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

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abstract

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/m^2 twice a day 14 d/21 d) with loperamide prophylaxis, or to lapatinib (1,250 mg once every day) plus capecitabine (1,000 mg/m^2 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% *v* 29.2%; P = .043). 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% *v* L+C 66%) and nausea (53% *v* 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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ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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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 (Nerlynx; 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[11] and the US Food and Drug Administration (FDA) for extended adjuvant treatment of early-stage, HER2-positive breast cancer[12] on the basis of the phase III ExteNET trial (ClinicalTrials.gov identifier: NCT00878709).[13] 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.[14] The primary toxicity associated with neratinib is diarrhea. In the NEfERT-T trial (ClinicalTrials.gov identifier: NCT00915018), which did not mandate primary diarrhea prophylaxis, 30% of patients had grade 3 diarrhea[15]; prophylaxis or dose-escalation regimens reduced grade 3 diarrhea to as little as 15% in the extended adjuvant CONTROL trial (ClinicalTrials.gov identifier: NCT02400476).[16]

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,[17] and other challenges continue, including de novo and acquired resistance to HER2-targeted antibody therapy.[5,18] 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.[19] Although CNS recurrence is a particular challenge in breast cancer,[20,21] 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,[22] and EGF100151 reported numerically fewer CNS metastases with L+C versus capecitabine in HER2-positive advanced breast cancer.[6]

Neratinib has demonstrated activity in preventing and treating brain metastases in HER2-positive MBC. In NEfERT-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.[15] 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.[10]

On the basis of prior phase I/II safety and efficacy results for N+C in HER2-positive MBC,[9] 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,[23] 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[24]] *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

accordance with the Declaration of Helsinki. All patients provided written informed consent.

This was an open-label study; central assessments were performed by independent reviewers blinded to patients' treatment assignments. The sponsor's statisticians were blinded to assignments until unblinding at time of primary progression-free survival (PFS) and OS analyses.

Treatment

Patients 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/m^2 orally daily in 2 evenly spaced doses [750 mg/m^2 twice a day] on days 1-14 of 21-day cycles) or L+C (lapatinib 1,250 mg orally once daily continuously, plus capecitabine 2,000 mg/m^2 orally daily in 2 evenly spaced doses [1,000 mg/m^2 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 I/II trial of N+C in HER2-positive MBC[9] (maximum tolerated dose, 1,500 mg/m^2/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.[25] Concurrent 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 $\geq$ 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 $\geq$ 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 χ^2 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).

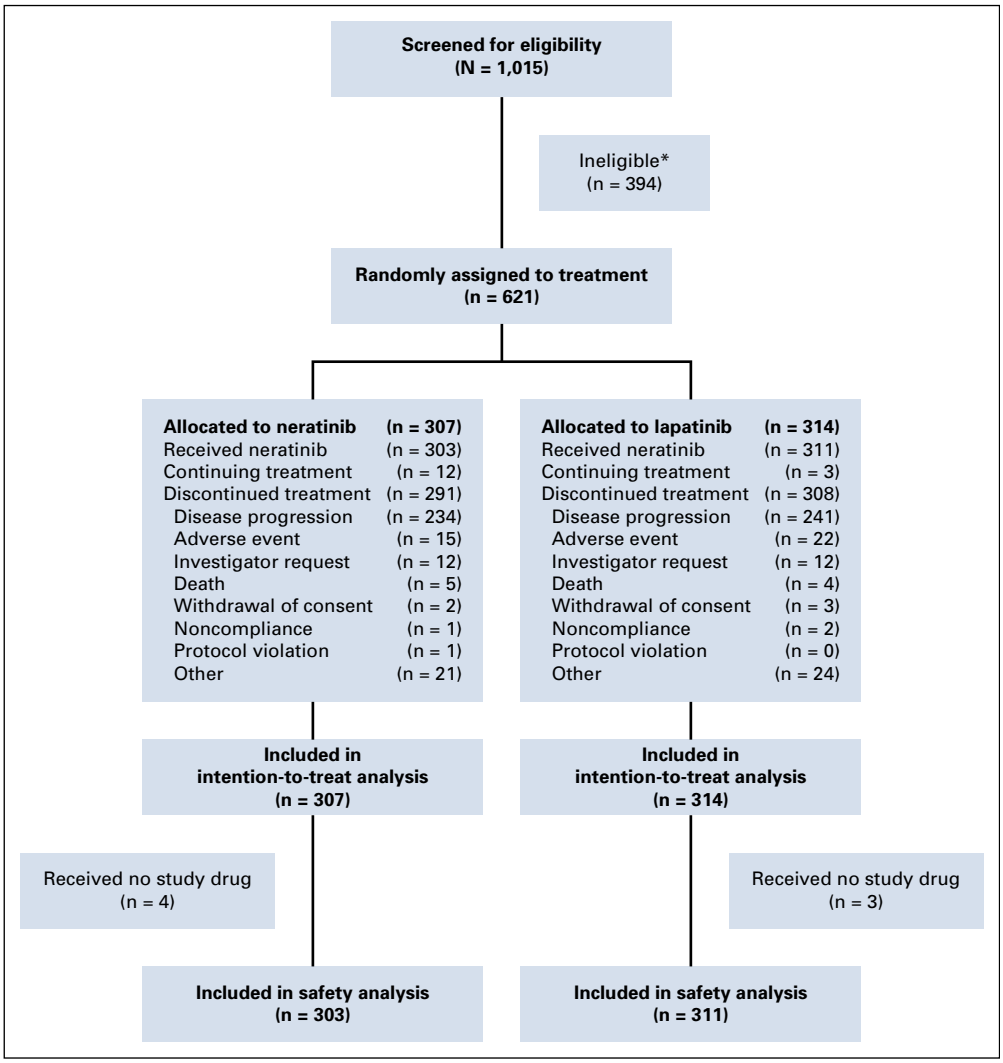

FIG 1. NALA trial profile. Screening failures were as follows: 251 patients did not meet the inclusion criteria, 118 of whom did not have centrally assessed HER2 overexpression of gene-amplified tumor; 152 patients were ineligible on the basis of the exclusion criteria; 11 patients were ineligible on the basis of both inclusion and exclusion criteria; and the reason for screen failure was not given for 2 patients. There could have been > 1 reason for each patient to have failed screening. (*) No previous treatment with capecitabine, neratinib, lapatinib, or other HER2-directed TKI was permitted. Patients were excluded if they had received previous treatment resulting in an anthracycline dose equivalent to a cumulative doxorubicin dose > 450 mg/m^2. Patients with symptomatic or unstable CNS metastatic disease were not eligible; patients with asymptomatic CNS metastases (treated or untreated) were eligible. Patients undergoing treatment for asymptomatic CNS metastases had to be on a stable dose of corticosteroids for ≥ 14 days before randomization. Patients with diarrhea as a major symptom of a significant chronic GI disorder were excluded.

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+C, n = 307; L+C, n = 314; Fig 1). At the analysis cutoff date (September 28, 2018), the safety population included 614 patients (N+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

TABLE 1. Baseline Demographics and Disease Characteristics for the Intention-to-Treat Population

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[a]		
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	134 (43.6)	148 (47.1)
Brain[b]	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[c]		
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.

[a]Hormone receptor positive: ER positive, PR positive, or both. Hormone receptor negative: ER and PR negative.

[b]Two patients in each arm indicated location as other, with additional explanations indicating brain.

[c]Prior non–HER2-directed therapies not included in this table.

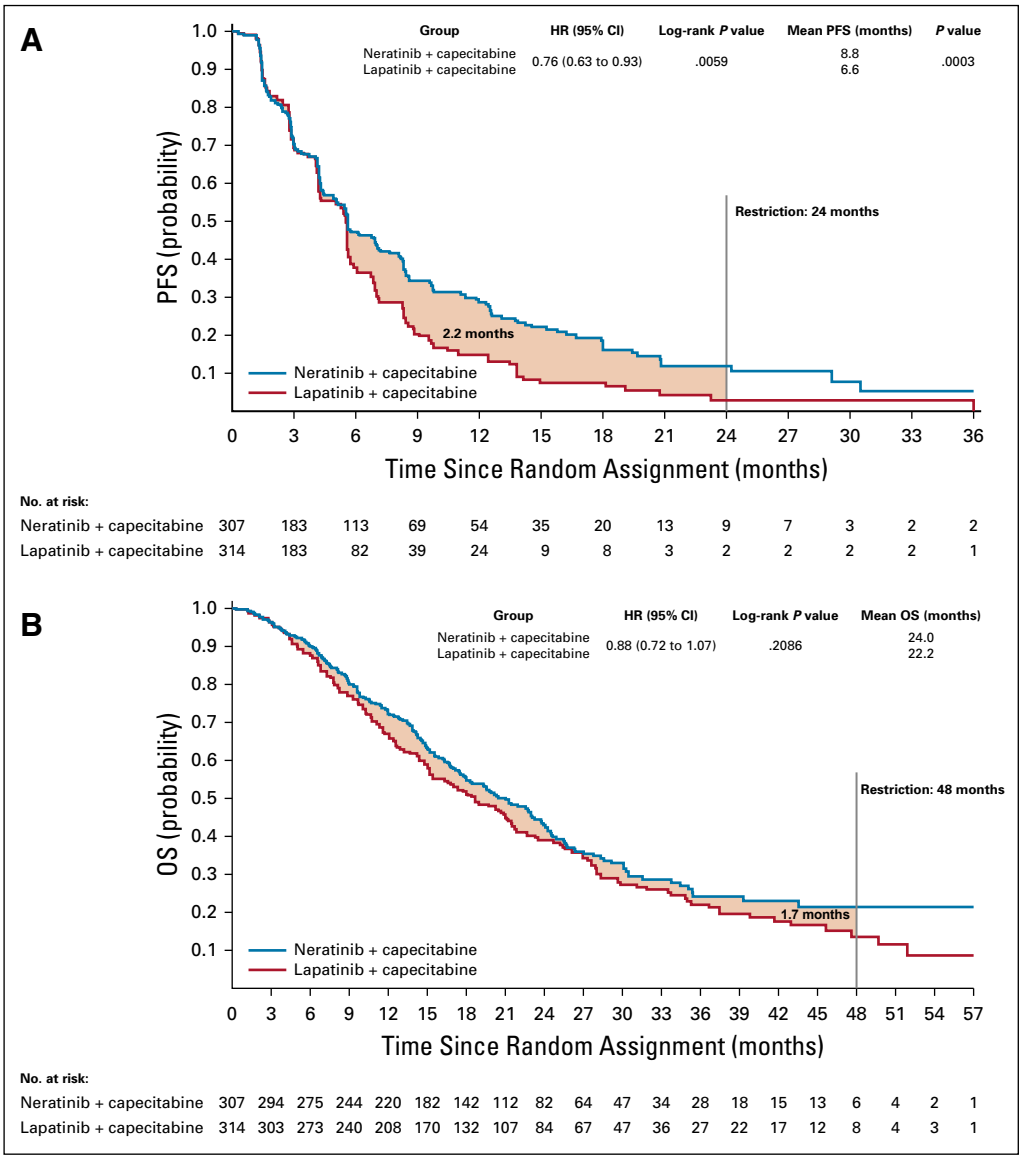

FIG 2. Kaplan-Meier curves for (A) centrally assessed progression-free survival (PFS), and (B) overall survival (OS) in the intention-to-treat population.

(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 ≥ 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

Variable[a]	N+C (n = 307)	L+C (n = 314)	Hazard Ratio (95% CI)[b]	*P*[c]
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)	.043[d]
Best overall response[e]	(n = 256)	(n = 270)	—	—
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)	—	.1201[e]
Clinical benefit rate, %[f]	44.5 (38.3 to 50.8)	35.6 (29.8 to 41.6)	—	.0328[e]

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.
[a]Centrally confirmed or assessed unless otherwise stated.
[b]Stratified Cox proportional hazards model.
[c]Stratified 2-sided log-rank test.
[d]Gray's method.
[e]Cochran-Mantel-Haenszel test adjusted by hormone receptor status, number of prior HER2-directed regimens in metastatic setting, and visceral disease versus nonvisceral disease.
[f]Confirmed 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).

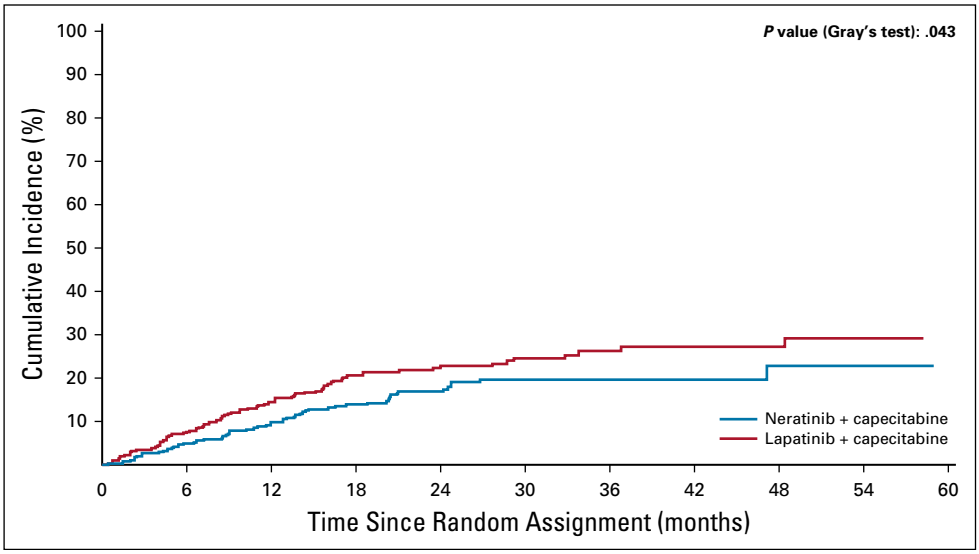

FIG 3. Intervention for CNS disease.

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

	N+C (n = 303)		L+C (n = 311)	
AE	**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)	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 hematoma, 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 bacteremia, 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 [29.9%]), 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/m^2/d for N+C and 1,143 mg/m^2/d 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.

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.[26] 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.[26]

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 in the metastatic setting. 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)[27] but in contrast to the extended adjuvant ExteNET trial, which showed a greater benefit in hormone receptor–positive disease.[13] 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.[28,29] The existence of bidirectional crosstalk between HER2 and estrogen-receptor

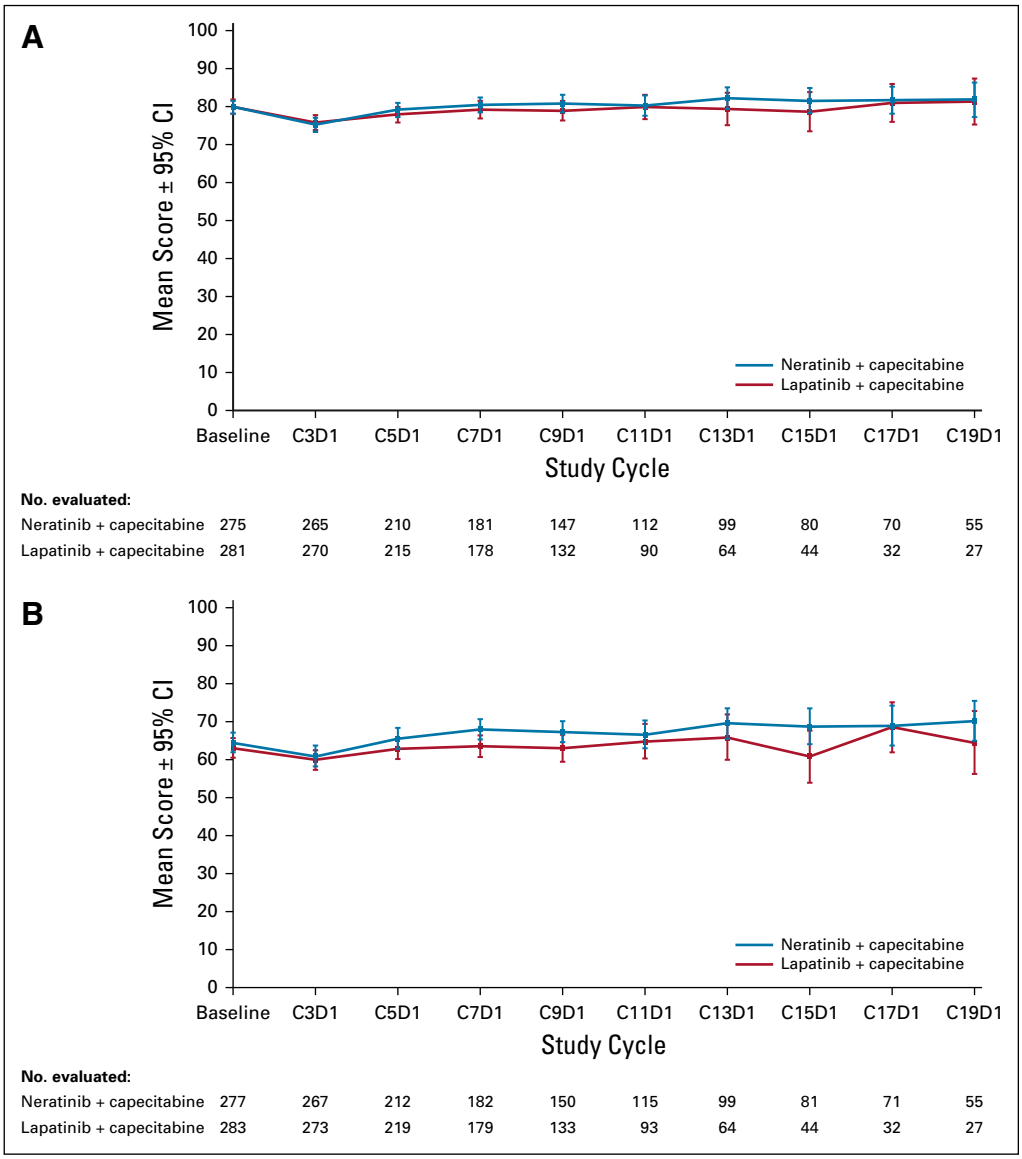

FIG 4. Changes over time in European Organization for Research and Treatment of Cancer (A) Quality of Life Questionnaire core module (QLQ-C30) summary score, and (B) QLQ-C30 Global Health Status score. Higher scores represent higher quality of life/levels of functioning. CxDy, cycle x day y.

pathways[30] means that estrogen-receptor signaling may be activated with inhibition of HER2 alone.[28] The ExteNET study in the early-disease setting permitted endocrine therapy in hormone receptor–positive patients,[13] whereas NALA and I-SPY,[27] 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.[19] 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% *v* 29.2%, respectively). This is consistent with findings from NEfERT-T, which reported a benefit for neratinib in patients with CNS metastases,[15] and TBCRC 022, which showed activity against refractory HER2-positive breast cancer brain metastases.[10]

FDA approval of neratinib in third-line MBC on the basis of NALA[14] follows approval of trastuzumab deruxtecan in the same setting (DS-8201; Daiichi Sankyo and AstraZeneca).[31] 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%.[32] 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

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% *v* placebo-capecitabine-trastuzumab, 12.3%), translating to a 2.2-month median PFS benefit and significant OS benefit.[33] 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 *v* 30% in NEfERT-T[15] and 40% in ExteNET[13]). The duration of grade 3 diarrhea and rate of diarrhea-related discontinuations (N+C 2.6% *v* 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^2 days 1-14 every 3 weeks) than L+C (2,000 mg/m^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.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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No other potential conflicts of interest were reported.

APPENDIX

Supplementary Methods

Study design. Central confirmation of HER2 overexpression or gene amplification according to DAKO (Agilent Technologies, Santa Clara, CA) kit guidelines[23] 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 or progesterone receptor positive or both; estrogen or progesterone receptor positivity was defined per DAKO test kit guidelines[24]] *v* hormone receptor negative [defined as estrogen and 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.

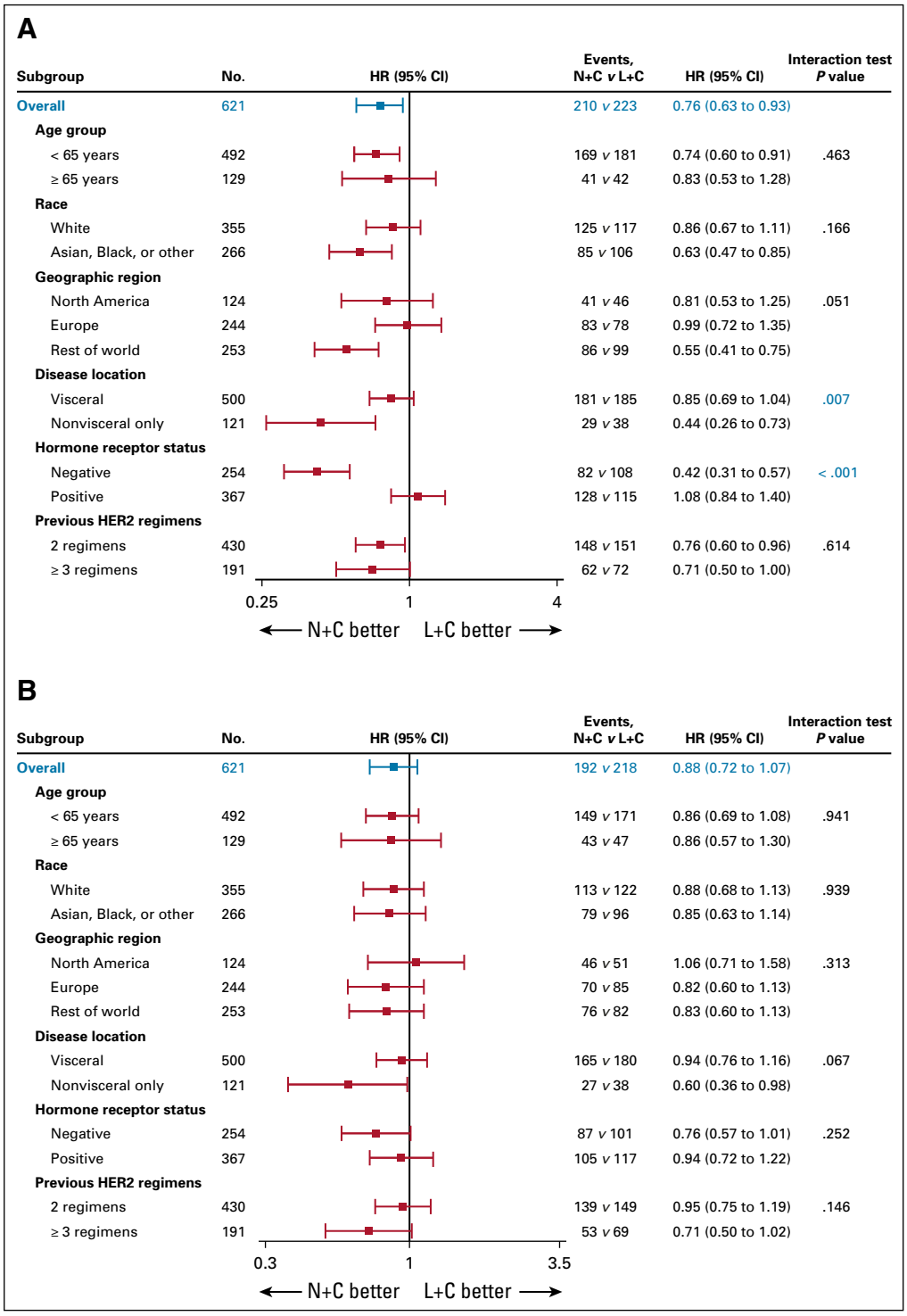

FIG A1. Subgroup analyses of (A) centrally assessed progression-free survival, and (B) overall survival in the intention-to-treat population. C, capecitabine; HR, hazard ratio; L, lapatinib; N, neratinib.

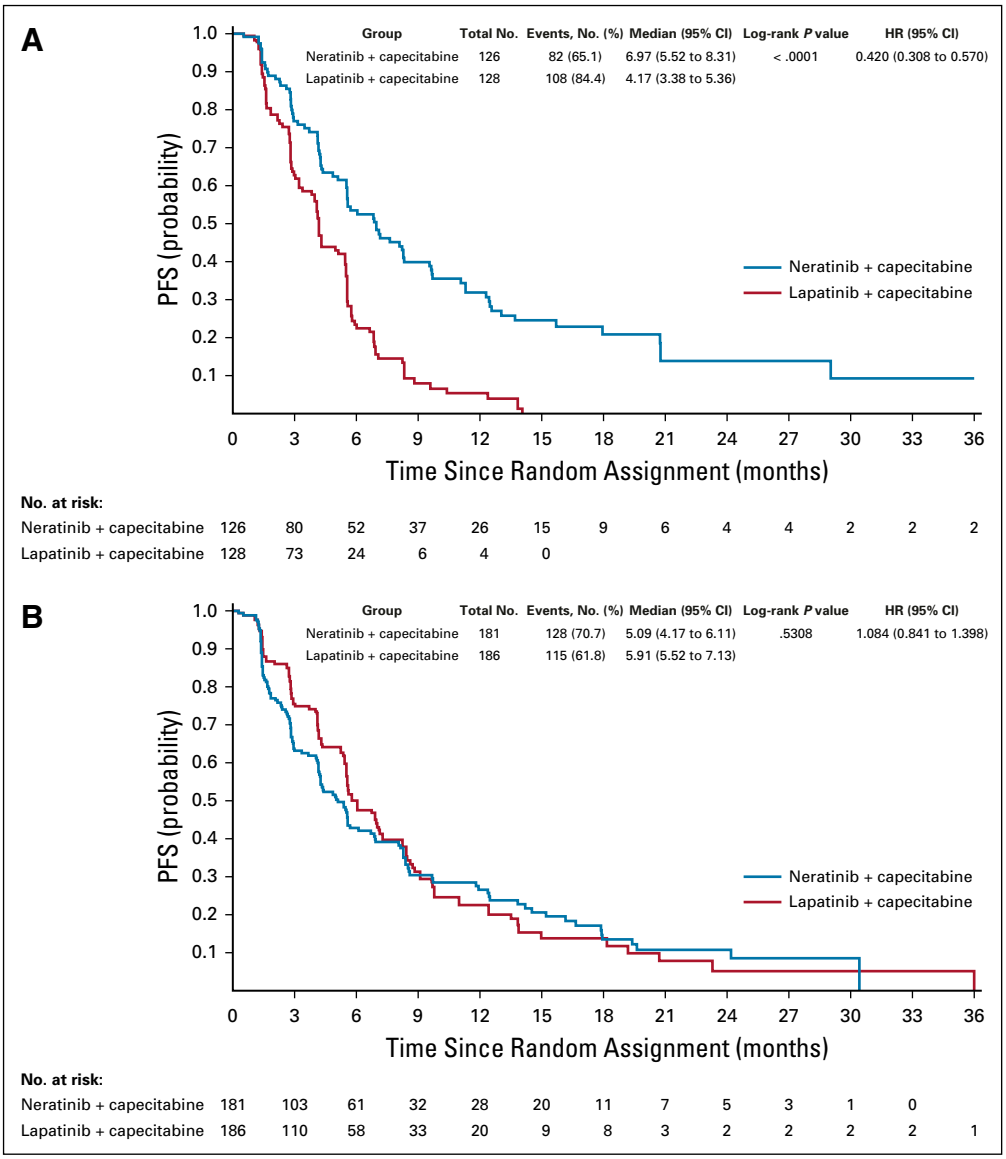

FIG A2. Kaplan-Meier analysis of progression-free survival (PFS) according to hormone receptor status: patients with (A) hormone receptor–negative and (B) hormone receptor–positive disease. HR, hazard ratio.

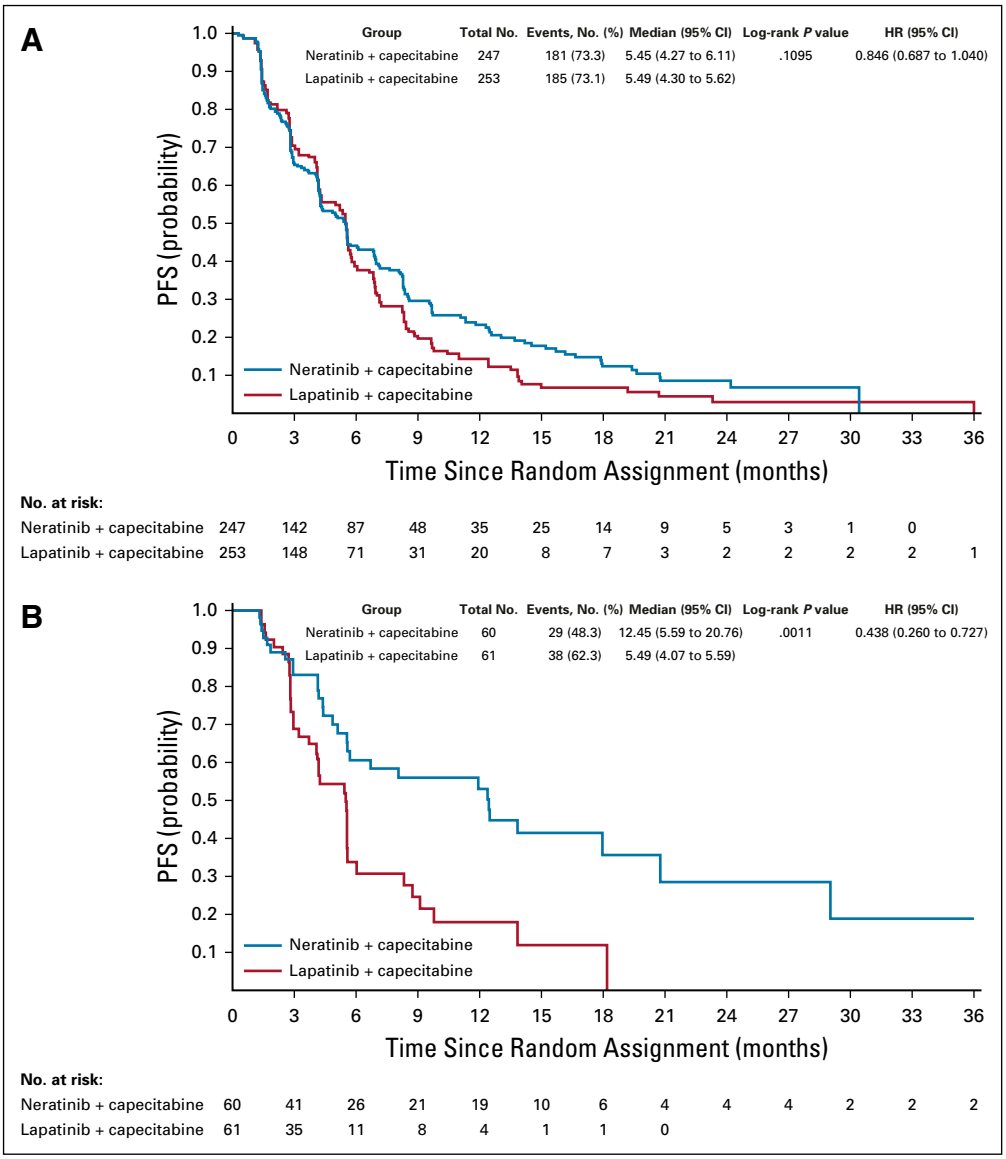

FIG A3. Kaplan-Meier analysis of progression-free survival (PFS) according to disease location: (A) visceral disease, and (B) nonvisceral disease. HR, hazard ratio.

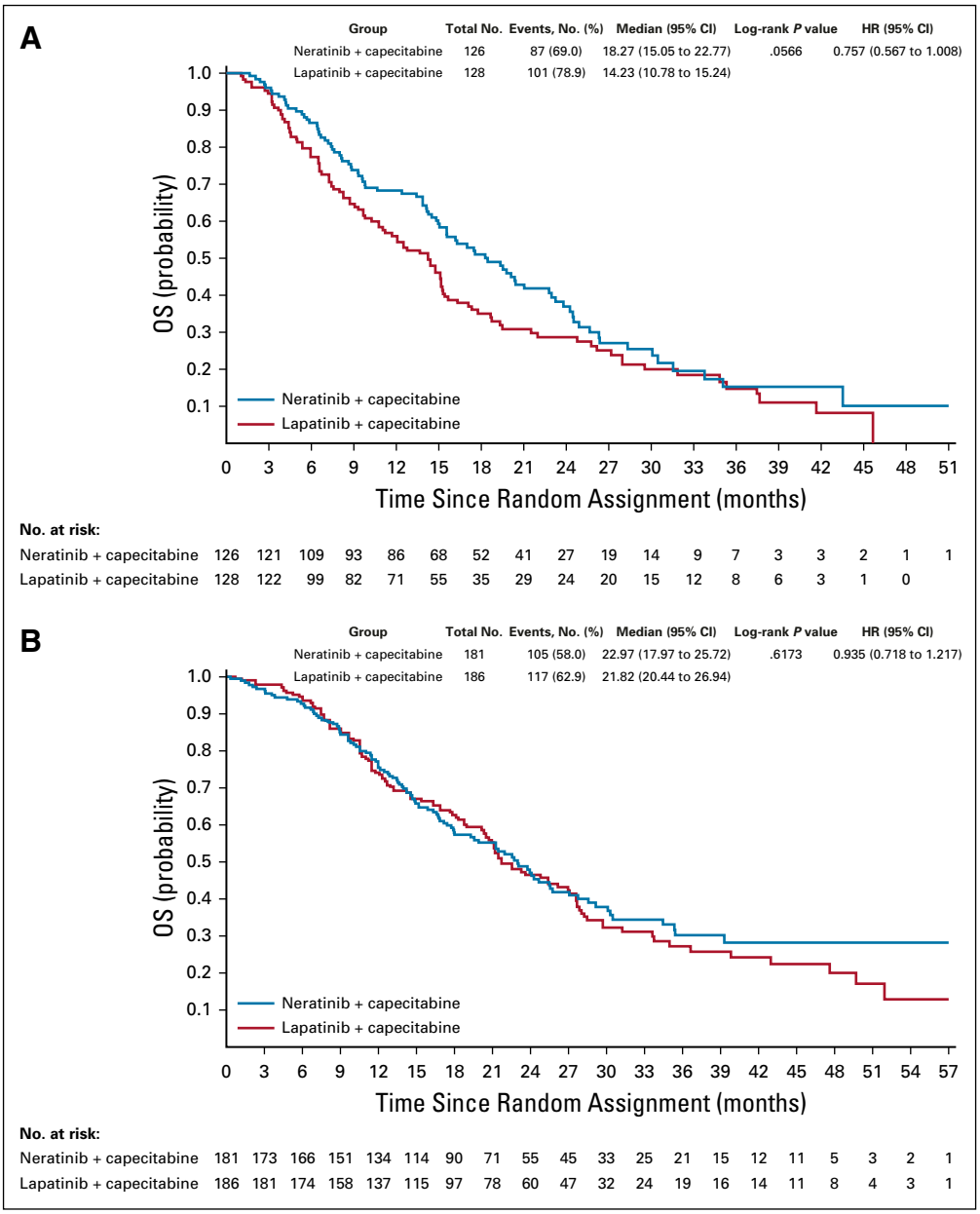

FIG A4. Kaplan-Meier analysis of overall survival (OS) according to hormone receptor status: patients with (A) hormone receptor–negative, and (B) hormone receptor–positive disease. HR, hazard ratio.

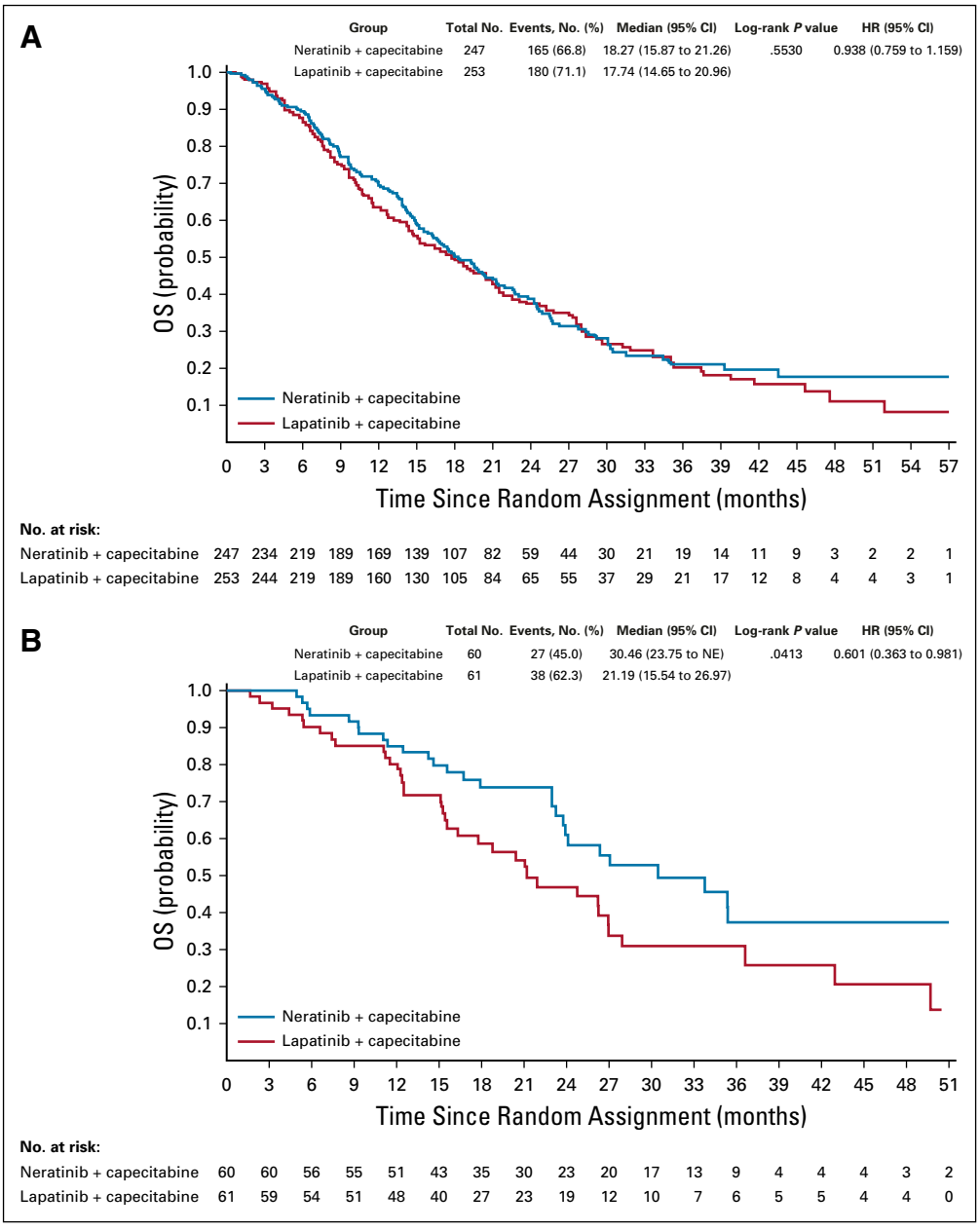

FIG A5. Kaplan-Meier analysis of overall survival (OS) according to disease location: (A) visceral disease, and (B) nonvisceral disease. HR, hazard ratio; NE, not estimable.

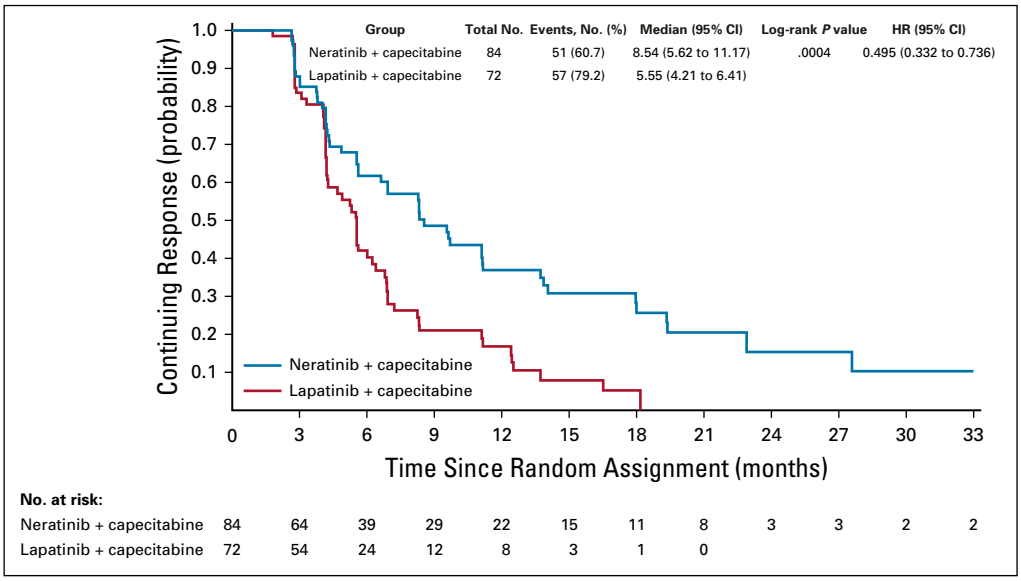

FIG A6. Kaplan-Meier analysis of response duration. HR, hazard ratio.

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[a]	.0059	
Stratified Cox proportional hazards model, HR	0.76 (0.63 to 0.93)	
Additional results		
Mean (95% CI)[a]	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[b]	.2086	
Stratified Cox proportional hazards model,[b] HR	0.88 (0.72 to 1.07)	
Additional results		
Mean (95% CI)[b]	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.
[a]Restricted at 24 months.
[b]Restricted at 48 months.

TABLE A2. First Intervention for CNS Disease

Intervention[a]	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.
[a]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/m^2/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.