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/m² 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-stage1,2 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.3,10

Neratinib (Puma Biotechnology Inc) is an oral small-molecule tyrosine kinase inhibitor of ERBB1, ERBB2, and ERBB4 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 agent13 and in combination with various chemotherapeutic agents, including paclitaxel.14 Diarrhea is the most common toxic effect associated with neratinib13 and is now managed with intensive primary anti-diarrheal 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 to 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.

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 CHAT57 and HERNATA18 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.

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.

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/m² 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/m² 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 demographics (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 end point. 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.

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 2A). 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).
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 (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.

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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. 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,
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 points9,10 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 setting14 but...
not in the first-line setting.35 In the neoadjuvant and adjuvant settings, lapaatinib-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 Ib/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.

Conflict of Interest Disclosures: Drs Awada and Colomer received research support 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 Kirm 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 Boe is a consultant to Genentech/Roche for the MyPathway clinical trial and has received honoraria from Novartis, Genentech, and the Reinsureance 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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Role of the Funder/Sponsor: The sponsors were involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data. Puma Biotechnology, Inc was involved in the preparation and review of the manuscript.

Previous Presentation: This study was presented as a poster presentation at the 2015 American Society of Clinical Oncology Annual Meeting, May 29 to June 2, 2015: Chicago, Illinois.

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