing risks; the Gray test was used to compare treatments.[19] Prespecified subgroup analyses were performed to examine whether treatment effect on PFS varied across prognostic factors. Adverse events were summarized by treatment arm for the safety population (ie, all patients who received ≥1 dose of study treatment). Changes in health-related QoL scores from baseline were analyzed using a linear mixed-model for repeated measures with baseline score, treatment, cycles and interaction of treatment and cycles as covariates. No multiplicity adjustments were applied in the statistical tests. All *P* values are nominal at a significance level of .05. All analyses were performed using SAS Enterprise Guide 5.1 (SAS Institute Inc).

Results

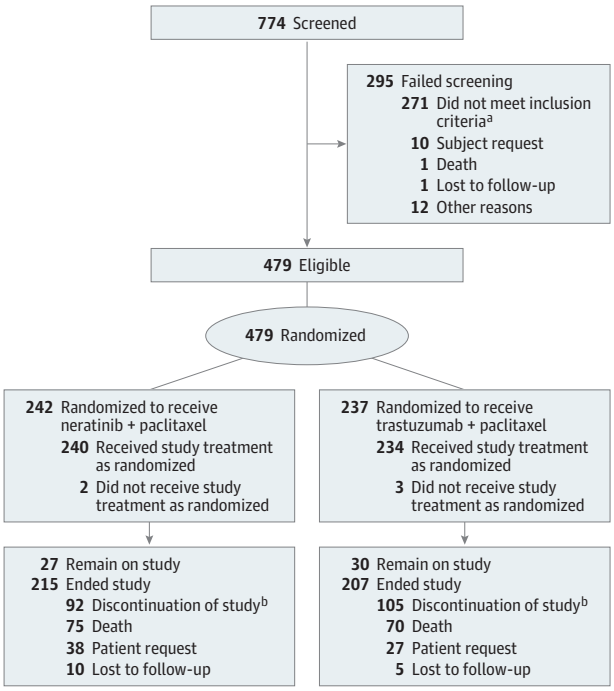
Between August 21, 2009, and August 21, 2011, 479 patients were enrolled from 188 centers and randomly assigned to neratinib-paclitaxel (n = 242) or trastuzumab-paclitaxel (n = 237) (**Figure 1**). Treatment groups were well balanced in terms of baseline characteristics (eTable 2 in Supplement 2). The median (interquartile range [IQR]) follow-up of the study was 23.0 (13.8-32.3) months.

Efficacy

Overall, 167 patients (69.0%) in the neratinib-paclitaxel group had PFS events compared with 156 patients (65.8%) in the trastuzumab-paclitaxel group (**Table**). Median PFS was 12.9 (95% CI, 11.1-14.9) months in the neratinib-paclitaxel group and 12.9 (95% CI, 11.1-14.8) months in the trastuzumab-paclitaxel group (hazard ratio [HR], 1.02; 95% CI, 0.81-1.27; *P* = .89) (**Figure 2**A). Subgroup analyses of PFS showed similar outcomes in all patient subgroups (ie, age, race, region, hormone receptor status, prior trastuzumab exposure), although there was some heterogeneity around the HR point estimates for smaller subgroups (eFigure 1 in Supplement 2). Kaplan-Meier curves of PFS according to hormone receptor status are shown in eFigure 2 in Supplement 2.

At the cut-off date, 78 patients (32.2%) in the neratinib-paclitaxel group had died compared with 72 patients (30.4%) in the trastuzumab-paclitaxel group (HR, 1.05; 95% CI, 0.76-1.45; *P* = .77) (Figure 2B).

Figure 1. NEfERT-T Patient Flowchart



[a] Patients referred for ERBB2 testing but the testing was not performed.

[b] Long-term follow-up for overall survival was removed from the study protocol March 2012 (amendment 6). Patients who ended study for this reason were recorded as "discontinuation of study by sponsor."

The objective response rate was 74.8% (181 patients) in the neratinib-paclitaxel group and 77.6% (184 patients) in the trastuzumab-paclitaxel group (P = .52), and the clinical benefit rates were 88.4% (214 patients) and 85.2% (202 patients), respectively (P = .24). The median duration of response was also similar in both groups (HR, 1.01; 95% CI, 0.78-1.32; P = .92) (Table).

The median (IQR) duration of treatment was 44.6 (23.4-72.0) weeks in the neratinib-paclitaxel group and 44.1 (25.3-72.1) weeks in the trastuzumab-paclitaxel group (eTable 3 in Supplement 2). The most common reason for discontinuing study treatment was disease progression (neratinib-paclitaxel, n = 157; trastuzumab-paclitaxel, n = 149). Mean relative dose intensity exceeded 90% for all agents.

Symptomatic or progressive CNS recurrences occurred in 20 patients (8.3%) in the neratinib-paclitaxel group and 41 patients (17.3%) in the trastuzumab-paclitaxel group (relative risk, 0.48; 95% CI, 0.29-0.79; P = .002) (Table); in 50 patients this was an isolated CNS event. The estimated Kaplan-Meier 2-year incidence of CNS recurrences was 16.3% in the neratinib-paclitaxel group and 31.2% in the trastuzumab-paclitaxel group (HR, 0.45; 95% CI, 0.26-0.78; P = .004). Based on the competing risks model, the 2-year estimated cumulative incidence was 10.1% in the neratinib-paclitaxel group and 20.2% in the trastuzumab-paclitaxel group (P = .002) (Figure 2C). Neratinib treatment effect on both CNS end points appeared similar in those with and without baseline CNS disease and remained statistically significant after adjusting for the imbalance of baseline CNS metastases (Cochran Mantel-Haenszel P = .02; Cox model HR 0.56; P = .045).

Safety

The most common treatment-emergent adverse events in the neratinib-paclitaxel group were diarrhea (92.5% vs 33.3% with trastuzumab-paclitaxel), alopecia (52.1% vs 56.4%), and nausea (44.2% vs 30.3%) (eTable 4 in Supplement 2). The most common grade 3 events were diarrhea (30.4%, neratinib-paclitaxel vs 3.8%, trastuzumab-paclitaxel; P < .001), neutropenia (11.3% vs 12.4%, respectively), and leukopenia (6.7% vs 10.3%, respectively). Grade 4 events occurred in 5.8% of patients in the neratinib-paclitaxel group and 4.7% of patients in the trastuzumab-paclitaxel group. Grade 4 febrile neutropenia occurred in 1 (0.4%) neratinib-paclitaxel-treated patient, and no grade 4 diarrhea was observed. Peripheral neuropathy and fatigue occurred at similar rates in both groups (eTable 4 in Supplement 2). Grade 3 or higher cardiac events (ie, cardiac failure, decreased ejection fraction, left ventricular dysfunction and [peripheral] edema) were reported in 3 patients (1.3%) in the neratinib-paclitaxel group and 7 patients (3.0%) in the trastuzumab-paclitaxel group.

The incidence of grade 3 diarrhea in the neratinib-paclitaxel group was highest in the first month of treatment; most events thereafter were grade 1 or 2 (eFigure 3 in Supplement 2). Median (IQR) time to onset of grade 3 diarrhea was 16 (6-65) days, with a median (IQR) duration of 2 (1-3) days per event and 5 (3-9) days per patient (eTable 5 in Supplement 2). Diarrhea led to discontinuation of study treatment in 9 neratinib-paclitaxel-treated patients (3.8%) and 1 trastuzumab-paclitaxel-treated patient (0.4%).

Three patients in the neratinib-paclitaxel group died as a result of treatment-related adverse events (septic shock, n = 1; intestinal obstruction, shock, n = 1; ascites, n = 1), as did 1 patient in the trastuzumab-paclitaxel group (pneumonitis).

Patient-Reported Health-Related QoL

Mean scores by treatment over time showed similar patterns for FACT-B and EQ-5D-VAS (eFigures 4 and 5 in Supplement 2). While early treatment differences appeared to favor trastuzumab-paclitaxel, none exceeded the differences considered to be clinically meaningful for either instrument.[20,21] Later treatment differences appeared to favor neratinib-paclitaxel, but sample sizes were small. Treatment-by-time interaction was significant in the mixed-effect model for FACT-B (P = .02) but not for EQ-5D-VAS (P = .13) (eFigures 4 and 5 in Supplement 2).

Discussion

This randomized controlled study did not demonstrate the superiority of neratinib-paclitaxel in terms of PFS compared with trastuzumab-paclitaxel as first-line therapy in women with ERBB2-positive metastatic breast cancer. Also, no statistically significant differences were observed between the 2 treatment groups for 3 of 5 secondary efficacy end points (ie,

Table. Efficacy Analyses in the Intent-to-Treat Population[a]

Variable	Neratinib Plus Paclitaxel (n = 242)	Trastuzumab Plus Paclitaxel (n = 237)	Hazard Ratio or Difference (95% CI)	*P* Value
Primary end points				
Patients with PFS event, No. (%)	167 (69.0)	156 (65.8)	1.02 (0.81 to 1.27)	.89[b]
Median PFS, mo	12.9	12.9	...	...
95% CI	11.1-14.9	11.1-14.8	...	...
Secondary end points				
Objective response rate, No. (%)[c]	181 (74.8)	184 (77.6)	-2.8 (-10.5 to 4.8)[d]	.52[c]
95% CI	68.8-80.1	71.8-82.8	...	...
Complete response[e]	4 (1.7)	9 (3.8)	...	...
Partial response[e]	177 (73.1)	175 (73.8)	...	...
Clinical benefit rate, No. (%)	214 (88.4)	202 (85.2)	3.2 (-2.9 to 9.3)[d]	.24[c]
95% CI	83.7-92.2	80.1-89.5		
Median duration of response, mo[f]	13.4	12.9	1.01 (0.78 to 1.32)	.92[b]
95% CI	11.4-16.8	11.0-15.9	...	...
Incidence of symptomatic or progressive CNS events, No. (%)	20 (8.3)	41 (17.3)	0.48 (0.29 to 0.79)[g]	.002[c]
First quartile, 25%, time to CNS events, mo, (95% CI)	Not reached	18.3 (12.3-41.3)	...	...

Abbreviations: CI, confidence interval; CNS, central nervous system; PFS, progression-free survival; ellipses, data not applicable.

[a] All end points by investigator assessment.

[b] Stratified log-rank test.

[c] Adjusted Cochran Mantel-Haenszel test.

[d] Difference.

[e] Confirmed responses.

[f] Assessed in 181 and 184 patients in the neratinib-paclitaxel and trastuzumab-paclitaxel groups, respectively.

[g] Relative risk.

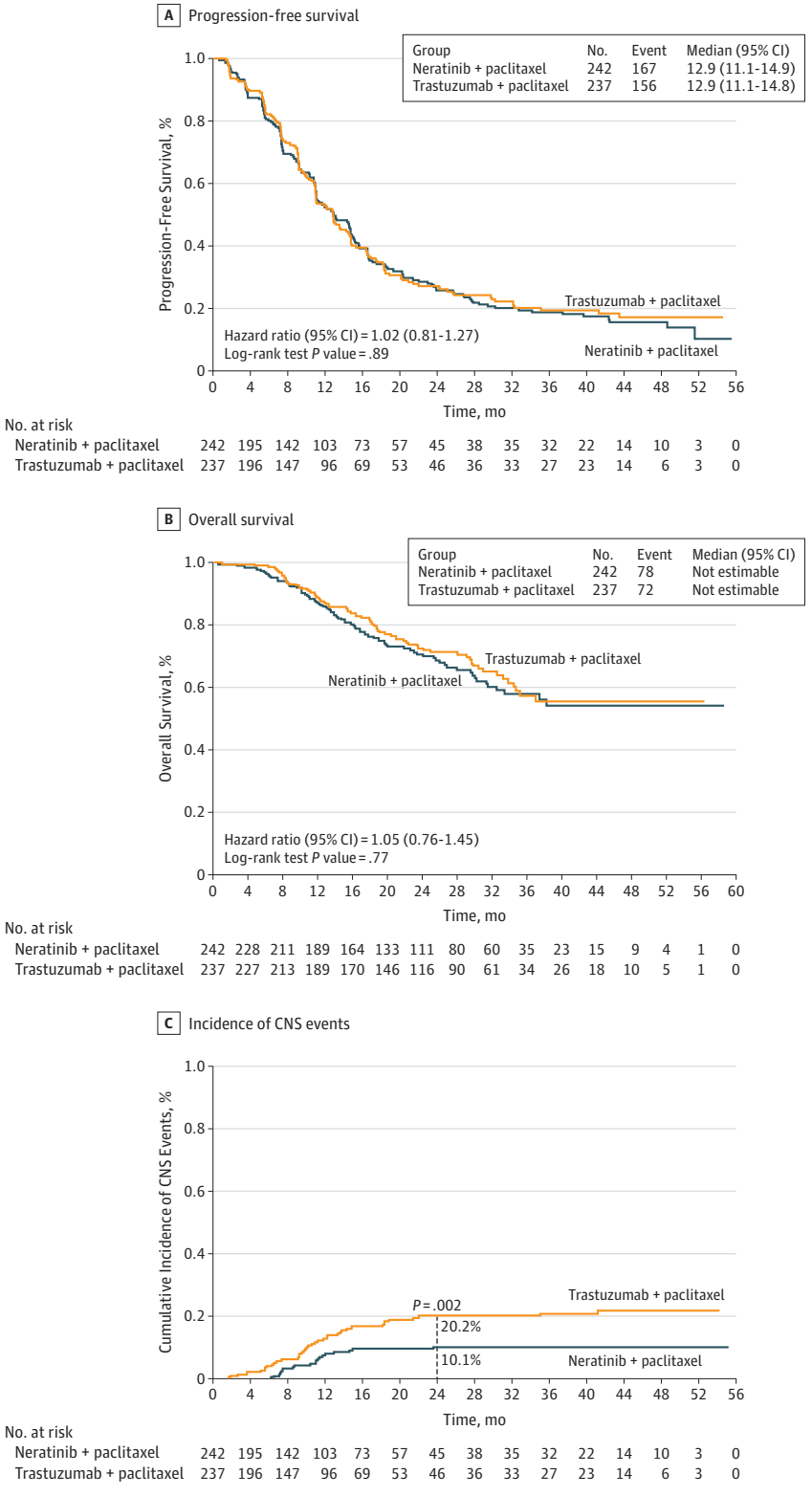
objective response rate, clinical benefit rate, and duration of response), which suggests that the 2 regimens have similar efficacy in this patient population. This was further supported by a prespecified subgroup analysis of PFS that showed consistent outcomes across most subgroups and the analysis of overall survival that showed similar outcomes in both treatment groups. The control group in the NEfERT-T trial performed as expected, with a median PFS of 12.9 months compared with 11.1 to 14.6 months reported with trastuzumab-taxane combinations in other first-line randomized controlled studies,[6,17,22-26] reinforcing the validity of the present study.

Central nervous system events are a challenging problem in ERBB2-positive breast cancer, as demonstrated by the focus on this end point in multiple studies of novel ERBB2-targeting approaches in metastatic breast cancer.[27-30] Phase 2 studies suggest modest activity of lapatinib-based combinations upon CNS end points[9,10] as predicted by preclinical data reporting some CNS penetration.[31-33] However, a prospective randomized trial, CEREBEL,[27] found no difference between lapatinib-capecitabine and trastuzumab-capecitabine with respect to CNS end points in patients with metastatic ERBB2-positive disease without CNS involvement at entry, although the rates of CNS progression were very low (3%-5%). In the NEfERT-T trial, CNS recurrence and timing were prospectively defined secondary efficacy end points, and we observed a reduction in the frequency of symptomatic or progressive CNS recurrences, as well as an improvement in the time to the occurrence of these events in the neratinib-paclitaxel group compared with the trastuzumab-paclitaxel group. Between-group differences remained after adjusting for imbalances in CNS metastases at baseline. As the study protocol did not include screening for CNS metastases but rather identified CNS metastases on presentation of symptoms, it is likely that CNS events were underestimated in this study. We acknowledge that there was an imbalance between study arms with twice as many patients having prior CNS disease at baseline in the control compared with the experimental arm and, therefore, a possible inherent bias toward imaging the brain in these patients that might have resulted in more frequent detection of CNS metastases in the control arm. We suggest that CNS outcomes with neratinib are worthy of further investigation in a large phase 3 trial which includes predefined CNS end points.

Diarrhea and gastrointestinal toxic effects (ie, nausea, vomiting) were the main adverse events associated with neratinib-paclitaxel and consistent with the safety profile previously documented for this combination,[14] although primary prophylaxis for diarrhea was not mandatory in NEfERT-T. Recent trials with neratinib show that diarrhea can be managed with intensive primary antidiarrheal prophylaxis administered with the first cycle of neratinib therapy.[15,16] Despite the lack of effective preventive measures in NEfERT-T, treatment exposure was similar in both treatment groups, overall health-related QoL was maintained, 12 of 240 patients (5%) required hospital admission because of diarrhea, and no grade 4 diarrhea was observed. Other common toxic effects observed in NEfERT-T were those typically associated with paclitaxel (ie, hematological events, peripheral neuropathy) that occurred at similar rates in both treatment groups.

The current landscape of treatment for ERBB2-positive breast cancer includes demonstration in the randomized phase 3 setting of survival benefits for pertuzumab-trastuzumab-paclitaxel compared with trastuzumab-paclitaxel alone in the first-line metastatic setting,[4,23] and ado-trastuzumab emtansine over lapatinib-capecitabine in the pretreated setting[34] but

Figure 2. Estimates for Progression-Free Survival, Overall Survival, and Cumulative Incidence of Symptomatic or Progressive Central Nervous System (CNS) Lesions



Panels show (A) the primary end point of progression-free survival in the intent-to-treat population; (B) overall survival in the intent-to-treat population; and (C) the cumulative incidence of symptomatic or progressive CNS lesions by competing risks method in the intent-to-treat population.

not in the first-line setting.[35] In the neoadjuvant and adjuvant settings, lapatinib-paclitaxel is less effective than trastuzumab-paclitaxel.[36-38] The NEfERT-T study, which demonstrates similar efficacy of neratinib-paclitaxel to trastuzumab-paclitaxel in the first-line metastatic setting, suggests that neratinib is no more effective than trastuzumab

in unselected ERBB2-positive breast cancer but may have a potential role in patients at risk for CNS metastatic events and has more side effects (particularly diarrhea). To investigate further the efficacy of neratinib in metastatic ERBB2-positive breast cancer, the National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation has recently initiated a phase 1b/2 study of neratinib in combination with ado-trastuzumab emtansine as second-line therapy (NCT02236000).

We acknowledge the limitations of this study, including changes to the study protocol, the most notable of which was a reduction in accrual goal from 1200 to 480 patients for aforementioned reasons. As such, the NEfERT-T study gives a preliminary, rather than definitive, understanding of the efficacy and safety of neratinib-paclitaxel in the first-line treatment of ERBB2-positive metastatic breast cancer. Furthermore, because patients with progressive or symptomatic CNS disease were excluded from this study, it is not possible to provide any estimate of efficacy in this subgroup.

Conclusions

Neratinib in combination with paclitaxel was not superior in terms of PFS compared with trastuzumab-paclitaxel in the first-line treatment of women with ERBB2-positive metastatic breast cancer but showed similar efficacy and may delay the onset and reduce the frequency of CNS metastases. Diarrhea was more common with neratinib-paclitaxel; this drug regimen requires aggressive primary prophylaxis of this adverse effect for the first cycle of therapy.

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Author Contributions: Dr Awada had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Awada, Colomer, Inoue, Kim.
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Statistical analysis: Xu, Yao.
Administrative, technical, or material support: Inoue, Bondarenko, Demetriou, Lee, Mehta, Wong.
Study supervision: Awada, Bose, Bryce, Carey.
Other: Badwe.

Conflict of Interest Disclosures: Drs Awada and Colomer received an honorarium from Wyeth in relation to the study in question for attending an advisory board meeting to discuss the early development of neratinib. Dr Inoue received research grants from Puma Biotechnology Inc and Pfizer in relation to the study in question. Dr Inoue also received research grants from Novartis, GlaxoSmithKline, Chugai, Taiho, Daiichi Sankyo and Nipponkayaku that are unrelated to the study but present 36 months prior to submission. Dr Lee received study drug support for investigator-initiated studies from GlaxoSmithKline and ASLAN Pharmaceuticals that are unrelated to the study in question but present during the 36 months prior to submission. Dr Kim received a research grant from Novartis that is unrelated to the study in question but present during the 36 months prior to submission. Dr Bachelot received research grants, personal fees and non-financial support from Roche and Novartis that were unrelated to the study in question but present during the 36 months prior to submission. Dr Bose is a consultant to Genentech/Roche for the MyPathway clinical trial and has received honoraria from Novartis, Genentech, and the Reinsurance Group of America (RGA) that are unrelated to the study in question but present during the 36 months prior to submission. Messrs Wong, Xu, and Yao and Dr Bryce are employed by one of the sponsors of the study in question (Puma Biotechnology, Inc.). No other conflicts are reported.

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