Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With ≥ 2 HER2-Directed Regimens: Phase III NALA Trial

Cristina Saura, MD1; Mafalda Oliveira, MD, PhD2; Yin-Hsun Feng, MD, PhD2; Ming-Shen Dai, MD, PhD2; Shang-Wen Chen, MD1; Sara A. Hurvitz, MD, PhD1; Sung-Bae Kim, MD, PhD1; Beverly Moy, MD, PhD1; Suzette Delaloge, MD, MSc1; William Gradishar, MD2; Norikazu Masuda, MD, PhD2; Marketa Palacova, MD2; Maureen E. Trudeau, MD17; Johanna Mattson, MD, PhD12; Yoon Sim Yap, MBBS12; Ming-Feng Hou, MD11; Michelino De Laurentiis, MD, PhD4; Yu-Min Yeh, MD11; Hong-Tai Chang, MD16; Thomas Yau, MBBS, MD11; Hans Wildiers, MD, PhD11,12; Barbara Haley, MD20; Daniele Fagnani, MD21; Yen-Shen Lu, MD, PhD24; John Crown, MBChB23; Johnson Lin, MD24; Masato Takahashi, MD, PhD25; Toshimi Takano, MD26; Miki Yamaguchi, MD, PhD27; Takaaki Fujii, MD, PhD28; Bin Yao, MS29; Judith Bebchuk, ScD29; Kiana Keyvanjah, PharmD29; Richard Bryce, MBChB29; and Adam Brufsky, MD, PhD30; for the NALA Investigators

PURPOSE NALA (ClinicalTrials.gov identifier: NCT01808573) is a randomized, active-controlled, phase III trial comparing neratinib, an irreversible pan-HER tyrosine kinase inhibitor (TKI), plus capecitabine (N+C) against lapatinib, a reversible dual TKI, plus capecitabine (L+C) in patients with centrally confirmed HER2-positive, metastatic breast cancer (MBC) with ≥ 2 previous HER2-directed MBC regimens.

METHODS Patients, including those with stable, asymptomatic CNS disease, were randomly assigned 1:1 to neratinib (240 mg once every day) plus capecitabine (750 mg/m² twice a day 14 d/21 d) with loperamide prophylaxis, or to lapatinib (1,250 mg once every day) plus capecitabine (1,000 mg/m² twice a day 14 d/21 d). Coprimary end points were centrally confirmed progression-free survival (PFS) and overall survival (OS). NALA was considered positive if either primary end point was met (α split between end points). Secondary end points were time to CNS disease intervention, investigator-assessed PFS, objective response rate (ORR), duration of response (DoR), clinical benefit rate, safety, and health-related quality of life (HRQoL).

RESULTS A total of 621 patients from 28 countries were randomly assigned (N+C, n = 307; L+C, n = 314). Centrally reviewed PFS was improved with N+C (hazard ratio [HR], 0.76; 95% CI, 0.63 to 0.93; stratified log-rank P = .0059). The OS HR was 0.88 (95% CI, 0.72 to 1.07; P = .2098). Fewer interventions for CNS disease occurred with N+C versus L+C (cumulative incidence, 22.8% vs 29.2%; P = .0043). ORRs were N+C 32.8% (95% CI, 27.1 to 38.9) and L+C 26.7% (95% CI, 21.5 to 32.4; P = .1201); median DoR was 8.5 versus 5.6 months, respectively (HR, 0.50; 95% CI, 0.33 to 0.74; P = .0004). The most common all-grade adverse events were diarrhea (N+C 83% vs L+C 66%) and nausea (53% vs 42%). Discontinuation rates and HRQoL were similar between groups.

CONCLUSION N+C significantly improved PFS and time to intervention for CNS disease versus L+C. No new N+C safety signals were observed.

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INTRODUCTION Systemic treatment of HER2-positive metastatic breast cancer (MBC) may include trastuzumab, pertuzumab, and trastuzumab emtansine (T-DM1),1,2 which demonstrated efficacy in the CLEOPATRA (ClinicalTrials.gov identifier: NCT00567190),3 EMILIA (ClinicalTrials.gov identifier: NCT00829166),4 and TH3RESA (ClinicalTrials.gov identifier: NCT01419197)5 studies. Lapatinib, a reversible, dual tyrosine kinase inhibitor (TKI), plus capecitabine (L+C) was superior to capecitabine in the EGF100151 study (ClinicalTrials.gov identifier: NCT00078572),6 which led to approval of L+C for HER2-positive MBC in patients who received prior anthracycline, a taxane, and trastuzumab.7 Neratinib (Nerlyx; Puma Biotechnology, Los Angeles, CA) is an irreversible pan-HER (HER1, HER2, and HER4) TKI,8 which demonstrated preliminary efficacy in combination with capecitabine (N+C) in MBC.9,10 Neratinib was approved by the European Medicines Agency for
CONTEXT

Key Objective
The NALA trial (N = 621) was designed to compare neratinib plus capecitabine (N+C) versus lapatinib plus capecitabine (L+C) in patients with HER2-positive metastatic breast cancer (MBC) who received ≥ 2 HER2-directed regimens in the metastatic setting, including those with asymptomatic or stable (treated or untreated) CNS metastases.

Knowledge Generated
N+C was superior to L+C in NALA: there was a statistically significant benefit in progression-free survival (PFS) favoring N+C (hazard ratio, 0.76; 1-year PFS, N+C 29% v L+C 15%), translating to a 2.2-month mean improvement in PFS. Significantly fewer patients treated with N+C required intervention for CNS disease, suggesting prevention of—or delayed time to development of—CNS disease compared with L+C.

Relevance
NALA is the first study to demonstrate superiority of one HER2-directed tyrosine kinase inhibitor over another in MBC. N+C is an appropriate treatment option for patients with HER2-positive MBC progressing after ≥ 2 lines of HER2-directed treatment.

extended adjuvant treatment of early-stage, hormone receptor–positive, HER2-positive breast cancer and the US Food and Drug Administration (FDA) for extended adjuvant treatment of early-stage, HER2-positive breast cancer on the basis of the phase III ExteNET trial (ClinicalTrials.gov identifier: NCT00878709). On the basis of results described herein, the FDA approved neratinib in combination with capecitabine for patients with advanced/metastatic disease after ≥ 2 prior lines of HER2-directed therapy in MBC. The primary toxicity associated with neratinib is diarrhea. In the NEIERT-T trial (ClinicalTrials.gov identifier: NCT00915018), which did not mandate primary diarrhea prophylaxis, 30% of patients had grade 3 diarrhea; prophylaxis or dose-escalation regimens reduced grade 3 diarrhea to as little as 15% in the extended adjuvant CONTROL trial (ClinicalTrials.gov identifier: NCT02400476).

Although overall survival (OS) has improved dramatically in HER2-positive MBC in the past decade, it remains much higher for de novo MBC than relapsed disease, and other challenges continue, including de novo and acquired resistance to HER2-targeted antibody therapy. Furthermore, pertuzumab or T-DM1 efficacy in MBC is unknown after adjuvant treatment with either agent, and few agents have demonstrated activity in reducing the incidence of CNS metastases. Although CNS recurrence is a particular challenge in breast cancer, the LANDSCAPE study (ClinicalTrials.gov identifier: NCT00967031) reported a CNS response rate of 66% with lapatinib in HER2-positive MBC and previously untreated brain metastases, and EGF100151 reported numerically fewer CNS metastases with L+C versus capecitabine in HER2-positive advanced breast cancer. Neratinib has demonstrated activity in preventing and treating brain metastases in HER2-positive MBC. In NEIERT-T, CNS recurrences were lower (relative risk, 0.48; 95% CI, 0.29 to 0.79; P = .002) and time to CNS metastases delayed (hazard ratio [HR], 0.45; 95% CI, 0.26 to 0.78; P = .004) with neratinib plus paclitaxel versus trastuzumab plus paclitaxel. In TBCRC 022 (ClinicalTrials.gov identifier: NCT01494662), N+C was also active against refractory, HER2-positive breast cancer brain metastases, with composite CNS overall response rates of 49% in lapatinib-naïve patients and 33% in lapatinib-pretreated patients.

On the basis of prior phase I/II safety and efficacy results for N+C in HER2-positive MBC, the NALA trial was designed to compare N+C versus L+C in patients with HER2-positive MBC who received ≥ 2 HER2-directed regimens in the metastatic setting, including those with asymptomatic CNS metastases.

METHODS

Study Design
NALA is a randomized, active-controlled, phase III trial comparing N+C and L+C in HER2-positive MBC. Eligible patients were age ≥ 18 years, with an Eastern Cooperative Oncology Group performance status ≤ 1, centrally confirmed HER2-positive MBC, and ≥ 2 previous HER2-directed therapies for MBC. Patients with brain metastases were eligible unless they had symptomatic or unstable brain metastases (Data Supplement). Eligible patients were randomly assigned (1:1) to N+C or L+C. The randomization sequence was stratified by: hormone receptor status (hormone receptor positive [estrogen or progesterone receptor positive or both; positivity defined per DAKO test kit]) v hormone receptor negative [estrogen and progesterone receptor negative]), number of previous HER2-directed therapies for MBC (2 or ≥ 3), geographic region (North America or Europe [including Israel] or rest of world), and visceral disease (yes/no).

The protocol was approved by national/institutional ethics committees at participating sites and conducted in
Treatments were randomly assigned to N+C (neratinib 240 mg orally once daily continuously in 21-day cycles with no break between cycles, plus capecitabine 1,500 mg/m² orally once daily in 2 evenly spaced doses [750 mg/m² twice a day] on days 1-14 of 21-day cycles) or L+C (lapatinib 1,250 mg orally once continuously, plus capecitabine 2,000 mg/m² orally daily in 2 evenly spaced doses [1,000 mg/m² twice a day] on days 1-14 of 21-day cycles). The capecitabine dose in N+C was based on that used in the phase II/I trial of N+C in HER2-positive MBC (maximum tolerated dose, 1,500 mg/m²/d in combination with neratinib). Prophylactic antidiarrheal medication was mandated in N+C for the duration of cycle 1 (Appendix, online only). The L+C doses and the decision to not include mandatory antidiarrheal prophylaxis in L+C was based on the prescribing information. Concomitant endocrine therapy was not permitted.

Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). Patient assessments are detailed in the Appendix.

Outcomes and Procedures
Coprimary end points were independently adjudicated PFS (the interval from date of random assignment until first date on which progression [per RECIST; version 1.1] or death due to any cause was documented, censored at the last assessable evaluation or at initiation of new anticancer therapy; blinded central review) and OS (time from random assignment to death due to any cause). Tumor assessments were performed every 6 weeks using computed tomography and magnetic resonance imaging (MRI). Baseline MRI and screening for CNS metastases were not mandated. Secondary end points were: time to intervention for metastatic CNS disease (included radiotherapy, surgery, or CNS-directed concomitant medications), investigator-assessed PFS, objective response rate (ORR), duration of response (DoR), and clinical benefit rate (CBR; complete response + partial response + stable disease lasting ≥ 24 weeks; Appendix).

Other secondary end points included safety and health-related quality of life (HRQoL; assessed every 6 weeks), measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ-C30; version 3), EORTC breast cancer–specific module (QLQ-BR23), and EuroQol 5-dimensions 5-levels (EQ-5D-5L) health status questionnaire.

Statistical Analysis
Coprimary end points were analyzed using an overall type I error rate of 0.01 for PFS and 0.04 for OS. It was estimated that 419 PFS events and 378 OS events were required to obtain 85% power to detect an HR (control v treatment) of 0.70 for PFS and 0.725 for OS. The primary analysis of each end point was event driven. The trial was considered positive if either PFS or OS were statistically significant at the split α level. Approximately 600 patients were to be enrolled and randomly assigned equally between the 2 groups. No interim analyses were performed.

Primary efficacy end points were assessed in the intention-to-treat population. Safety analyses were conducted for all patients who received ≥ 1 dose of investigational treatment. The primary analysis method was stratified log-rank test for hypothesis testing and stratified Cox proportional hazards model to estimate HRs and 95% CIs. Differences between treatment groups were examined using a log-rank test statistic stratified by hormone receptor status, number of prior HER2-directed regimens in the metastatic setting, and disease location. If the proportional hazards assumption was not met, a prespecified supportive analysis on the basis of restricted means was added and performed with restrictions at 24 months for PFS and 48 months for OS. The Kaplan-Meier method was used to represent time-to-event end points.

Time to intervention for CNS disease was analyzed after PFS and OS end points were met using a competing risk model, with death considered a competing risk. Patients with no intervention for CNS metastases and still alive were censored on the date last known to be alive. The stratified Gray’s test was used to assess equality of cumulative incidence functions between groups. Subgroup analyses by demographic variables and randomization stratification factors were presented using forest plots.

ORR and CBR were analyzed using Cochran-Mantel-Haenszel χ² tests on the basis of patients with measurable disease at baseline. Investigator-assessed PFS and DoR (for patients with an objective response) were analyzed using similar methods to the primary efficacy end points. Analyses were performed using SAS (version 9.1; SAS Institute, Cary, NC).

An Independent Data Monitoring Committee acted in an advisory capacity concerning patient safeguarding, assessing interim safety data, and monitoring overall study conduct.

NALA is registered with Clinicaltrials.gov (NCT01808573).

Data Sharing
Data are available on request from the corresponding author (Cristina Saura).
**RESULTS**

**Patients**

Between May 29, 2013 and July 21, 2017, 621 patients (618 women, 3 men) were enrolled at 203 sites in 28 countries in Europe, North and South America, Asia, and Australia. Patients randomly assigned to study treatment constituted the intention-to-treat population (N+L+C, n = 307; L+C, n = 314; **Fig 1**). At the analysis cutoff date (September 28, 2018), the safety population included 614 patients (N+L+C, n = 303; L+C, n = 311). Baseline characteristics were well balanced between treatment groups (Table 1).

**Efficacy**

At the cutoff date, there were 433 PFS events on the basis of central review and 410 deaths. The median follow-up duration was 29.9 months (interquartile range [IQR], 21.9-40.6 months). Treatment with N+C significantly improved PFS as assessed by central review (HR, 0.76; 95% CI, 0.63 to 0.93; stratified log-rank P = .0059; **Fig 2A**). Although a numerical difference favoring N+C was observed for OS, statistical significance was not reached (HR, 0.88; 95% CI, 0.72 to 1.07; stratified log-rank P = .2086; **Fig 2B**). Kaplan-Meier curves for PFS overlapped during the first 24 weeks and clearly separated after 24 weeks. The shape of the PFS curves indicated the proportional hazards assumption was violated, which was confirmed by statistical testing. The restricted means analysis (P = .0003) was performed and was supportive of the primary analysis, demonstrating a mean PFS difference of 2.2 (95% CI, 1.0 to 3.3) months in favor of N+C (Table 2; **Appendix Table A1**, online only).

Most prespecified subgroup analyses of PFS showed a neratinib benefit: most point estimates for HRs were < 1.0 (**Appendix Fig A1A**, online only). Two factors had interaction P values < .05: hormone receptor status (P < .001) and disease location (P = .007; Kaplan-Meier curves for PFS shown in **Appendix Figs A2 and A3**, online only). Subgroups were also examined for OS, but the interaction test was not significant for the subgroups analyzed.
| Characteristic                             | N+C (n = 307) | L+C (n = 314) |
|-------------------------------------------|---------------|---------------|
| Age, years                                | 55 (47-63)    | 54 (47-62)    |
| Age < 65 years                            | 244 (79.5)    | 248 (79.0)    |
| Sex                                       |               |               |
| Female                                    | 307 (100)     | 311 (99.0)    |
| Male                                      | 0             | 3 (1.0)       |
| ECOG performance status at enrollment     |               |               |
| 0                                         | 174 (56.7)    | 164 (52.2)    |
| 1                                         | 133 (43.3)    | 150 (47.8)    |
| Geographic region                         |               |               |
| Europe                                    | 121 (39.4)    | 123 (39.2)    |
| North America                             | 59 (19.2)     | 65 (20.7)     |
| Rest of world                             | 127 (41.4)    | 126 (40.1)    |
| Hormone receptor status<sup>a</sup>       |               |               |
| Positive                                  | 181 (59.0)    | 186 (59.2)    |
| Negative                                  | 126 (41.0)    | 128 (40.8)    |
| Disease location at enrollment            |               |               |
| Nonvisceral only                          | 48 (15.6)     | 44 (14.0)     |
| Lymph node                                | 27 (8.8)      | 29 (9.2)      |
| Bone                                      | 21 (6.8)      | 21 (6.7)      |
| Visceral only and visceral/nonvisceral    | 259 (84.4)    | 270 (86.0)    |
| Lung                                      | 156 (50.8)    | 174 (55.4)    |
| Liver<sup>b</sup>                         | 134 (43.6)    | 148 (47.1)    |
| Brain<sup>b</sup>                         | 51 (16.6)     | 50 (15.9)     |
| Lymph node                                | 130 (42.3)    | 159 (50.6)    |
| Bone                                      | 128 (41.7)    | 148 (47.1)    |
| Previous systemic anticancer therapy      |               |               |
| Neoadjuvant                               | 52 (16.9)     | 73 (23.2)     |
| Adjuvant                                  | 146 (47.6)    | 149 (47.5)    |
| Metastatic/locally advanced               | 307 (100)     | 313 (99.7)    |
| No. of previous HER2-directed regimens<sup>c</sup> | 2   | | |
| 2                                         | 215 (70.0)    | 215 (68.5)    |
| ≥ 3                                       | 92 (30.0)     | 99 (31.5)     |
| Prior HER2 therapies for metastatic breast cancer | | |
| Trastuzumab only                          | 124 (40.4)    | 113 (36.0)    |
| Trastuzumab, pertuzumab                   | 24 (7.8)      | 23 (7.3)      |
| Trastuzumab, T-DM1                        | 58 (18.9)     | 64 (20.4)     |
| Trastuzumab, pertuzumab, T-DM1            | 101 (32.9)    | 114 (36.3)    |

NOTE. Data presented as No. (%) or median (interquartile range). Because of rounding, not all percentages add up to 100%.

Abbreviations: C, capecitabine; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; L, lapatinib; N, neratinib; PR, progesterone receptor; T-DM1, trastuzumab emtansine.

<sup>a</sup>Hormone receptor positive: ER positive, PR positive, or both. Hormone receptor negative: ER and PR negative.

<sup>b</sup>Two patients in each arm indicated location as other, with additional explanations indicating brain.

<sup>c</sup>Prior non–HER2-directed therapies not included in this table.
Appendix Fig A1B): Kaplan-Meier OS curves according to hormone receptor status and disease location are shown in Appendix Figures A4 and A5, online only.

The overall cumulative incidence of intervention for CNS disease was 22.8% (95% CI, 15.5% to 30.9%) for neratinib versus 29.2% (95% CI, 22.5% to 36.1%) for lapatinib (Gray’s test for equality, \( P = .043 \); Fig 3). Overall, 130/621 patients had interventions for CNS disease, 55 (17.9%) in the neratinib group and 75 (23.9%) in the lapatinib group (Appendix Table A2, online only).

The confirmed ORR in patients with measurable disease at screening was 32.8% (84/256 patients; 95% CI, 27.1% to 38.9%) for N+C and 26.7% (72/270 patients; 95% CI, 21.5% to 32.4%) for L+C (\( P = .1201 \); Table 2). The median DoR was 8.5 (95% CI, 5.6 to 11.2) months for neratinib versus 5.6 (95% CI, 4.2 to 6.4) months for lapatinib (HR, 0.50; 95% CI, 0.33 to 0.74; \( P = .0004 \); Appendix Fig A6, online only). A larger proportion of N+C patients had responses lasting \( \geq \) 12 months versus L+C (36.9% v 16.8%). The CBR was higher in patients treated with N+C versus L+C (45% v 36%; \( P = .0328 \); Table 2).

Safety
Median treatment duration was 5.7 (IQR, 2.7-10.4) months for neratinib and 4.4 (IQR, 2.3-7.1) months for lapatinib (Appendix Table A3, online only). The safety population included 614 patients (neratinib, \( n = 303 \); lapatinib, \( n = 311 \)): 611 patients had treatment-emergent AEs of any grade, 196 had a serious treatment-emergent AE (N+C, \( n = 103 \) [34.0%]; L+C, \( n = 93 \) [29.9%]), and 588 had treatment-related AEs (N+C, \( n = 289 \) [95.4%]; L+C, \( n = 299 \) [96.1%]; Appendix Table A4, online only).

Diarrhea, nausea, palmar-plantar erythrodysesthesia syndrome, and vomiting were the most common treatment-emergent
TABLE 2. Efficacy End Point Analyses in the Intention-to-Treat Population

| Variablea | N+C (n = 307) | L+C (n = 314) | Hazard Ratio (95% CI)b | Pc |
|------------|---------------|---------------|------------------------|----|
| PFS        | —             | —             | 0.76 (0.63 to 0.93)    | .0059 |
| Mean PFS, months | 8.8 (7.8 to 9.8) | 6.6 (5.9 to 7.4) | — | — |
| Median PFS, months | 5.6 (4.9 to 6.9) | 5.5 (4.3 to 5.6) | — | — |
| Kaplan-Meier estimate, % | — | — | — | — |
| 6 months | 47.2 (41.1 to 53.1) | 37.8 (31.8 to 43.9) | — | — |
| 12 months | 28.8 (23.1 to 34.8) | 14.8 (10.3 to 20.1) | — | — |
| 18 months | 16.3 (11.3 to 22.1) | 7.4 (4.1 to 12.0) | — | — |
| Overall survival | — | — | 0.881 (0.72 to 1.07) | .2086 |
| Mean overall survival, months (locally assessed) | 24.0 (22.1 to 25.9) | 22.2 (20.4 to 24.0) | — | — |
| Intervention for CNS disease, cumulative incidence (locally assessed) | 22.8 (15.5 to 30.9) | 29.2 (22.5 to 36.1) | 0.78 (0.60 to 1.01) | .043d |
| Best overall response* (n = 256) | — | — | — | — |
| Complete response | 4 (1.6) | 1 (0.4) | — | — |
| Partial response | 100 (39.1) | 91 (33.7) | — | — |
| Stable disease | 90 (35.2) | 119 (44.1) | — | — |
| Progressive disease | 47 (18.4) | 41 (15.2) | — | — |
| Not evaluable | 2 (0.8) | 2 (0.7) | — | — |
| Unavailable | 13 (5.1) | 16 (5.9) | — | — |
| Objective response rate, %f | 32.8 (27.1 to 38.9) | 26.7 (21.5 to 32.4) | — | .1201e |
| Clinical benefit rate, %f | 44.5 (38.3 to 50.8) | 35.6 (29.8 to 41.6) | — | .0328e |

NOTE. Data are presented as No. (%) or median (95% CI) unless otherwise stated. Definitions for efficacy end points are provided in the Appendix. Abbreviations: C, capecitabine; CI, confidence interval; L, lapatinib; N, neratinib; PFS, progression-free survival.

*aCentrally confirmed or assessed unless otherwise stated.

bStratified Cox proportional hazards model.

cStratified 2-sided log-rank test.

dGray's method.

eCochran-Mantel-Haenszel test adjusted by hormone receptor status, number of prior HER2-directed regimens in metastatic setting, and visceral disease versus nonvisceral disease.

fConfirmed responses.

AEs of any grade in the overall population (Table 3). Grade 3 diarrhea occurred in 74 patients (24.4%) with neratinib and 39 patients (12.5%) with lapatinib; there was no grade 4 diarrhea. Grade 3 diarrhea was most prevalent during the first cycle (N+C 16%, L+C 5%; Appendix Table A5, online only).

FIG 3. Intervention for CNS disease.
There were no new safety concerns for cardiac events. The incidence of cardiac arrhythmia was 3.3% for N+C and 3.5% for L+C. The incidence of ischemic heart disease was 0.7% for N+C and 0.6% for L+C. The incidence of QT prolongation was 2.3% for N+C and 3.9% for L+C and of left ventricular ejection fraction decrease was 4.3% for N+C and 2.3% for L+C.

Quality of Life

Patients were included in the HRQoL population if they had received study treatment and had a baseline assessment and ≥1 postbaseline assessment (up to last dose day +28 days) for that scale. Higher scores (range, 0-100) represent higher levels of functioning; a 10-point difference was considered the minimum important difference. Questionnaire completion rates were 91% for patients in the HRQoL population (EORTC QLQ-C30). Mean QLQ-C30 summary score and Global Health Status/QOL subscale scores were similar between the arms over time (Fig 4). None of the observed changes over time or between groups at individual time points were greater than the minimum important difference.

DISCUSSION

The NALA trial demonstrated superiority of N+C over L+C after ≥2 lines of HER2-directed therapies in the metastatic setting. There was a statistically significant benefit in PFS favoring N+C (HR, 0.76; 1-year PFS, N+C 29% v L+C 15%), translating to a 2.2-month mean PFS improvement without a significant benefit in OS. Significantly fewer patients in N+C versus L+C required intervention for CNS disease, suggesting prevention of—or delayed time to development of—CNS disease.

DoR was significantly prolonged in patients treated with N+C versus L+C (8.5 v 5.6 months, respectively). This DoR was promising, considering patients’ prior treatment load in the metastatic setting (99.7% trastuzumab, 41.7% pertuzumab, 54.3% T-DM1) and may explain the clear separation of PFS curves beyond 24 weeks. The largely indistinguishable PFS curves up until 24 weeks suggest a group of patients resistant to HER2-directed therapies, capecitabine, or both, with patients having received ≥2 lines of HER2-directed therapies. Ongoing biomarker analysis may help identify patients likely to benefit from N+C.

Patients in NALA who had hormone receptor–negative disease derived the greatest PFS benefit from N+C, consistent with the neoadjuvant I-SPY study (ClinicalTrials.gov identifier: NCT01042379) but in contrast to the extended adjuvant ExteNET trial, which showed a greater benefit in hormone receptor–positive disease. Although these differences may simply be spurious findings due to the exploratory nature of the subgroup analyses, they are more likely explained by HER2 and estrogen-receptor crosstalk. The existence of bidirectional crosstalk between HER2 and estrogen-receptor

### TABLE 3. Treatment-Emergent AEs Occurring in ≥10% of Patients in the Safety Population

| AE                  | N+C (n = 303) | L+C (n = 311) |
|---------------------|---------------|---------------|
|                     | All Grade     | Grade 3/4     | All Grade     | Grade 3/4     |
| Diarrhea            | 252 (83.2)    | 74 (24.4)     | 206 (66.2)    | 39 (12.5)     |
| Nausea              | 161 (53.1)    | 13 (4.3)      | 132 (42.4)    | 9 (2.9)       |
| PPE syndrome        | 139 (45.9)    | 29 (9.6)      | 175 (56.3)    | 35 (11.3)     |
| Vomiting            | 138 (45.5)    | 12 (4.0)      | 97 (31.2)     | 6 (1.9)       |
| Decreased appetite  | 107 (35.3)    | 8 (2.6)       | 67 (21.5)     | 7 (2.3)       |
| Fatigue             | 104 (34.3)    | 9 (3.0)       | 97 (31.2)     | 10 (3.2)      |
| Constipation        | 94 (31.0)     | 4 (1.3)       | 41 (13.2)     | 1 (0.3)       |
| Stomatitis          | 62 (20.5)     | 6 (2.0)       | 83 (26.7)     | 8 (2.6)       |
| Weight decreased    | 60 (19.8)     | 1 (0.3)       | 41 (13.2)     | 2 (0.6)       |
| Rash                | 30 (9.9)      | 0             | 69 (22.2)     | 2 (0.6)       |
| Anemia              | 45 (14.9)     | 6 (2.0)       | 51 (16.4)     | 11 (3.5)      |
| Dizziness           | 43 (14.2)     | 1 (0.3)       | 31 (10.0)     | 2 (0.6)       |
| Cough               | 37 (12.2)     | 0             | 34 (10.9)     | 9 (3.0)       |
| Abdominal pain      | 36 (11.9)     | 3 (1.0)       | 45 (14.5)     | 6 (1.9)       |
| Asthenia            | 36 (11.9)     | 8 (2.6)       | 36 (11.6)     | 5 (1.6)       |
| Hypokalemia         | 35 (11.6)     | 14 (4.6)      | 44 (14.1)     | 20 (6.4)      |
| Paronychia          | 35 (11.6)     | 2 (0.7)       | 49 (15.8)     | 3 (1.0)       |
| Pyrexia             | 33 (10.9)     | 0             | 32 (10.3)     | 1 (0.3)       |
| Headache            | 32 (10.6)     | 1 (0.3)       | 51 (16.4)     | 3 (1.0)       |

NOTE. Data are presented as No. (%). Grade 5 events for N+C (n = 8) were abdominal infection, lung infection, cerebral hemotoma, increased intracranial pressure, multiple organ dysfunction syndrome, hepatic failure, acute kidney injury, and atelectasis (all n = 1). Grade 5 events for L+C (n = 10) were bactereemia, subarachnoid hemorrhage, hepatic failure, fulminant hepatitis, pulmonary embolism, cardiac arrest, cardiac tamponade, and shock (all n = 1), and general physical health deterioration (n = 2); the fulminant hepatitis observed in the L+C group was the only grade 5 AE considered to be related to treatment. Treatment-emergent AEs leading to discontinuation of any study drug occurred in 98 patients (16.0%) overall (N+C, n = 42 [13.9%]; L+C, n = 56 [18.0%]); AEs leading to dose reduction occurred in 165 patients (26.9%) overall (N+C, n = 72 [23.8%]; L+C, n = 93 [29.3%]); and AEs leading to dose holds occurred in 394 patients (64.2%) overall (N+C, n = 194 [64.0%]; L+C, n = 200 [64.3%]; Appendix Table A4).

Abbreviations: AE, adverse event; C, capecitabine; L, lapatinib; N, neratinib; PPE, palmar-plantar erythrodysesthesia.

Diarrhea resulted in dose reduction of study drug in 16 patients (5.3%) with neratinib and 13 patients (4.2%) with lapatinib; mean capecitabine dose intensity was 929 mg/m²/day for N+C and 1,143 mg/m²/day for L+C (Appendix Table A3, online only). Diarrhea resulted in permanent discontinuation in 8 (2.6%) N+C and 7 (2.3%) L+C patients. Antidiarrheal medication was used by 298 patients in N+C (98.3%) and 193 patients (62.1%) in L+C. Loperamide (54% overall; N+C 77%; L+C 31%), loperamide hydrochloride (30% overall; N+C 30%; L+C 30%), and diphenoxylate and atropine combination (8% overall; N+C 10%; L+C 6%) were the most commonly used antidiarrheals.
pathways means that estrogen-receptor signaling may be activated with inhibition of HER2 alone. The ExteNET study in the early-disease setting permitted endocrine therapy in hormone receptor–positive patients, whereas NALA and I-SPY, which combined neratinib with a chemotherapeutic agent, did not include concomitant endocrine therapy for hormone receptor–positive disease, as this is not recommended in the advanced setting.

The CNS is a frequent site of progression in HER2-positive MBC, with 30% to 55% of patients developing CNS metastases. Patients with asymptomatic or stable CNS brain metastases (treated or untreated) were eligible for NALA, including those on stable corticosteroid doses. Although baseline scans were not mandated, 16% (101/621) of included patients had known brain disease at baseline. Fewer patients in N+C versus L+C required intervention for CNS metastases (cumulative incidence of intervention, 22.8% vs 29.2%, respectively). This is consistent with findings from NEFERT-T, which reported a benefit for neratinib in patients with CNS metastases, and TBCRC 022, which showed activity against refractory HER2-positive breast cancer brain metastases.

FDA approval of neratinib in third-line MBC on the basis of NALA follows approval of trastuzumab deruxtecan in the same setting (DS-8201; Daiichi Sankyo and AstraZeneca). The single-arm DESTINY-Breast01 trial (ClinicalTrials.gov identifier: NCT03248492) demonstrated a 60.9% ORR and median PFS duration of 16.4 (95% CI, 12.7 to not reached) months; interstitial lung disease, reported in 13.6% of the patients, was fatal in 2.2%. The antibody–drug conjugate mechanism of action of DS-8201 clearly distinguishes this agent from neratinib and other TKIs like tucatinib. The HER2Climb trial (ClinicalTrials.gov identifier: NCT02614794) compared the tucatinib-trastuzumab-capecitabine triplet versus placebo-trastuzumab-capecitabine (ie, dual HER2 control in the treatment arm versus a single...
Neratinib vs Lapatinib in Previously Treated HER2+ MBC: NALA Trial

HER2 agent in the control arm). The trial demonstrated a significant PFS benefit for tucatinib versus placebo (HR, 0.54; 1-year PFS: tucatinib-capecitabine-trastuzumab, 33.1% vs placebo-capecitabine-trastuzumab, 12.3%), translating to a 2.2-month median PFS benefit and significant OS benefit.\textsuperscript{34} HER2Climb mandated scans at baseline and enrolled a substantial proportion of patients with brain metastases (47.5% overall). The 3 trials differed in design: DESTINY-Breast01 included a single arm, HER2Climb compared adding a TKI versus placebo to the trastuzumab and capecitabine combination, and NALA compared 2 TKIs in combination with capecitabine.

Safety data in NALA were consistent with previous studies. Diarrhea was managed with mandatory prophylaxis in cycle 1 and loperamide as needed thereafter and was less severe than observed previously (24% grade 3 diarrhea with N+C in NALA vs 30% in NEfERT-T\textsuperscript{19} and 40% in ExteNET\textsuperscript{13}). The duration of grade 3 diarrhea and rate of diarrhea-related discontinuations (N+C 2.6% vs L+C 2.3%) were similar between groups. HRQoL was generally maintained, supporting the use of neratinib with appropriate management strategies.

Limitations of the study exist. N+C used a lower capecitabine dose (1,500 mg/m\textsuperscript{2} days 1-14 every 3 weeks) than L+C (2,000 mg/m\textsuperscript{2} days 1-14 every 3 weeks); only 35% of patients in NALA received previous treatment with trastuzumab, pertuzumab, and T-DM1, which may be considered standard of care for MBC; and HER2 status was largely determined from primary tumor tissue (63%). Furthermore, the presence of CNS disease at baseline was not confirmed with MRI.

In conclusion, NALA is the first study to demonstrate superiority of one HER2-directed TKI over another in MBC and provides evidence for the efficacy and tolerability of N+C in this setting. The primary end point of centrally assessed PFS was significantly improved with N+C versus L+C, and there were favorable outcomes across secondary end points, including DoR and time to intervention for CNS disease. N+C is an appropriate treatment option for patients with HER2-positive MBC progressing after ≥ 2 lines of HER2-directed treatment.

AFFILIATIONS
1Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology (VHIO), SOLTI Breast Cancer Cooperative Group, Barcelona, Spain
2Chi Mei Medical Centre, Liouying, Tainan, Taiwan and Tri-Service General Hospital, Taipei, Taiwan
3University of California Los Angeles/Jonsson Comprehensive Cancer Center, Los Angeles, CA
4University of Ulsan College of Medicine, Seoul, Republic of Korea
5Massachusetts General Hospital Cancer Center, Boston, MA
6Gustave Roussy, Villejuif, France
7Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL
8National Hospital Organization, Osaka National Hospital, Osaka, Japan
9Masaryk Memorial Cancer Institute, Brno, Czech Republic
10Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
11Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland
12National Cancer Centre Singapore, Singapore
13Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
14National Cancer Institute Fondazione Pascale, Napoli, Italy
15National Cheng Kung University, Tainan, Taiwan
16Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
17Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong
18University Hospital Leuven, Leuven, Belgium
19Department of Oncology, KU Leuven, Leuven, Belgium
20UT Southwestern Medical Center, Dallas, TX
21ASST di Vimercate, Vimercate, Italy
22National Taiwan University Hospital, Taipei City, Taiwan
23St Vincent’s University Hospital, Dublin, Ireland
24MacKay Memorial Hospital, Taipei, Taiwan
25National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan
26Toranomon Hospital, Tokyo, Japan
27Department of Breast Surgery, JCHO Kurume General Hospital, Kurume, Japan
28Graduate School of Medicine, Gunma University, Gunma, Japan
29Puma Biotechnology, Los Angeles, CA
30Magee-Womens Hospital of UPMC, Pittsburgh, PA
31Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology (VHIO), SOLTI Breast Cancer Cooperative Group, Barcelona, Spain
32Chutoran Medical Centre, Liouying, Tainan, Taiwan and Tri-Service General Hospital, Taipei, Taiwan
33University of California Los Angeles/Jonsson Comprehensive Cancer Center, Los Angeles, CA
34University of Ulsan College of Medicine, Seoul, Republic of Korea
35Massachusetts General Hospital Cancer Center, Boston, MA
36Gustave Roussy, Villejuif, France
37Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL
38National Hospital Organization, Osaka National Hospital, Osaka, Japan
39Masaryk Memorial Cancer Institute, Brno, Czech Republic
40Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
41Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland
42National Cancer Centre Singapore, Singapore
43Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
44National Cancer Institute Fondazione Pascale, Napoli, Italy
45National Cheng Kung University, Tainan, Taiwan
46Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
47Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong
48University Hospital Leuven, Leuven, Belgium
49Department of Oncology, KU Leuven, Leuven, Belgium
50UT Southwestern Medical Center, Dallas, TX
51ASST di Vimercate, Vimercate, Italy
52National Taiwan University Hospital, Taipei City, Taiwan
53St Vincent’s University Hospital, Dublin, Ireland
54MacKay Memorial Hospital, Taipei, Taiwan
55National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan
56Toranomon Hospital, Tokyo, Japan
57Department of Breast Surgery, JCHO Kurume General Hospital, Kurume, Japan
58Graduate School of Medicine, Gunma University, Gunma, Japan
59Puma Biotechnology, Los Angeles, CA
60Magee-Womens Hospital of UPMC, Pittsburgh, PA
61Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology (VHIO), SOLTI Breast Cancer Cooperative Group, Barcelona, Spain
62Chutoran Medical Centre, Liouying, Tainan, Taiwan and Tri-Service General Hospital, Taipei, Taiwan
63University of California Los Angeles/Jonsson Comprehensive Cancer Center, Los Angeles, CA
64University of Ulsan College of Medicine, Seoul, Republic of Korea
65Massachusetts General Hospital Cancer Center, Boston, MA
66Gustave Roussy, Villejuif, France
67Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL
68National Hospital Organization, Osaka National Hospital, Osaka, Japan
69Masaryk Memorial Cancer Institute, Brno, Czech Republic
70Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
71Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland
72National Cancer Centre Singapore, Singapore
73Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
74National Cancer Institute Fondazione Pascale, Napoli, Italy
75National Cheng Kung University, Tainan, Taiwan
76Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
77Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong
78University Hospital Leuven, Leuven, Belgium
79Department of Oncology, KU Leuven, Leuven, Belgium
80UT Southwestern Medical Center, Dallas, TX
81ASST di Vimercate, Vimercate, Italy
82National Taiwan University Hospital, Taipei City, Taiwan
83St Vincent’s University Hospital, Dublin, Ireland
84MacKay Memorial Hospital, Taipei, Taiwan
85National Hospital Organization Hokkaido Cancer Center, Sapporo, Japan
86Toranomon Hospital, Tokyo, Japan
87Department of Breast Surgery, JCHO Kurume General Hospital, Kurume, Japan
88Graduate School of Medicine, Gunma University, Gunma, Japan
89Puma Biotechnology, Los Angeles, CA
90Magee-Womens Hospital of UPMC, Pittsburgh, PA

CORRESPONDING AUTHOR
Cristina Saura, MD, Breast Cancer Unit, Vall d’Hebron University Hospital, Vall d’Hebron University Hospital, 08035, Barcelona, Spain; e-mail: csaura@vhio.net.

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AUTHOR CONTRIBUTIONS
Conception and design: Cristina Saura, Beverly Moy, Suzette Delaloge, Ming-Feng Hou, Richard Bryce, Adam Brufsky
Financial support: Daniele Fagnani
Administrative support: Shang-Wen Chen, Hong-Tai Chang
Provision of study material or patients: Cristina Saura, Mafalda Oliveira, Yin-Hsun Feng, Ming-Shen Dai, Shang-Wen Chen, Sara A. Hurvitz, Sung-Bae Kim, Beverly Moy, Nonikazu Masuda, Yoon Sim Yap, Yu-Min Yeh, Hong-Tai Chang, Hans Wildiers, Barbara Haley, John Crown, Johnson Lin, Takaaki Fujii, Adam Brufsky
Collection and assembly of data: Cristina Saura, Mafalda Oliveira, Yin-Hsun Feng, Ming-Shen Dai, Shang-Wen Chen, Sara A. Hurvitz, Sung-Bae Kim, Suzette Delaloge, Norikazu Masuda, Marketa Palacova, Maureen E. Trudeau, Johanna Mattson, Yoon Sim Yap, Ming-Feng Hou,

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Michelino De Laurentiis, Yu-Min Yeh, Hong-Tai Chang, Thomas Yau, Barbara Haley, Daniele Fagnani, Yen-Shen Lu, John Crown, Johnson Lin, Masato Takahashi, Toshimri Takano, Miki Yamaguchi, Takaaki Fuji, Bin Yao, Judith Bebchuk, Kiana Keyvanjäh, Adam Brufsky

Data analysis and interpretation: Cristina Saura, Mafalda Oliveira, Sung-Bae Kim, Beverly Moy, Suzette Delaloge, William Gradishar, Norikazu Masuda, Maureen E. Trudeau, Hans Wildiers, Yen-Shen Lu, John Crown, Masato Takahashi, Bin Yao, Judith Bebchuk, Kiana Keyvanjah, Richard Bryce, Adam Brufsky

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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Cristina Saura
Consulting or Advisory Role: Puma Biotechnology, Roche, Pfizer, AstraZeneca, Celgene, Daiichi Sankyo, Eisai, Genomic Health, Novartis, Pierre Fabre, Syntthon, PIQUR Therapeutics, BMS, Philips Healthcare, MSD, Sanofi
Research Funding: Genentech (Inst), AstraZeneca (Inst), Roche (Inst), MacroGenics (Inst), Novartis (Inst), Pfizer (Inst), Puma Biotechnology (Inst), Syntthon (Inst), PIQUR Therapeutics (Inst)
Travel, Accommodations, Expenses: Pfizer, Novartis, Roche, AstraZeneca, Genomic Health, Puma Biotechnology

Yoon Sim Yap
Honoraria: Novartis, Eli Lilly, Pfizer, AstraZeneca, Eisai
Consulting or Advisory Role: Novartis, Eli Lilly, Pfizer, AstraZeneca, Eisai
Travel, Accommodations, Expenses: Pfizer, AstraZeneca, Eisai, Eli Lilly, Roche, Novartis

Michelino De Laurentiis
Honoraria: Roche, Novartis, Pfizer, Eli Lilly, Eisai, Amgen, Celgene, Pierre Fabre, AstraZeneca, MSD
Consulting or Advisory Role: Roche, Novartis, Pfizer, Eli Lilly, Amgen, Celgene, AstraZeneca, MSD, Pierre Fabre, Eisai
Speakers’ Bureau: Novartis
Research Funding: Novartis, Roche, Puma Biotechnology, Eli Lilly, Pfizer, Daiichi Sankyo, MSD, Macrogenics, Bristol-Myers Squibb

Yu-Min Yeh
Travel, Accommodations, Expenses: Bayer

Thomas Yau
Honoraria: Bristol-Myers Squibb, MSD Oncology
Consulting or Advisory Role: Bristol-Myers Squibb

Hans Wildiers
Consulting or Advisory Role: Roche (Inst), Eli Lilly (Inst), Pfizer (Inst), Sirtex (Inst), Orin (Inst), Puma Biotechnology (Inst), AstraZeneca (Inst), Biocartis (Inst), Novartis (Inst), Daiichi Sankyo (Inst)
Research Funding: Roche (Inst), Novartis (Inst)
Travel, Accommodations, Expenses: Pfizer, Roche (Inst)

Barbara Haley
Research Funding: Pfizer (Inst), Eli Lilly (Inst), Daiichi Sankyo (Inst), Roche (Inst), Puma Biotechnology (Inst), AstraZeneca (Inst), Sanofi (Inst)

Yen-Shen Lu
Honoraria: Pfizer, Roche, Merck Sharp & Dohme, Novartis, Eli Lilly
Consulting or Advisory Role: Pfizer, Roche, Novartis, Eli Lilly
Research Funding: Novartis (Inst), Roche (Inst), Merck Sharp & Dohme (Inst)
Travel, Accommodations, Expenses: Roche, Pfizer, Eisai, Novartis

John Crown
Employment: OncoMark
Stock and Other Ownership Interests: OncoMark
Honoraria: Eisai, Amgen, Puma Biotechnology, Seattle Genetics, Boehringer Ingelheim, Pfizer, Vertex, Genomic Health, Roche, MSD Oncology, Novartis
Consulting or Advisory Role: Eisai, Puma Biotechnology, Boehringer Ingelheim, Pfizer, Vertex, Roche, Seattle Genetics, G1 Therapeutics
Speakers’ Bureau: Pfizer, Eisai, Genomic Health
Research Funding: Roche (Inst), Eisai (Inst), Boehringer Ingelheim (Inst), Puma Biotechnology (Inst)
Patents, Royalties, Other Intellectual Property: WO2020011770 (A1)—A method of predicting response to treatment in patients with cancer
Travel, Accommodations, Expenses: MSD, Pfizer, Roche, AstraZeneca, AbbVie, Novartis

Masato Takahashi
Honoraria: AstraZeneca, Eisai, Pfizer, Eli Lilly, Chugai, Nippon Kayaku
Research Funding: Taiho Pharmaceutical (Inst), Kyowa Hakko Kirin (Inst), Eisai (Inst), Nippon Kayaku (Inst)

Toshimi Takano
Honoraria: Daiichi Sankyo, Eisai, Pfizer, Eli Lilly, Chugai, Kyowa Kirin, Celtrion Healthcare
Research Funding: Taiho Pharmaceutical (Inst), Novartis (Inst), Ono Pharmaceutical (Inst), MSD (Inst), Merck Serono (Inst), Daiichi Sankyo (Inst), Eisai (Inst), Bristol-Myers Squibb (Inst), Chugai (Inst)
Research Funding: Kyowa Kirin (Inst)

Miki Yamaguchi
Speakers’ Bureau: Chugai Pharma, Pfizer

Bin Yao
Employment: Puma Biotechnology
Stock and Other Ownership Interests: Puma Biotechnology

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Adam Brufsky
Consulting or Advisory Role: Pfizer, Genentech/Roche, Agendia, Celgene, Novartis, Bayer, Eli Lilly, Biotheranostics, NanoString Technologies, Genomic Health, Puma Biotechnology, Bioarray Therapeutics, Merck, Myriad Pharmaceuticals, Eisai, Immunomedics, Seattle Genetics, Daiichi Sankyo/Eli Lilly
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Supplementary Methods

Study design. Central confirmation of HER2 overexpression or gene amplification according to DAKO (Agilent Technologies, Santa Clara, CA) kit guidelines was required. Patients had to have ≥ 1 measurable lesion as defined by RECIST (version 1.1) and adequate organ function.

Patients with CNS disease were eligible for enrollment unless they had symptomatic or unstable brain metastases. Asymptomatic patients with metastatic brain disease who were on a stable dose of corticosteroids for CNS metastases, including high-dose corticosteroids, were eligible so long as the dose was constant for at least 2 weeks before enrollment.

Eligible patients were randomly assigned (1:1 ratio) to neratinib plus capecitabine (N+C) or lapatinib plus capecitabine (L+C) through an interactive voice and web-response system. The randomization sequence was generated with permuted blocks (block size 4; 24 strata; 150 blocks per stratum). One list was created with 14,400 randomization numbers (600 numbers per stratum). The randomization sequence was stratified by: hormone receptor status (hormone receptor positive [defined as estrogen and progesterone receptor positive or both]; estrogen or progesterone receptor negative [defined as estrogen or progesterone receptor negative]), number of previous HER2-directed therapies for metastatic breast cancer (2 or ≥ 3), geographic region (North America or Europe [including Israel] or rest of the world), and visceral disease (yes or no).

Treatment. Cardiac monitoring was performed at the start of cycles 3 and 6, and every 6 cycles thereafter.

Definitions. Progression-free survival was defined as the interval from the date of randomization until the first date on which recurrence, progression (per RECIST; version 1.1), or death due to any cause was documented, censored at the last assessable evaluation or at the initiation of new anticancer therapy.

Overall survival was defined as the time from randomization to death due to any cause.

The objective response rate was defined as the proportion of patients demonstrating either a complete or partial response according to RECIST (version 1.1) as their best overall response during the study.

The duration of response was measured from the time at which measurement criteria were first met for complete or partial response (whichever status was recorded first) until the first date on which recurrence, progressive disease, or death was objectively documented, taking as a reference for progressive disease the smallest measurements recorded since enrollment, according to RECIST.

Clinical benefit rate was defined as the proportion of patients who achieved overall tumor response (complete or partial response) or stable disease lasting at least 24 weeks. Stable disease was measured from enrollment until the criteria for disease progression or response were met, per RECIST.

Time to intervention for metastatic CNS disease was defined as the date of initiation of intervention or therapy for CNS disease determined by the investigator to be due to CNS metastasis. This could include brain, leptomeningeal, or epidural metastases, including epidural spinal cord compression arising from tumor growth in the epidural space.

Procedures. Study drug treatment was continued for as long as it was tolerated and while there was no disease progression. Patients who discontinued study therapy were followed during the long-term follow-up phase. If a patient discontinued study therapy because of toxicity, tumor assessments continued every 6 weeks until documented disease progression, death, or withdrawal of consent. Patients were also contacted every 12 weeks for survival status and to collect details of additional anticancer therapy. The long-term follow-up phase continued until the patient’s death or withdrawal of consent.

Physical examinations were performed at baseline and at the start of every cycle from cycle 2 onward. Screening activities were conducted within 21 days before randomization. Tumor scans (computed tomography and magnetic resonance imaging [MRI]) were performed within 28 days before randomization, and preferably no more than 28 days before the start of treatment. Screening for CNS metastases was not required/mandated at baseline. Tumor imaging assessments were performed at the start of every second cycle until documented disease progression or death. Baseline MRI scans were not mandated. Cardiac monitoring was performed at the start of cycles 3 and 6 and every 6 cycles thereafter using single standard 12-lead digital electrocardiogram evaluations and multiple-gated acquisition scans or echocardiograms to determine the left ventricular ejection fraction.

Patients who ended therapy for any reason other than radiologically confirmed disease progression (eg, for “clinical” progression, adverse events or intolerance, or withdrawal of consent for therapy) continued to be imaged every 6 weeks until radiologically confirmed progression was documented.

Antidiarrheal medication. Loperamide, the recommended standard antidiarrheal therapy, was administered with the first dose of neratinib (initial dose, 4 mg), followed by 2 mg every 4 hours for the first 3 days. Thereafter, loperamide 2 mg was taken every 6-8 hours until the end of the first cycle, regardless of whether the patient experienced diarrhea or not. Second-line antidiarrheal treatments and adjunctive therapies were also recommended for use when appropriate. Antidiarrheal medication use was not specified in the lapatinib Summary of Product Characteristics (https://www.ema.europa.eu/en/documents/product-information/tyverb-epar-product-information_en.pdf) at the time of treatment initiation; however, antidiarrheal prophylaxis beyond cycle 1 was at the discretion of the treating physician, irrespective of treatment group.
**FIG A1.** Subgroup analyses of (A) centrally assessed progression-free survival, and (B) overall survival in the intention-to-treat population. C, capecitabine; HR, hazard ratio; L, lapatinib; N, neratinib.
FIG A2. Kaplan-Meier analysis of progression-free survival (PFS) according to hormone receptor status: patients with (A) hormone receptor–negative and (B) hormone receptor–positive disease. HR, hazard ratio.
FIG A3. Kaplan-Meier analysis of progression-free survival (PFS) according to disease location: (A) visceral disease, and (B) nonvisceral disease. HR, hazard ratio.
FIG A4. Kaplan-Meier analysis of overall survival (OS) according to hormone receptor status: patients with (A) hormone receptor–negative, and (B) hormone receptor–positive disease. HR, hazard ratio.
FIG A5. Kaplan-Meier analysis of overall survival (OS) according to disease location: (A) visceral disease, and (B) nonvisceral disease. HR, hazard ratio; NE, not estimable.
TABLE A1. Primary Efficacy End Point Results

| End Point                        | N+C | L+C |
|----------------------------------|-----|-----|
| **Progression-free survival (centrally assessed)** |     |     |
| Primary analysis                 |     |     |
| Stratified log-rank test P value*| .0059 |     |
| Stratified Cox proportional hazards model, HR | 0.76 (0.63 to 0.93) |     |
| **Additional results**           |     |     |
| Mean (95% CI)*                   | 8.8 (7.8 to 9.8) | 6.6 (5.9 to 7.4) |
| Median                           | 5.6 (4.9 to 6.9) | 5.5 (4.3 to 5.6) |
| Kaplan-Meier estimate, % (95% CI)|     |     |
| 6 months                         | 47.2 (41.1 to 53.1) | 37.8 (31.8 to 43.9) |
| 12 months                        | 28.8 (23.1 to 34.8) | 14.8 (10.3 to 20.1) |
| 18 months                        | 16.3 (11.3 to 22.1) | 7.4 (4.1 to 12.0) |
| **Overall survival (primary analysis)** |     |     |
| Stratified log-rank test P value*| .2086 |     |
| Stratified Cox proportional hazards model,* HR | 0.88 (0.72 to 1.07) |     |
| **Additional results**           |     |     |
| Mean (95% CI)*                   | 24.0 (22.1 to 25.9) | 22.2 (20.4 to 24.0) |
| Median                           | 21.0 (17.7 to 23.8) | 18.7 (15.5 to 21.2) |
| Kaplan-Meier estimate, % (95% CI)|     |     |
| 6 months                         | 90.2 (86.2 to 93.0) | 87.5 (83.3 to 90.7) |
| 12 months                        | 72.5 (67.0 to 77.1) | 66.7 (61.2 to 71.6) |
| 18 months                        | 54.7 (48.8 to 60.2) | 51.4 (45.7 to 56.9) |
| 24 months                        | 42.9 (36.8 to 48.8) | 39.2 (33.4 to 45.0) |
| 36 months                        | 24.4 (18.3 to 30.9) | 22.1 (16.6 to 28.2) |

NOTE. Data are presented as median (95% CI) unless otherwise stated.
Abbreviations: C, capecitabine; L, lapatinib; N, neratinib.
*Restricted at 24 months.
†Restricted at 48 months.
### TABLE A2. First Intervention for CNS Disease

| Intervention                                      | N+C (n = 307) | L+C (n = 314) | Total (N = 621) |
|--------------------------------------------------|---------------|---------------|-----------------|
| Post-treatment cancer-related radiotherapy       | 34 (11.1)     | 48 (15.3)     | 82 (13.2)       |
| Concomitant medication                           | 14 (4.6)      | 16 (5.1)      | 30 (4.8)        |
| Post-treatment cancer-related surgery/procedure | 5 (1.6)       | 9 (2.9)       | 14 (2.3)        |
| Post-treatment anticancer medication             | 3 (1.0)       | 3 (1.0)       | 6 (1.0)         |
| Concomitant therapy                              | 0             | 1 (0.3)       | 1 (0.2)         |

NOTE. Data are presented as No. (%).

Abbreviations: C, capecitabine; L, lapatinib; N, neratinib.

*Three patients had 2 different CNS interventions on the same date as their first intervention and are counted in both categories as appropriate.

### TABLE A3. Summary of Study Drug Exposure (safety population)

| Study Drug Exposure | N+C (n = 303) | L+C (n = 311) |
|---------------------|---------------|---------------|
| Median dose intensity, mg/m²/d | | |
| N/L                 | 240 (207-240) | 1,250 (1,138-1,250) |
| C                   | 929 (732-1,000) | 1,143 (946-1,333) |
| Relative dose intensity, % | | |
| N/L                 | 100 (86-100) | 100 (91-100) |
| C                   | 93 (73-100) | 86 (71-100) |
| Treatment duration, months | | |
| N/L                 | 5.7 (2.7-10.4) | 4.4 (2.3-7.1) |
| C                   | 5.5 (2.8-10.4) | 4.8 (2.8-6.9) |
| Dose reduction      | | |
| N/L                 | 73 (24)       | 61 (20)       |
| C                   | 117 (39)      | 152 (49)      |
| Dose hold           | | |
| N/L                 | 145 (48)      | 134 (43)      |
| C                   | 178 (59)      | 184 (59)      |

NOTE. Data are presented as No. (%) or median (interquartile range).

Abbreviations: C, capecitabine; L, lapatinib; N, neratinib.
### TABLE A4. Overall Summary of TEAEs (safety population)

| AE                                      | N+C (n = 303) | L+C (n = 311) | Total (N = 614) |
|-----------------------------------------|---------------|---------------|-----------------|
| Any TEAE                                | 302 (99.7)    | 309 (99.4)    | 611 (99.5)      |
| Grade 1                                 | 26 (8.6)      | 20 (6.4)      | 46 (7.5)        |
| Grade 2                                 | 92 (30.4)     | 101 (32.5)    | 193 (31.4)      |
| Grade 3                                 | 165 (54.5)    | 160 (51.4)    | 325 (52.9)      |
| Grade 4                                 | 11 (3.6)      | 18 (5.8)      | 29 (4.7)        |
| Grade 5                                 | 8 (2.6)       | 10 (3.2)      | 18 (2.9)        |
| Serious AE                              | 103 (34.0)    | 93 (29.9)     | 196 (31.9)      |
| Treatment-related AE                    | 289 (95.4)    | 299 (96.1)    | 588 (95.8)      |
| AE related to N/L                       | 280 (92.4)    | 276 (88.7)    | 556 (90.6)      |
| AE related to C                         | 283 (93.4)    | 292 (93.9)    | 575 (93.6)      |
| TEAE leading to treatment discontinuation | 42 (13.9)    | 56 (18.0)     | 98 (16.0)       |
| TEAE leading to N/L discontinuation     | 33 (10.9)     | 45 (14.5)     | 78 (12.7)       |
| TEAE leading to C discontinuation       | 33 (10.9)     | 37 (11.9)     | 70 (11.4)       |
| TEAE leading to dose reduction          | 72 (23.8)     | 93 (29.9)     | 165 (26.9)      |
| TEAE leading to N/L reduction           | 30 (9.9)      | 33 (10.6)     | 63 (10.3)       |
| TEAE leading to C reduction             | 63 (20.8)     | 89 (28.6)     | 152 (24.8)      |
| TEAE leading to dose hold               | 194 (64.0)    | 200 (64.3)    | 394 (64.2)      |
| TEAE leading to N/L hold                | 152 (50.2)    | 145 (46.6)    | 297 (48.4)      |
| TEAE leading to C hold                  | 177 (58.4)    | 189 (60.8)    | 366 (59.6)      |
| TEAE leading to hospitalization         | 94 (31.0)     | 87 (28.0)     | 181 (29.5)      |

NOTE. Data are presented as No. (%).
Abbreviations: AE, adverse event; C, capecitabine; L, lapatinib; N, neratinib; TEAE, treatment-emergent adverse event.

### TABLE A5. Treatment-Emergent Diarrhea by Treatment Cycle (safety population)

| Adverse Event                | N+C (n = 303) | L+C (n = 311) | Total (N = 614) |
|------------------------------|---------------|---------------|-----------------|
| Patients treated in cycle 1  | 303           | 311           | 614             |
| Grade 3 diarrhea             | 48 (15.8)     | 17 (5.5)      | 65 (10.6)       |
| Patients treated in cycle 2  | 290           | 291           | 581             |
| Grade 3 diarrhea             | 14 (4.8)      | 10 (3.4)      | 24 (4.1)        |
| Patients treated in cycles 3-5| 265           | 272           | 537             |
| Grade 3 diarrhea             | 13 (4.9)      | 13 (4.8)      | 26 (4.8)        |
| Patients treated in cycles 6-8| 202           | 196           | 398             |
| Grade 3 diarrhea             | 4 (2.0)       | 1 (0.5)       | 5 (1.3)         |
| Patients treated in cycles 9-11| 155          | 126           | 281             |
| Grade 3 diarrhea             | 2 (1.3)       | 0 (0.0)       | 2 (0.7)         |
| Patients treated in cycles 12-14| 115          | 73            | 188             |
| Grade 3 diarrhea             | 2 (1.7)       | 1 (1.4)       | 3 (1.6)         |
| Patients treated in cycles 15-17| 84           | 41            | 125             |
| Grade 3 diarrhea             | 2 (2.4)       | 1 (2.4)       | 3 (2.4)         |
| Patients treated in cycles 18-20| 64           | 31            | 95              |
| Grade 3 diarrhea             | 2 (3.1)       | 1 (3.2)       | 3 (3.2)         |
| Patients treated in cycles ≥ 21| 51           | 22            | 73              |
| Grade 3 diarrhea             | 3 (5.9)       | 1 (4.5)       | 4 (5.5)         |

Data are presented as No. or No. (%).
Abbreviations: C, capecitabine; L, lapatinib; N, neratinib.