ORIGINAL ARTICLE

Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer

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ABSTRACT

BACKGROUND

Pertuzumab increases the rate of pathological complete response in the preoperative context and increases overall survival among patients with metastatic disease when it is added to trastuzumab and chemotherapy for the treatment of human epidermal growth factor receptor 2 (HER2)–positive breast cancer. In this trial, we investigated whether pertuzumab, when added to adjuvant trastuzumab and chemotherapy, improves outcomes among patients with HER2-positive early breast cancer.

METHODS

We randomly assigned patients with node-positive or high-risk node-negative HER2-positive, operable breast cancer to receive either pertuzumab or placebo added to standard adjuvant chemotherapy plus 1 year of treatment with trastuzumab. We assumed a 3-year invasive-disease–free survival rate of 91.8% with pertuzumab and 89.2% with placebo.

RESULTS

In the trial population, 63% of the patients who were randomly assigned to receive pertuzumab (2400 patients) or placebo (2405 patients) had node-positive disease and 36% had hormone-receptor–negative disease. Disease recurrence occurred in 171 patients (7.1%) in the pertuzumab group and 210 patients (8.7%) in the placebo group (hazard ratio, 0.81; 95% confidence interval [CI], 0.66 to 1.00; P=0.045). The estimates of the 3-year rates of invasive-disease–free survival were 94.1% in the pertuzumab group and 93.2% in the placebo group. In the cohort of patients with node-positive disease, the 3-year rate of invasive-disease–free survival was 92.0% in the pertuzumab group, as compared with 90.2% in the placebo group (hazard ratio for an invasive-disease event, 0.77; 95% CI, 0.62 to 0.96; P=0.02). In the cohort of patients with node-negative disease, the 3-year rate of invasive-disease–free survival was 97.5% in the pertuzumab group and 98.4% in the placebo group (hazard ratio for an invasive-disease event, 1.13; 95% CI, 0.68 to 1.86; P=0.64). Heart failure, cardiac death, and cardiac dysfunction were infrequent in both treatment groups. Diarrhea of grade 3 or higher occurred almost exclusively during chemotherapy and was more frequent with pertuzumab than with placebo (9.8% vs. 3.7%).

CONCLUSIONS

Pertuzumab significantly improved the rates of invasive-disease–free survival among patients with HER2-positive, operable breast cancer when it was added to trastuzumab and chemotherapy. Diarrhea was more common with pertuzumab than with placebo. (Funded by F. Hoffmann–La Roche/Genentech; APHINITY ClinicalTrials.gov number, NCT01358877.)

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Combining trastuzumab, an anti–human epidermal growth factor receptor 2 (HER2) monoclonal antibody, with adjuvant chemotherapy has markedly improved outcomes among patients with HER2-positive early breast cancer, reducing the risk of disease recurrence and death.[1-3] The combination of chemotherapy and 1 year of treatment with trastuzumab is the current standard of care for this patient population.[4]

Pertuzumab is a humanized monoclonal antibody that has mechanisms of action complementary to those of trastuzumab, binding to different domains.[5,6] Trastuzumab binds close to the transmembrane domain, inhibiting HER2 dimerization, whereas pertuzumab binds to the dimerization domain, inhibiting HER2 heterodimerization with other HER family receptors. Both antibodies induce antibody-dependent cell-mediated cytotoxicity.

In patients with HER2-positive metastatic breast cancer, pertuzumab added to trastuzumab and docetaxel has been shown to significantly prolong both progression-free survival and overall survival.[7,8] Higher frequencies of grade 3 or 4 febrile neutropenia, any neutropenia, and diarrhea were associated with the addition of pertuzumab, but the rate of cardiac adverse events was similar to that in the control group.[9] Dual HER2 blockade with pertuzumab and trastuzumab is the standard of care as first-line therapy for patients with advanced HER2-positive disease.

As part of a neoadjuvant regimen, pertuzumab added to trastuzumab plus docetaxel was shown to significantly increase the rate of pathological complete response, which led to its approval by health authorities.[10,11] Here we report the results of adding pertuzumab or placebo to chemotherapy plus trastuzumab as adjuvant treatment for patients with HER2-positive early breast cancer.

METHODS

TRIAL DESIGN

We conducted a prospective, two-group, randomized, multicenter, multinational, double-blind, placebo-controlled trial. Eligible patients were randomly assigned to receive chemotherapy and 1 year of treatment with trastuzumab plus pertuzumab or chemotherapy and 1 year of treatment with trastuzumab plus placebo (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

TRIAL OVERSIGHT

The trial, which involved 549 centers across 43 countries, was designed by the Breast International Group in collaboration with the sponsor, Hoffmann–La Roche/Genentech, and was conducted under the auspices of an independent data and safety monitoring committee. Data were gathered and analyzed at the Breast European Adjuvant Study Team data center. All parties involved in the trial were unaware of the treatment assignments. The sponsor had no access to the full database before the release of the results by the steering committee. The first draft of the manuscript was written by the first author. The steering committee vouches for the accuracy and completeness of the data and the fidelity of the trial to the protocol, available at NEJM.org. No one who is not an author contributed to writing the manuscript. The institutional review board at each participating center approved the trial protocol. All patients provided written informed consent.

PATIENTS AND ELIGIBILITY CRITERIA

Patients with nonmetastatic, adequately excised, histologically confirmed invasive HER2-positive breast cancer were eligible for participation in the trial. HER2 positivity had to be centrally confirmed and was defined as an immunohistochemical score of 3+ (scores range from 0 to 3+, with higher scores indicating higher staining intensity) in more than 10% of immunoreactive cells or amplification of *ERBB2* (the gene encoding HER2) by in situ hybridization.[12] Patients with synchronous bilateral invasive disease were eligible if both lesions were HER2-positive. Eligible patients had to have either node-positive disease or node-negative disease with a tumor diameter greater than 1.0 cm. Patients with node-negative tumors between 0.5 and 1.0 cm in diameter were initially eligible if at least one of the following high-risk features was present: histologic or nuclear grade 3, negativity for estrogen and progesterone receptors, or age younger than 35 years. Under a protocol amendment that was added after 3655 patients had undergone randomization, patients with node-negative disease were no longer eligible for enrollment, in order to enroll a patient population with the nodal-status distribution that had been anticipated when the trial was designed. The interval between definitive breast surgery and the first chemotherapy dose had to be within 8 weeks. The baseline left ventricular ejection fraction had to

be at least 55%. Patients with any of the following conditions or previous treatments were ineligible: previous invasive breast cancer; nonbreast cancer within 5 years before randomization, with the exception of carcinoma in situ of the cervix or colon, melanoma in situ, and skin basal-cell or squamous-cell carcinomas; any previous chemotherapy or radiotherapy for cancer; any previous anti-HER2 therapy or other previous anticancer biologic therapy or immunotherapy; and concurrent serious diseases interfering with planned treatment, especially serious cardiac or cardiovascular disease or severe pulmonary conditions.

RANDOMIZATION AND TREATMENT

A Web-based system was used to collect patient screening information and to randomly assign eligible patients in a 1:1 ratio to one of the two treatment groups. A permuted-blocks randomization procedure was used, with patients stratified according to nodal status, adjuvant chemotherapy regimen, hormone-receptor status, geographic region, and protocol version.

Participants received pertuzumab or placebo (840 mg as a loading dose administered intravenously, followed by 420 mg intravenously every 3 weeks) and trastuzumab (8 mg per kilogram of body weight intravenously as a loading dose, followed by 6 mg per kilogram intravenously every 3 weeks), both beginning at the first cycle of taxane therapy and continuing for a maximum of 18 cycles within 1 year. Anti-HER2 treatment was given in combination with chemotherapy according to one of the following schedules: 3 or 4 cycles (every 3 weeks) of 5-fluorouracil plus either epirubicin or doxorubicin plus cyclophosphamide, followed by 3 or 4 cycles (every 3 weeks) of docetaxel or 12 weekly cycles of paclitaxel; 4 cycles (every 3 weeks or every 2 weeks) of cyclophosphamide plus either doxorubicin or epirubicin, followed by either 4 cycles (every 3 weeks) of docetaxel or 12 weekly cycles of paclitaxel; or 6 cycles (every 3 weeks) of docetaxel plus carboplatin. Patients with hormone-receptor–positive tumors received standard endocrine therapy starting at the end of chemotherapy; the endocrine therapy was planned to continue for at least 5 years. Radiotherapy was given as clinically indicated at the end of chemotherapy and concomitantly with anti-HER2 treatment.

A physical examination and an assessment of safety and concomitant medications were conducted every 3 months during the first 24 months of participation in the trial and every 6 months thereafter. Cardiac monitoring, including an assessment of the left ventricular ejection fraction, was performed every 3 months during treatment, every 6 months up to month 36, and yearly thereafter. Hematologic and liver-function tests were conducted every 6 months up to month 60 and then annually for a total of 10 years thereafter. Other investigations were recommended only when clinically indicated.

STATISTICAL ANALYSIS

Primary End Point

The primary end point, invasive-disease–free survival, was defined as the time from randomization until the date of the first occurrence of one of the following events (hereafter referred to as invasive-disease events): recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive disease, a distant disease recurrence, contralateral invasive breast cancer, or death from any cause. Data from patients without documented events were censored at the date the patient was last known to be disease-free. This definition of invasive-disease–free survival (which excludes second primary nonbreast cancer as events) differs from the standardized definitions for efficacy end points (STEEP) definition.[13]

The stratified log-rank test was used to compare the rates of invasive-disease–free survival between the two treatment groups. The Kaplan–Meier approach was used to estimate 3-year percentages for each treatment group. The stratified Cox proportional-hazards model was used to estimate the hazard ratio and its 95% confidence interval. The primary analysis was based on the intention-to-treat population. The trial was designed to have 80% power to detect a hazard ratio of 0.75 at a 5%, two-sided significance level. A 3-year rate of invasive-disease–free survival of 89.2% was assumed for the placebo group, on the basis of the results of the Breast Cancer International Research Group 006 trial,[3] and a rate of 91.8% was assumed for the pertuzumab group, with approximately 379 events required for the primary analysis.

Secondary End Points

The secondary end points included overall survival, disease-free survival (including noninvasive breast cancers), invasive-disease–free survival (in-

cluding second primary nonbreast cancer, per the STEEP definition), relapse-free interval and distant-relapse–free interval, safety, and health-related quality of life. The final (event-driven) overall survival analysis is planned to be conducted when 640 deaths have occurred. Three interim overall survival analyses are planned, with the first reported here at an adjusted two-sided significance level of 0.00001 to control the overall alpha level at 0.05.

Cardiac Safety

Patients who received at least one dose of study treatment were included in safety analyses, according to the treatment that was actually received. The primary cardiac end point was defined as heart failure of New York Heart Association (NYHA) class III or IV and a substantial decrease in left ventricular ejection fraction, defined as a decrease of at least 10 percentage points from baseline and to below 50%, or cardiac death. Cardiac death was identified by the cardiac advisory board for the trial in accordance with a prospective definition.

A secondary cardiac end point was an asymptomatic or mildly symptomatic (NYHA class II) substantial decrease in left ventricular ejection fraction, as assessed by multiple-gated acquisition (MUGA) scanning or echocardiography, confirmed by a second left ventricular ejection fraction assessment conducted within approximately 3 weeks also showing a substantial decrease or as confirmed by the cardiac advisory board. Health-related quality of life was measured with the use of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire.

RESULTS

PATIENT CHARACTERISTICS AND ADHERENCE TO ANTI-HER2 TREATMENT

From November 2011 through August 2013, a total of 4805 patients were randomly assigned to receive chemotherapy and trastuzumab plus either pertuzumab (2400 patients) or placebo (2405 patients) (Fig. S2 in the Supplementary Appendix). The baseline characteristics of the patients were balanced between the two groups, with 63% having node-positive disease and 36% having hormone-receptor–negative disease (Table 1, and Table S1 in the Supplementary Appendix). The median follow-up period in the intention-to-treat population was 45.4 months (48.3 months for patients with node-negative disease and 44.5 months for patients with node-positive disease).

One year of treatment was completed by 84.5% of the patients in the pertuzumab group and 87.4% of the patients in the placebo group. Treatment was discontinued for safety reasons by 7.8% of the patients in the pertuzumab group and 6.4% of the patients in the placebo group (Table S5 in the Supplementary Appendix).

EFFICACY

In the analysis of the primary end point, the addition of pertuzumab was found to be associated with a significantly higher rate of invasive-disease–free survival than placebo (Fig. 1A). In total, invasive-disease events were reported in 171 patients (7.1%) in the pertuzumab group and 210 patients (8.7%) in the placebo group. The 3-year rate of invasive-disease–free survival was 94.1% in the pertuzumab group and 93.2% in the placebo group, with a hazard ratio for an invasive-disease event of 0.81 (95% confidence interval [CI], 0.66 to 1.00; P=0.045) in favor of pertuzumab. Distant recurrence occurred as the first invasive-disease event in 112 patients (4.7%) in the pertuzumab group and 139 patients (5.8%) in the placebo group, whereas the numbers of patients with locoregional recurrences were 26 (1.1%) and 34 (1.4%), respectively. Central nervous system metastases occurred as the first invasive-disease event in 1.9% of the patients in the pertuzumab group and 1.8% of the patients in the placebo group (Table 2). A visceral or central nervous system site was more common than bone as the site of first distant recurrence (Table S3 in the Supplementary Appendix). When the occurrence of a second primary nonbreast cancer was included in the analysis of invasive-disease–free survival, the number of patients with an event increased to 189 in the pertuzumab group and 230 in the placebo group, resulting in a significant between-group difference (hazard ratio, 0.82; 95% CI, 0.68 to 0.99; P=0.04) (Table S4 in the Supplementary Appendix).

The effect of pertuzumab on invasive-disease–free survival was homogeneous among the different patient subgroups (Fig. 2). Preplanned subgroup analysis revealed that the number of invasive-disease events was low among patients with node-negative disease (32 patients [3.6%] in the pertuzumab group and 29 patients [3.2%] in the placebo group), and no treatment effect was

Table 1. Demographic and Baseline Disease Characteristics of the Patients.

Characteristic	Pertuzumab Group (N=2400)	Placebo Group (N=2404)
Nodal status — no. of patients (%)		
0 positive nodes and tumor ≤1 cm*	90 (3.8)	84 (3.5)
0 positive nodes and tumor >1 cm*	807 (33.6)	818 (34.0)
1–3 positive nodes	907 (37.8)	900 (37.4)
≥4 positive nodes	596 (24.8)	602 (25.0)
Adjuvant chemotherapy regimen — no. of patients (%)†		
Anthracycline-containing regimen	1865 (77.7)	1877 (78.1)
Non–anthracycline-containing regimen	535 (22.3)	527 (21.9)
Hormone-receptor status — no. of patients (%)‡		
Negative	864 (36.0)	858 (35.7)
Positive	1536 (64.0)	1546 (64.3)
Protocol version — no. of patients (%)*		
Protocol A	1828 (76.2)	1827 (76.0)
Protocol B	572 (23.8)	577 (24.0)
Age — no. of patients (%)		
<40 yr	326 (13.6)	327 (13.6)
40–64 yr	1759 (73.3)	1784 (74.2)
≥65 yr	315 (13.1)	293 (12.2)
Pathological tumor size — no. of tumors/total no. (%)§		
0 to <2 cm	978/2400 (40.8)	948/2405 (39.4)
2 to <5 cm	1275/2400 (53.1)	1283/2405 (53.3)
≥5 cm	147/2400 (6.1)	174/2405 (7.2)

* Under the original protocol (protocol A), patients with node-negative tumors were initially eligible for participation in the trial if at least one of the following high-risk features was present: histologic or nuclear grade 3, negativity for estrogen and progesterone receptors, or age younger than 35 years. Under protocol B, which included an amendment that was added after 3655 patients had undergone randomization, patients with node-negative disease were no longer eligible for enrollment, in order to enroll a patient population with the nodal-status distribution that had been anticipated when the trial was designed.

† The chemotherapy regimen that was planned at the time of randomization is shown; the regimen that patients received may have differed.

‡ Hormone-receptor status was based on the test results determined by a central laboratory, which repeated the testing that was performed locally at each participating center. Negative denotes estrogen-receptor–negative and progesterone-receptor–negative; positive denotes estrogen-receptor–positive, progesterone-receptor–positive, or both.

§ Patients with bilateral tumors have pathological characteristics reported for both tumors; therefore, pathological tumor characteristics are summarized at the tumor level.

detectable (hazard ratio, 1.13; 95% CI, 0.68 to 1.86; P=0.64) (Fig. 1B). In the cohort of patients with node-positive disease, 139 patients (9.2%) in the pertuzumab group and 181 patients (12.1%) in the placebo group had invasive-disease events; the 3-year rate of invasive-disease–free survival was 92.0% in the pertuzumab group and 90.2% in the placebo group (hazard ratio for an invasive-disease event, 0.77; 95% CI, 0.62 to 0.96; P=0.02) (Fig. 1C). In the cohort of patients with hormone-receptor–negative tumors, 71 patients (8.2%) in the pertuzumab group and 91 patients (10.6%) in the placebo group had invasive-disease events (hazard ratio, 0.76; 95% CI, 0.56 to 1.04; P=0.08); the 3-year rate of invasive-disease–free survival was 92.8% in the pertuzumab group and 91.2% in the placebo group (Fig. 2, and Fig. S3 in the Supplementary Appendix). In the cohort of patients with hormone-receptor–positive disease, 100 patients (6.5%) in the pertuzumab group and 119 patients (7.7%) in the placebo group had invasive-disease events (hazard ratio, 0.86; 95% CI, 0.66

to 1.13; P=0.28); the 3-year rate of invasive-disease–free survival was 94.8% in the pertuzumab group and 94.4% in the placebo group (Fig. 2, and Fig. S3 in the Supplementary Appendix). The tests for interaction of the treatment effect were not significant for any of the patient subgroups considered, including those based on nodal status and hormone-receptor status (Fig. 2). On the basis of the absolute risk of avoiding an invasive-disease event by 3 years, the numbers needed to treat are 112 for the overall population, 56 for the node-positive population, and 63 for hormone-receptor–negative population.

A total of 169 patients died, 80 (3.3%) in the pertuzumab group and 89 (3.7%) in the placebo group. There was no significant treatment effect with regard to mortality at this first interim overall survival analysis (hazard ratio, 0.89; 95% CI, 0.66 to 1.21; P=0.47) (Fig. S5 in the Supplementary Appendix). Death without a previous invasive-disease event occurred in 28 patients in the pertuzumab group and 26 patients in the placebo group (Table 2).

SAFETY

The safety analysis populations included 2364 patients who were treated with at least one dose of pertuzumab and 2405 patients who received study medication (including chemotherapy or trastuzumab) but no pertuzumab (placebo group) (Table 3). The adverse-event profile during the treatment period was generally balanced between the two groups.

Primary cardiac events occurred in 17 patients (0.7%) in the pertuzumab group and in 8 patients (0.3%) in the placebo group (95% CI of the treatment difference, 0.0 to 0.8 percentage points); 15 patients in the pertuzumab group and 6 patients in the placebo group had NYHA class III or IV heart failure and a substantial decrease in left ventricular ejection fraction, and 2 patients in each group died from cardiac causes (Table 3). In the pertuzumab group, a primary cardiac event occurred in 15 patients (0.8%) in the anthracycline cohort and 2 patients (0.4%) in the non-anthracycline cohort (Table S6 in the Supplementary Appendix). At the time of the clinical cutoff, 7 events in the pertuzumab group and 4 events in the placebo group had resolved, per investigator assessment and data on left ventricular ejection fraction (details not shown). Secondary cardiac events occurred in 64 patients (2.7%) in the

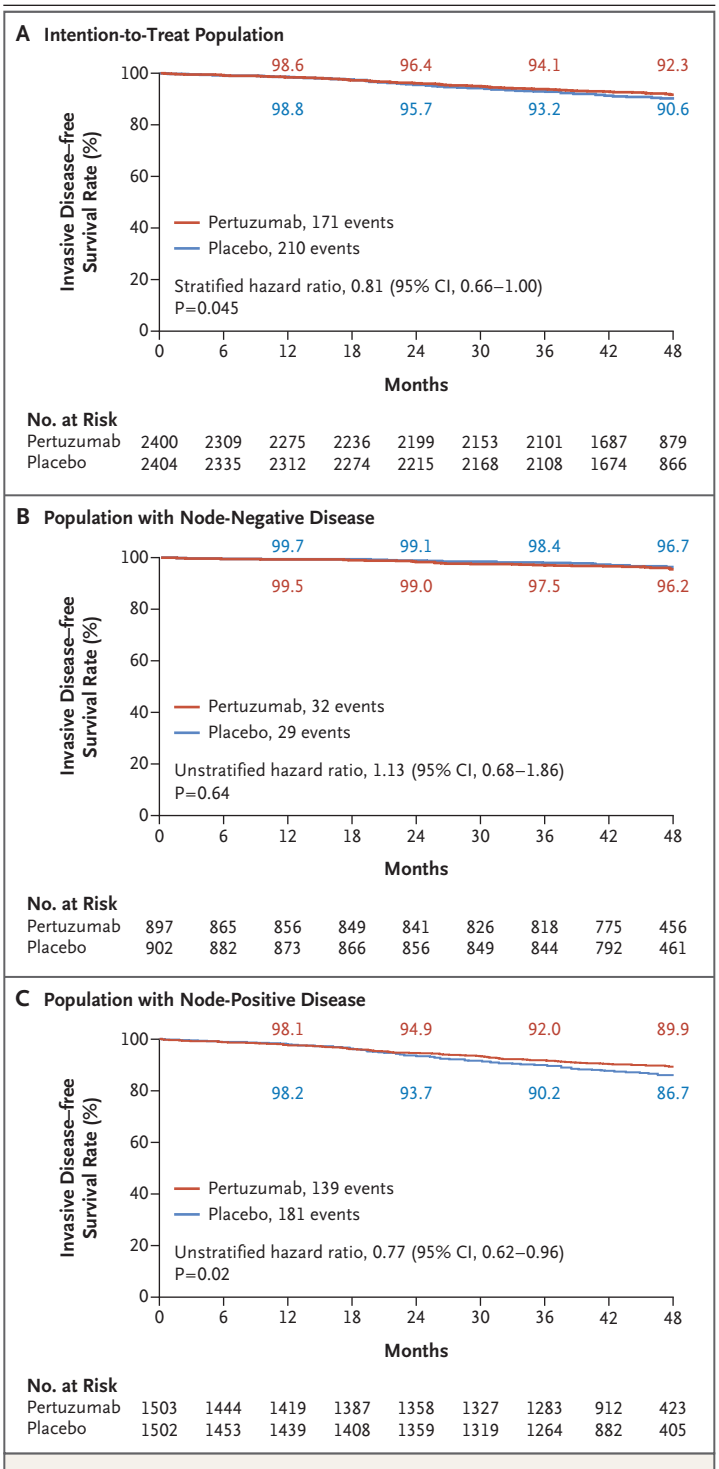

Figure 1. Kaplan–Meier Plot of Invasive-Disease–free Survival.

Invasive-disease–free survival was defined as the time from randomization until the date of the first occurrence of one of the following invasive-disease events: recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive disease, a distant disease recurrence, contralateral invasive breast cancer, or death from any cause.

Table 2. Site of First Invasive-Disease Event.*

Event	Pertuzumab Group (N = 2400)	Placebo Group (N = 2404)
	no. of patients (%)	
Any invasive-disease event	171 (7.1)	210 (8.7)
Category of first invasive-disease event		
Distant recurrence	112 (4.7)	139 (5.8)
CNS metastases	45 (1.9)	44 (1.8)
Locoregional recurrence	26 (1.1)	34 (1.4)
Contralateral breast cancer	5 (0.2)	11 (0.5)
Death without previous event	28 (1.2)	26 (1.1)

* Patients who had an additional invasive-disease event within 61 days of their first event are reported in the category according to the following hierarchy: distant recurrence, locoregional recurrence, contralateral breast cancer, and death without a previous event. A total of 38 additional patients (18 in the pertuzumab group and 20 in the placebo group) had an invasive-disease event under the standardized definitions for efficacy end points (STEEP) definition, which includes second primary nonbreast cancer. CNS denotes central nervous system.

pertuzumab group and 67 patients (2.8%) in the placebo group (95% CI of the treatment difference, –1.0 to 0.9 percentage points) (Table 3).

Diarrhea, anemia, and neutropenia were the most common (in >5% of patients) grade 3 or higher adverse events reported in the trial (Table 3). The largest absolute difference between the treatment groups was found for diarrhea (9.8% in the pertuzumab group and 3.7% in the placebo group). During targeted therapy alone, after cessation of chemotherapy, the incidence of grade 3 or higher diarrhea was 0.5% in the pertuzumab group and 0.2% in the placebo group (Table S7 in the Supplementary Appendix). The frequencies of grade 3 or higher diarrhea were lower in the anthracycline cohort (with anti-HER2 treatment started after anthracycline) than in the nonanthracycline cohort (Table S6 in the Supplementary Appendix). The largest differences between the treatment groups for all grades of adverse events were found for diarrhea (71.2% with pertuzumab and 45.2% with placebo) and rash (25.8% with pertuzumab and 20.3% with placebo) (details not shown). Baseline functional quality-of-life scores were similar between the treatment groups and remained stable during treatment, except for a temporary clinically meaningful decrease at the end of taxane treatment (Fig. S6 in the Supplementary Appendix).

DISCUSSION

The addition of pertuzumab to chemotherapy and trastuzumab as adjuvant treatment improved outcomes among patients with HER2-positive early breast cancer. A treatment effect was most detectable among patients who were at higher risk for relapse because of lymph-node involvement or hormone-receptor negativity, but the effect was statistically homogeneous throughout all subgroups. There were no new safety issues noted, but diarrhea was more common in the pertuzumab group than in the placebo group.[7,10]

The hazard ratio of 0.81 in this adjuvant context must be weighed against the absolute risk of disease recurrence. It should be noted that the 3-year invasive-disease–free survival rate of 93.2% in the placebo group was higher than our prospectively assumed rate of 89.2%, and therefore it took longer than expected to reach the required number of events for the primary analysis. The median period of follow-up for this primary analysis was 45.4 months, which might be too short for a full assessment of the effect size, especially in the cohorts of patients with hormone-receptor–positive or node-negative disease. Subsequent analyses are planned in accordance with the trial protocol, with up to 10 years of minimum follow-up and the next analysis 2.5 years after this primary analysis.

Evaluations of patient benefit must always relate the magnitude of the effect to potential side effects. Pertuzumab was associated with a higher rate of diarrhea that was generally mild (grade 1 or 2). The rate of treatment discontinuation due to adverse events was 1.1 percentage points higher with pertuzumab than with placebo. The positive results of our trial are consistent with those of the neoadjuvant NeoSphere trial, although the two trials did not use the same chemotherapy regimens. The addition of pertuzumab to trastuzumab–docetaxel neoadjuvant treatment for 12 weeks in the randomized, multicenter, open-label NeoSphere trial resulted in a significant increase in the pathological complete response rate, from 29.0% to 45.8%.[10] The NeoSphere trial showed a numerically higher 5-year rate of progression-free survival among patients receiving only 12 weeks of pertuzumab than among patients receiving trastuzumab alone (hazard ratio for progression or death, 0.69; 95% CI, 0.34 to 1.40).[11] The results seen in studies of dual HER2 blockade in the neoadjuvant context have not always been in concor-

Subgroup	Pertuzumab	Placebo	Unstratified Hazard Ratio for Invasive-Disease Event (95% CI)	3-Yr Invasive Disease–free Survival Rate		P Value for Interaction
				Pertuzumab	Placebo	
	no. of patients with an invasive-disease event/total no.			%		
All patients	171/2400	210/2404	0.82 (0.67–1.00)	94.1	93.2	NA
No. of positive nodes						0.37
0 Positive nodes, tumor ≤1 cm	2/90	4/84	0.48 (0.09–2.60)	97.7	97.5	
0 Positive nodes, tumor >1 cm	30/807	25/818	1.23 (0.72–2.10)	97.5	98.5	
1–3 Positive nodes	55/907	75/900	0.73 (0.52–1.04)	94.9	93.8	
≥4 Positive nodes	84/596	106/602	0.79 (0.59–1.05)	87.5	84.7	
Nodal status						0.17
Node-negative	32/897	29/902	1.13 (0.68–1.86)	97.5	98.4	
Node-positive	139/1503	181/1502	0.77 (0.62–0.96)	92.0	90.2	
Adjuvant chemotherapy regimen						1.00
Anthracycline	139/1865	171/1877	0.82 (0.66–1.03)	93.8	93.0	
Nonanthracycline	32/535	39/527	0.82 (0.51–1.31)	94.9	94.0	
Hormone-receptor status						0.54
Positive	100/1536	119/1546	0.86 (0.66–1.13)	94.8	94.4	
Negative	71/864	91/858	0.76 (0.56–1.04)	92.8	91.2	
Protocol version						0.69
Protocol A	120/1828	143/1827	0.84 (0.66–1.08)	94.7	94.1	
Protocol B	51/572	67/577	0.77 (0.53–1.11)	91.9	90.6	
Menopausal status at screening						0.07
Before menopause	93/1152	96/1173	0.99 (0.75–1.32)	93.5	93.7	
After menopause	78/1242	113/1220	0.68 (0.51–0.91)	94.5	92.7	
Age group						0.78
<40 yr	30/326	32/327	0.96 (0.59–1.59)	93.4	93.1	
40–49 yr	48/708	53/702	0.89 (0.60–1.32)	94.5	94.3	
50–64 yr	69/1051	91/1082	0.78 (0.57–1.07)	94.3	93.3	
≥65 yr	24/315	34/293	0.70 (0.41–1.17)	92.9	90.6	
Tumor size						0.20
<2 cm	41/977	64/944	0.62 (0.42–0.92)	97.0	94.6	
2 to <5 cm	108/1273	115/1283	0.96 (0.74–1.24)	92.5	93.0	
≥5 cm	22/147	31/174	0.85 (0.49–1.47)	87.5	87.5	
Female sex	171/2397	209/2396	0.82 (0.67–1.01)	94.1	93.2	NA

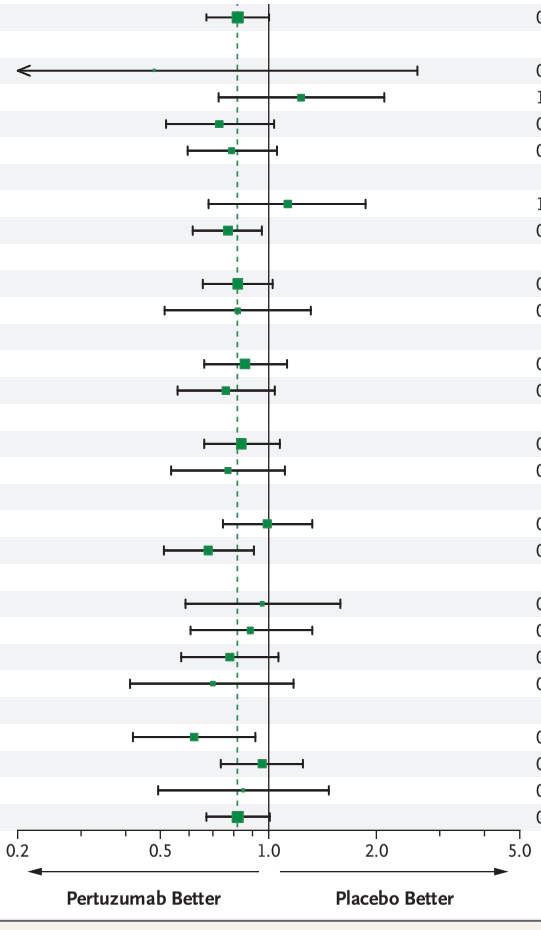

Figure 2. Forest Plot of Invasive-Disease–free Survival.

Hormone-receptor status was based on the test results determined by a central laboratory, which repeated the testing that was performed locally at each participating center. For hormone-receptor status, negative denotes estrogen-receptor–negative and progesterone-receptor–negative; positive denotes estrogen-receptor–positive, progesterone-receptor–positive, or both. Under the original protocol (protocol A), patients with node-negative tumors were initially eligible for participation in the trial if at least one of the following high-risk features was present: histologic or nuclear grade 3, negativity for estrogen and progesterone receptors, or age younger than 35 years. Under protocol B, which included an amendment that was added after 3655 patients had undergone randomization, patients with node-negative disease were no longer eligible for enrollment. NA denotes not applicable.

Table 3. Summary of Adverse Events (Safety Analysis Population).*

Event	Pertuzumab Group (N=2364)	Placebo Group (N=2405)
	no. of patients (%)	
Grade ≥3 adverse event	1518 (64.2)	1379 (57.3)
Neutropenia	385 (16.3)	377 (15.7)
Febrile neutropenia	287 (12.1)	266 (11.1)
Neutrophil count decreased	228 (9.6)	230 (9.6)
Diarrhea†	232 (9.8)	90 (3.7)
Anemia	163 (6.9)	113 (4.7)
Fatal adverse event‡	18 (0.8)	20 (0.8)
Primary cardiac event§	17 (0.7)	8 (0.3)
NYHA class III or IV heart failure and substantial decrease in LVEF¶	15 (0.6)	6 (0.2)
Definite or probable cardiac death	2 (0.1)	2 (0.1)
Secondary cardiac event‖	64 (2.7)	67 (2.8)
Identified automatically from LVEF assessments	50 (2.1)	47 (2.0)
Identified by cardiac advisory board	14 (0.6)	20 (0.8)

* The summary of grade 3 or higher adverse events includes adverse events with onset from the first dose of any study treatment through 28 days after the final dose of study treatment. The incidence of all other grade 3 or higher adverse events was lower than 5% in both safety analysis population groups. A summary of adverse events according to chemotherapy regimen is provided in Table S6 in the Supplementary Appendix. NYHA denotes New York Heart Association.

† For patients with diarrhea, early intervention with loperamide as well as fluid and electrolyte replacement was to be considered. The taxane dose had to be reduced by one dose level if grade 3 diarrhea occurred or unresolved grade 2 diarrhea required a delay of the next chemotherapy cycle.

‡ The fatal adverse events according to body system were neoplasms (benign, malignant, and unspecified) (9 patients in the pertuzumab group and 8 patients in the placebo group); cardiac disorders (2 and 3); infections and infestations (1 and 3); respiratory, thoracic, and mediastinal disorders (2 and 2); gastrointestinal disorders (0 and 3); injury, poisoning, and procedural complications (2 and 0); blood and lymphatic system disorders (1 and 0); metabolism and nutrition disorders (1 and 0); nervous system disorders (1 and 0); and psychiatric disorders (0 and 1). One patient in the pertuzumab group had a fatal adverse event that was reported in both the nervous system disorders and the injury, poisoning, and procedural complications body-system categories.

§ Primary cardiac events are counted over the whole trial period, including post-treatment follow-up. The 95% confidence interval (with Hauck–Anderson correction) for the between-group difference was 0.0 to 0.8 percentage points.

¶ A substantial decrease in left ventricular ejection fraction (LVEF) is defined as a decrease of 10 or more percentage points, to a value lower than 50%.

‖ Secondary cardiac events are counted up to the date of recurrence or the end of post-treatment follow-up, whichever occurs earlier, and are counted only for patients who have not had a primary cardiac event. The 95% confidence interval (with Hauck–Anderson correction) for the between-group difference was –1.0 to 0.9 percentage points.

dance with the results seen when it is used as adjuvant therapy.[14]

Our trial has several strengths and limitations. It is a large, adequately powered, double-blind, placebo-controlled, phase 3 trial. The protocol amendment to limit the number of patients with node-negative disease and increase the sample size was implemented during the recruitment phase, in order to yield a patient population with the nodal-status distribution that had been anticipated when the study was designed. The reasons for the higher-than-initially-foreseen enrollment of patients with node-negative disease remain unclear. Because only 1 year of pertuzumab treatment was investigated in this trial, the effectiveness of other treatment durations remains unknown. Ongoing studies are exploring whether after 6 months of neoadjuvant treatment with pertuzumab, patients will require additional treatment after surgery (ClinicalTrials.gov numbers, NCT02131064 and NCT02132949).

In conclusion, we found that pertuzumab, when added to chemotherapy and trastuzumab, significantly improved the rates of invasive-disease–free

survival among patients with HER2-positive early breast cancer. Pertuzumab was associated with more toxic effects than placebo — mainly low-grade diarrhea.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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