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Adaptive Randomization of Neratinib in Early Breast Cancer

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ABSTRACT

BACKGROUND

The heterogeneity of breast cancer makes identifying effective therapies challenging. The I-SPY 2 trial, a multicenter, adaptive phase 2 trial of neoadjuvant therapy for high-risk clinical stage II or III breast cancer, evaluated multiple new agents added to standard chemotherapy to assess the effects on rates of pathological complete response (i.e., absence of residual cancer in the breast or lymph nodes at the time of surgery).

METHODS

We used adaptive randomization to compare standard neoadjuvant chemotherapy plus the tyrosine kinase inhibitor neratinib with control. Eligible women were categorized according to eight biomarker subtypes on the basis of human epidermal growth factor receptor 2 (HER2) status, hormone-receptor status, and risk according to a 70-gene profile. Neratinib was evaluated against control with regard to 10 biomarker signatures (prospectively defined combinations of subtypes). The primary end point was pathological complete response. Volume changes on serial magnetic resonance imaging were used to assess the likelihood of such a response in each patient. Adaptive assignment to experimental groups within each disease subtype was based on Bayesian probabilities of the superiority of the treatment over control. Enrollment in the experimental group was stopped when the 85% Bayesian predictive probability of success in a confirmatory phase 3 trial of neoadjuvant therapy reached a prespecified threshold for any biomarker signature ("graduation"). Enrollment was stopped for futility if the probability fell to below 10% for every biomarker signature.

RESULTS

Neratinib reached the prespecified efficacy threshold with regard to the HER2-positive, hormone-receptor-negative signature. Among patients with HER2-positive, hormone-receptor-negative cancer, the mean estimated rate of pathological complete response was 56% (95% Bayesian probability interval [PI], 37 to 73%) among 115 patients in the neratinib group, as compared with 33% among 78 controls (95% PI, 11 to 54%). The final predictive probability of success in phase 3 testing was 79%.

CONCLUSIONS

Neratinib added to standard therapy was highly likely to result in higher rates of pathological complete response than standard chemotherapy with trastuzumab among patients with HER2-positive, hormone-receptor-negative breast cancer. (Funded by QuantumLeap Healthcare Collaborative and others; I-SPY 2 TRIAL ClinicalTrials.gov number, NCT01042379.)

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*A complete list of the participating centers and investigators in the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2 (I-SPY 2 TRIAL) is provided in the Supplementary Appendix, available at NEJM.org.

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THE TREATMENT OF AGGRESSIVE, LOCALLY advanced breast cancers increasingly includes neoadjuvant therapy before surgical resection, thus providing a window of opportunity to tailor treatments on the basis of early assessments of the molecular characteristics of the cancer and their response to therapy. The existence of a well-characterized, surrogate end point — pathological complete response as assessed at the time of surgery — that is strongly correlated with both event-free survival and overall survival makes neoadjuvant therapy a particularly useful context for the rapid clinical development of targeted therapies. The I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2) provided a standing, or “platform,” framework that used adaptive randomization for the efficient, focused clinical development of paired therapies and biomarkers. The overall objective of the trial was to reduce the cost, time, and number of patients that were needed to identify effective drugs for the treatment of aggressive, locally advanced breast cancer.^{1,2}

In this trial, patients underwent adaptive randomization to standard chemotherapy with an experimental regimen or standard chemotherapy alone. The adaptive randomization algorithm uses the molecular characteristics of the cancers and incorporates accumulated outcome data to efficiently identify the biomarker signatures of tumor subtypes — combinations of molecular subtypes — in which specific agents are most effective. Therapies that reach prespecified thresholds of efficacy in one or more specific biomarker signatures are said to “graduate” from the I-SPY 2 trial.

Here we report the efficacy and safety results from the experimental-therapy group of the I-SPY 2 trial that evaluated the tyrosine kinase inhibitor neratinib (HKI-272; Puma Biotechnology), an irreversible small-molecule inhibitor of the ErbB and the human epidermal growth factor receptor (HER) kinase family (epidermal growth factor receptor, HER2, and HER4). The primary end point of the trial was pathological complete response. The secondary end points of event-free survival and overall survival are not yet mature and are not reported in this article. The secondary end point of residual cancer burden, defined as a calculated assessment of residual carcinoma from routine pathological testing of sections of the primary breast-tumor site and the regional lymph nodes

after the completion of neoadjuvant therapy, is also not reported here. We have also described the results in the veliparib–carboplatin group (in which the experimental therapy reached the prespecified threshold for efficacy in this trial) and the AKT inhibitor MK-2206.^{3,4} Evaluations of other experimental-therapy groups have been completed or are ongoing.

Neratinib has shown promising activity against HER2-positive metastatic breast cancer.^{5,6} There is also evidence of preclinical activity against HER2-negative tumor cells,^{7,8} which suggests that the pan-ErbB–HER kinase activity against EGFR and possibly HER4 might have activity beyond HER2-positive tumors.⁹ The adaptive randomization approach used in this trial offered the opportunity to test the possibility of efficacy in HER2-negative tumors while minimizing the exposure of patients to treatments that may be ineffective. Because neratinib was introduced before the dual targeting of HER2 became the standard of care in neoadjuvant treatment, it was tested against, rather than being combined with, trastuzumab.

METHODS

TRIAL DESIGN

We designed this adaptive phase 2 multicenter, platform trial with multiple experimental-therapy groups to assess new agents combined with standard neoadjuvant therapy in patients with breast cancer who are at high risk for early recurrence.¹⁰ A common control group was used. No more than 120 patients could be assigned to any experimental-therapy group. The primary end point was pathological complete response (i.e., no residual cancer in the breast or lymph nodes at the time of surgery).¹¹

Biomarker assessments (according to HER2 status, hormone-receptor status, and results on a 70-gene profile (MammaPrint, Agendia) were performed at baseline and were used to classify patients according to eight prospectively defined subtypes for the purposes of randomization.^{1,2} Tumor receptors were assessed and used for adaptive randomization as described in Figure 1A and by Rugo et al. in this issue of the *Journal*.¹² Ten clinically relevant biomarker signatures were used to assess efficacy: any biomarker, hormone-receptor positive, hormone-receptor negative, HER2 positive, HER2 negative, high-risk category 2 on the MammaPrint assay, HER2 positive and hor-

hormone-receptor positive, HER2 positive and hormone-receptor negative, HER2 negative and hormone-receptor positive, and HER2 negative and hormone-receptor negative.¹² For details regarding the tumor subtypes and biomarker signatures, see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The prespecified thresholds of efficacy in this trial was defined as a Bayesian predictive probability of success of 85% or more in a simulated phase 3 trial of neoadjuvant therapy in 300 patients who had undergone randomization in a 1:1 ratio (see the Supplementary Appendix).^{1,14} Predictive probabilities of success were based on power calculations for a trial involving 300 patients, as described in the protocol, available at NEJM.org.^{1,14} The stringent prespecified efficacy threshold for moving a therapy out of phase 2 of this trial — compelling evidence of efficacy in a trial group — ensured that the sample size for the confirmatory phase 3 trial would be substantially reduced. Cessation of enrollment was announced only when all patients in the group and its concurrent controls completed their definitive surgical treatment with the assessment of pathological response or if a patient had disease progression or withdrew from the trial. Futility was considered to be reached if the predictive probability of success in a phase 3 trial was determined to be less than 10% for all 10 biomarker signatures.

ELIGIBILITY AND ENROLLMENT

Eligible women were 18 years of age or older, had clinical stage II or III disease, and had not received surgical or systemic therapy for this cancer previously. The longest diameter of the tumor had to be at least 2.5 cm by any clinical assessment; imaging also had to show that the tumor was at least 2 cm. Participants had to have an Eastern Cooperative Oncology Group performance-status score (scores range from 0 to 5, with higher numbers indicating greater disability) of 0 (asymptomatic) or 1 (mild symptoms). Participants had to be able to undergo multiple magnetic resonance imaging (MRI) examinations and had to be willing to undergo serial core biopsies. We excluded patients who had tumors that were designated as hormone-receptor positive and low risk according to the 70-gene assay, because such patients have a more favorable prognosis than those with a result on the 70-gene assay showing high risk, especially in the first 5 years,¹⁵ and the benefit

of chemotherapy is low in this population; thus, the exposure to investigational agents is not justified. Patients with HER2-positive, hormone-receptor-negative cancer were eligible regardless of the results on the 70-gene profile.¹⁶

All the patients provided written informed consent when they underwent screening for the trial. A second consent was obtained after the patient underwent randomization and before treatment was initiated.

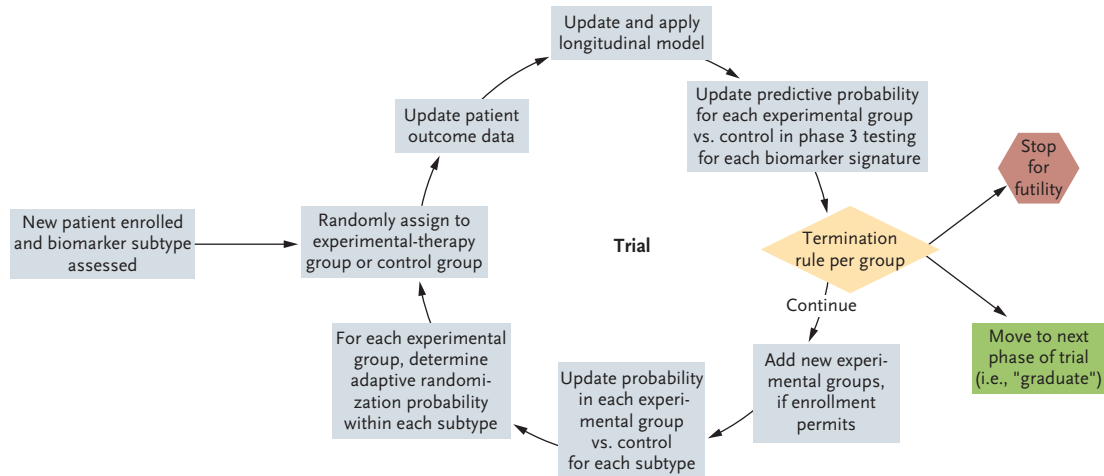
TREATMENT

All the participants received standard neoadjuvant therapy, which consisted of 12 weekly cycles of paclitaxel at a dose of 80 mg per square meter of body-surface area, administered intravenously, followed by 4 cycles of doxorubicin at a dose of 60 mg per square meter and cyclophosphamide at a dose of 600 mg per square meter, administered intravenously every 2 to 3 weeks. In the analyses presented in this article, we compared patients who were randomly assigned to receive neratinib (at a dose of 240 mg per day) for the first 12 weeks in addition to standard chemotherapy with those assigned to standard chemotherapy alone (control). Patients in the control group who had HER2-positive cancer also received trastuzumab for the first 12 weeks (with a loading dose of 4 mg per kilogram of body weight in the first cycle, followed by a maintenance dose of 2 mg per kilogram in cycles 2 through 12) (Fig. 1B).

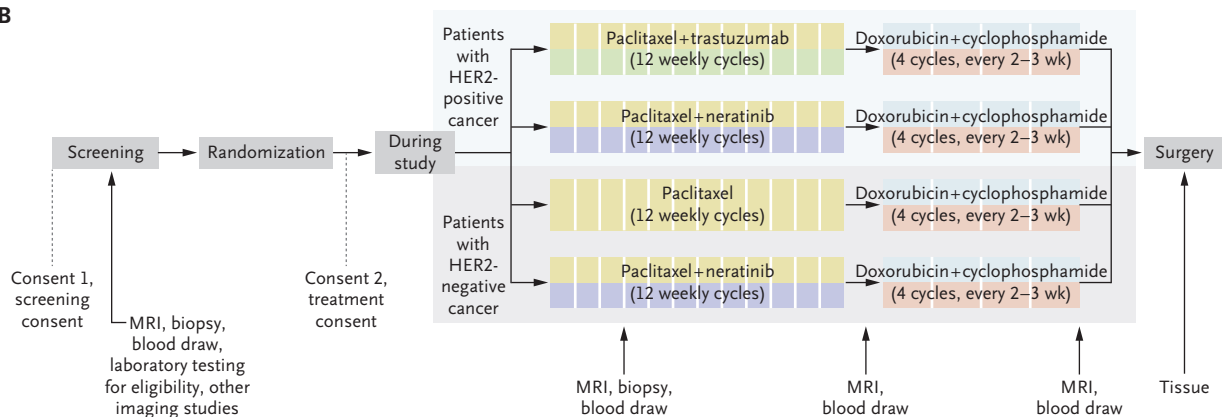
Subsequent surgery, which consisted of sentinel-node dissection in patients with node-negative cancer and axillary-node dissection in those with node-positive cancer at diagnosis, was performed according to National Comprehensive Cancer Network and local practice guidelines. Radiation therapy and endocrine adjuvant therapy were recommended after surgery according to standard guidelines.¹⁷

A modification to the protocol that was approved in January 2012 added a prophylactic course of loperamide to control diarrhea in patients receiving neratinib. Loperamide was administered on day 1 of neratinib therapy at an initial dose of 4 mg, followed 8 hours later by a dose of 2 mg, and then twice daily for 2 weeks at a dose of 2 mg. Patients were instructed to take an additional 2 mg immediately after the first unformed stool and then 2 mg every 4 hours until they had no diarrhea for 12 consecutive hours (a maximum of 16 2-mg pills per day). The frequency of loper-

A



B



C

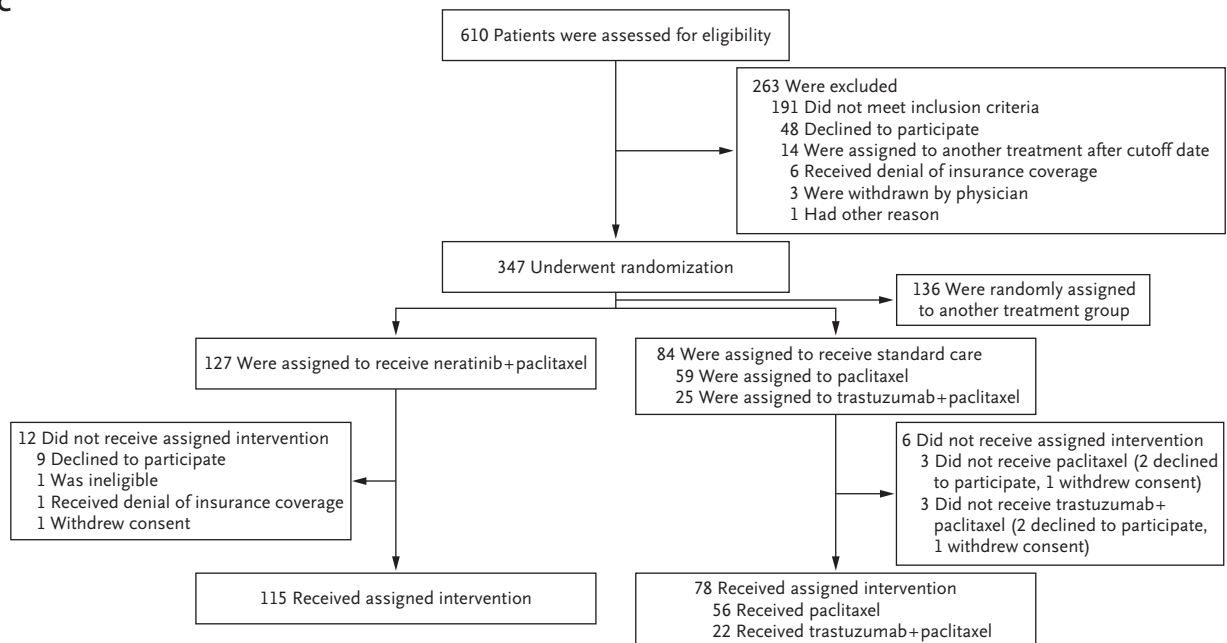


Figure 1 (facing page). Trial Design.

Panel A shows the steps in the adaptive-randomization process used in this trial. The longitudinal model refers to the course of the patient through the neoadjuvant therapy, as measured by serial magnetic resonance imaging (MRI) scans. Panel B shows the schema for the experimental-therapy group that received neratinib and for the control group. After screening, patients with human epidermal growth factor receptor 2 (HER2)-positive cancer were eligible to undergo adaptive randomization to receive neratinib plus paclitaxel. The control was trastuzumab plus paclitaxel. Patients with HER2-negative cancer were eligible to be randomly assigned to receive neratinib plus paclitaxel; the control was paclitaxel alone. Patients with HER2-positive cancer or HER2-negative cancer then received standard treatment with doxorubicin and cyclophosphamide to complete their neoadjuvant therapy. Panel C shows the details regarding the screening, randomization, and treatment of the patients. Patients were categorized according to whether they received no experimental therapy or at least one dose of experimental therapy.

amide administration was decreased at the discretion of the patient once the diarrhea was controlled.

ASSESSMENTS

MRI and core biopsy were performed during screening in all participants who provided consent; these procedures were repeated 3 weeks after the initiation of treatment. MRI was repeated between chemotherapy regimens and before surgery. Pathologists were trained in the method of assessment of the residual cancer burden (a secondary end point not reported here). All the patients had to have a core-biopsy specimen that was sufficient for expression-array profiling in order to generate the results of the 70-gene MammaPrint assay, the TargetPrint HER2 gene-expression assay,¹³ and the 44K full-genome microarray (all from Agendia). The gene assays were purchased at the research rate. Agendia supplied the analysis of the results of the 70-gene assay but had no role in the trial design, the accrual or interpretation of data, the preparation of the manuscript, or the decision to submit the manuscript for publication. Reverse phase phosphoprotein arrays were generated from the initial core.^{18,19} Patients were stratified according to risk status on the 70-gene profile (high-risk category 1 vs. 2), as determined by the prespecified median cutoff point on the continuous index score among participants in the

I-SPY 1 trial who met the eligibility criteria for inclusion in the I-SPY 2 trial (Fig. S1 in the Supplementary Appendix).²⁰

TRIAL OVERSIGHT

The trial was designed by the investigators. The sponsors had no role in the trial design, the writing of the manuscript, or the decision to submit the manuscript for publication. The drug manufacturer (Puma Biotechnology) supplied the agent but had no role in the design or execution of the trial, the collection or analysis of the data, the preparation of the manuscript, or the decision to submit it for publication. All the participating sites received approval from an institutional review board. A data and safety monitoring board met monthly and continues to do so in the ongoing trial. The manuscript was written entirely by the authors, who made the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and analyses reported (the secondary end points of event-free survival, overall survival, and residual cancer burden are not reported here, as stated above) and for adherence of the trial to the protocol.

STATISTICAL ANALYSIS

We report the final Bayesian probability distributions of the rates of pathological complete response in the neratinib group and the concurrently randomized control group for each of the 10 biomarker signatures by providing the estimated rates of pathological complete response (means of the final respective distributions) and 95% Bayesian probability intervals. These distributions were based on the final observed results according to the eight biomarker subtypes and were calculated with the use of a covariate-adjusted logistic model in which the covariates were HER2 status, hormone-receptor status, and results on the 70-gene assay. We do not provide the raw data for the individual biomarker subtypes because our analysis enables greater precision than would any raw-data estimates of the rate of pathological complete response, whether within subtypes or across subtypes in signatures. Using the final distributions of the rates of pathological complete response for each of the 10 biomarker signatures, we calculated the probabilities that the rate of pathological complete response with neratinib was greater than the rate in the control group, as well as the respective predictive

Table 1. Characteristics of the Patients at Baseline.*

| Characteristic | Neratinib (N=115) | Control (N=78) |
|---|-------------------|----------------|
| Median age (range) — yr | 51 (24–70) | 48 (24–71) |
| Race — no. (%)† | | |
| White | 92 (80) | 62 (79) |
| Asian | 16 (14) | 11 (14) |
| Black | 7 (6) | 5 (6) |
| Menopausal status — no. (%) | | |
| Premenopausal | 56 (49) | 40 (51) |
| Perimenopausal | 4 (3) | 6 (8) |
| Postmenopausal | 44 (38) | 22 (28) |
| Not applicable | 11 (10) | 10 (13) |
| Hormone-receptor status — no. (%) | | |
| Positive | 60 (52) | 43 (55) |
| Negative | 55 (48) | 35 (45) |
| HER2 status — no. (%)‡ | | |
| Positive | 65 (57) | 22 (28) |
| Negative | 50 (43) | 56 (72) |
| Clinical presentation | | |
| Median tumor diameter (range) on MRI — cm | 3.7 (1.5–11.8) | 4.0 (1.2–13.0) |
| Axillary-node status — no. (%) | | |
| Palpable | 54 (47) | 36 (46) |
| Nonpalpable | 61 (53) | 42 (54) |

* After screening, patients with human epidermal growth factor receptor 2 (HER2)-positive cancer were randomly assigned to receive either neratinib plus paclitaxel (neratinib group) or trastuzumab plus paclitaxel (control); patients with HER2-negative cancer were randomly assigned to receive either neratinib plus paclitaxel or paclitaxel alone (control). There were no significant differences between the trial groups except for HER2 status (owing to the effects of adaptive randomization) ($P<0.001$ by Fisher's exact test). Percentages may not total 100 because of rounding.

† Race was self-reported.

‡ HER2 status was determined by means of immunohistochemical and fluorescence in situ hybridization assays and the TargetPrint gene expression assay. A patient was considered to have HER2-positive cancer if any of the three assays were positive.

tients withdrew before receiving treatment, which left 115 patients who could be evaluated. Of the 84 patients who were randomly assigned to the control group, 78 could be evaluated for a pathological complete response (Fig. 1C).

At baseline, the neratinib group and the control group were well balanced with regard to demographic characteristics, hormone-receptor status, and clinical presentation (Table 1). The only significant difference between the two groups was HER2 status; adaptive randomization resulted in a larger percentage of participants with HER2-positive cancer in the neratinib group than in the control group (57% vs. 28%).

EFFICACY

Figure 2 shows the Bayesian posterior probability distributions for 4 of the 10 biomarker signatures. Neratinib reached the prespecified threshold of efficacy in the I-SPY 2 trial with regard to the HER2-positive, hormone-receptor-negative signature (Table 2). Among patients with HER2-positive, hormone-receptor-negative cancer, the estimated rate of pathological complete response was 56% (95% probability interval [PI], 37 to 73%) in the neratinib group, as compared with 33% (95% PI, 11 to 54%) in the control group (Fig. 2A). The resulting probability that neratinib was superior to standard therapy was 95%, and the probability of the success of neratinib in a phase 3 clinical trial involving 300 patients was 79% (Table 2).

Although neratinib reached the prespecified threshold of efficacy in this trial only with regard to patients with HER2-positive, hormone-receptor-negative cancer (Table 2), there was some evidence of superior activity over control with regard to several other biomarker signatures. Among participants with HER2-positive, hormone-receptor-positive cancer, the estimated rate of pathological complete response was 30% in the neratinib group, as compared with 17% in the control group (Fig. 2C). There was a 91% probability of the superiority of neratinib over standard therapy and a 65% predicted probability of success in a phase 3 trial. Similarly, among all the patients with HER2-positive cancer (regardless of hormone-receptor status), the rate of pathological complete response was 39% in the neratinib group, as compared with 23% in the control group (Fig. 2B). The probability of the superiority of neratinib over standard therapy was 95%, with a 73% pre-

probabilities of success in a future trial. Additional details of the trial design are provided in the Supplementary Appendix.

RESULTS

PATIENT POPULATION

During the period from March 2010 through January 2013, a total of 127 participants were enrolled and randomly assigned to receive neratinib; 12 pa-

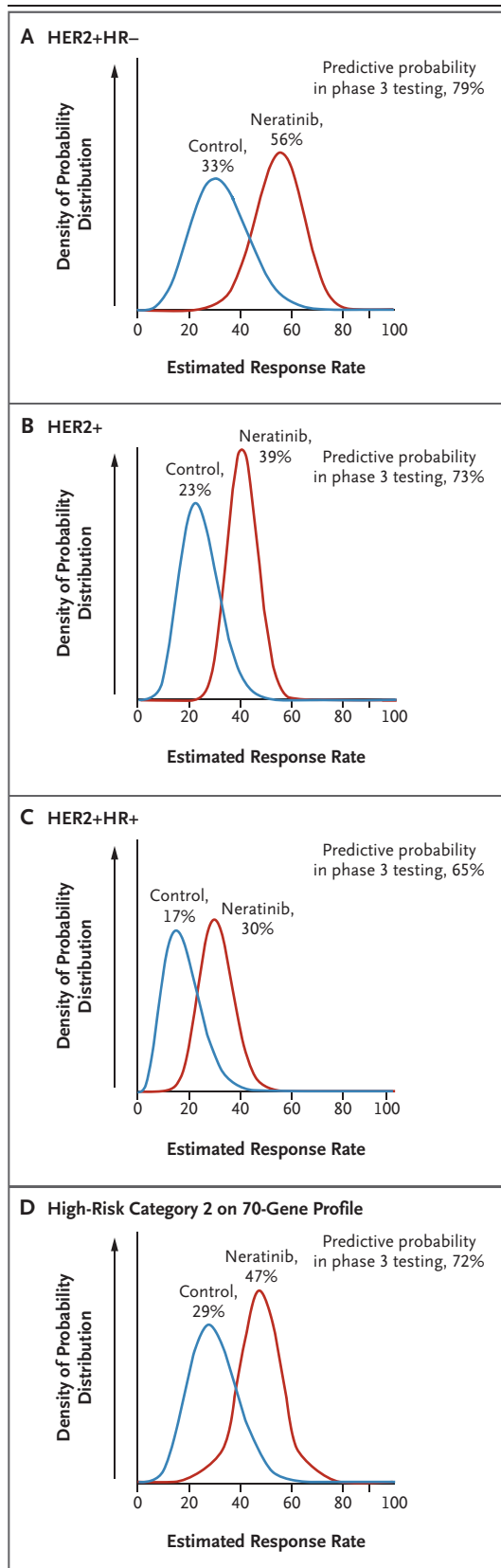


Figure 2. Probability Distributions for Selected Biomarker Signatures.

Shown are histograms of the posterior (final) probability distributions for the rates of pathological complete response in the neratinib group and the control group for 4 of the 10 biomarker signatures. Neratinib reached the prespecified threshold for efficacy in phase 2 of this adaptive randomization trial with regard to the HER2-positive, hormone-receptor (HR)-negative biomarker signature. The estimated rate of pathological complete response is the mean of the respective distribution. The predictive probability in phase 3 testing was a calculation that was based on the respective pair of histograms. The status of high-risk category 2 on the 70-gene profile was determined with the use of the MammaPrint assay (see the Supplementary Appendix).

dicted probability of success in a phase 3 trial of neoadjuvant therapy.

Patients who were identified as having the highest risk scores (category 2) on the 70-gene assay also appeared to have some benefit from neratinib as compared with the control, with comparative rates of pathological complete response of 48% versus 29% (Fig. 2D), a 93% probability of the superiority of neratinib over standard treatment, and a 72% predicted probability of success in a phase 3 trial. There was very little activity in participants with HER2-negative, hormone-receptor-positive cancer or with HER2-negative, hormone-receptor-negative cancer, especially those patients who had been categorized as having a high-risk category 1 status on the 70-gene profile (Table 2); the adaptive randomization algorithm stopped assigning patients with these subtypes to receive neratinib during the course of the trial (Table S2 in the Supplementary Appendix).

SAFETY

The combination of neratinib and paclitaxel in the context of neoadjuvant therapy was associated with safety and toxicity profiles that were similar to those in previous studies involving participants with advanced breast cancer.⁶ Diarrhea was the most common adverse event, and diarrhea of grade 3 or 4 was noted in 38% of the patients in the neratinib group. Diarrhea was mitigated by dose reductions, supportive measures, or both; further reductions in frequency or severity were noted after the protocol was modified to include prophylactic loperamide therapy (Table S3 in the Supplementary Appendix). The rates of several

Table 2. Final Posterior and Predictive Probabilities of Neratinib Efficacy with Regard to 10 Biomarker Signatures.

| Biomarker Signature | Estimated Rate of Pathological Complete Response (95% Probability Interval) | | Probability of Neratinib Being Superior to Control | Predictive Probability of Success in Phase 3 Trial |
|--|---|------------|---|---|
| | Neratinib | Control | | |
| | <i>percent</i> | | | |
| Any | 33 (24–40) | 23 (14–33) | 93 | 48 |
| Hormone-receptor positive | 23 (13–33) | 16 (6–28) | 81 | 40 |
| Hormone-receptor negative | 44 (30–55) | 31 (17–45) | 92 | 58 |
| HER2 positive | 39 (28–51) | 23 (8–38) | 95 | 73 |
| HER2 negative | 28 (15–37) | 24 (13–35) | 69 | 25 |
| High-risk category 2 on 70-gene profile* | 48 (30–60) | 29 (11–48) | 93 | 72 |
| HER2 positive, hormone-receptor positive | 30 (18–44) | 17 (3–32) | 91 | 65 |
| HER2 positive, hormone-receptor negative | 56 (37–73) | 33 (11–54) | 95 | 79 |
| HER2 negative, hormone-receptor positive | 14 (3–25) | 16 (5–27) | 42 | 14 |
| HER2 negative, hormone-receptor negative | 38 (22–50) | 31 (15–46) | 77 | 40 |

* The status of high-risk category 2 on the 70-gene profile was determined with the use of the MammaPrint assay (see the Supplementary Appendix).

hematologic and gastrointestinal adverse events were significantly higher in the neratinib group than in the control group, including vomiting of grade 1 or 2 ($P=0.045$), diarrhea of grade 1 or 2 or of grade 3 or 4 ($P<0.001$ for both comparisons), abnormalities in the aspartate aminotransferase level of grade 1 or 2 ($P<0.001$), and abnormalities in the alanine aminotransferase level of grade 1 or 2 ($P<0.001$) or of grade 3 or 4 ($P=0.009$) (Table 3).

Three serious adverse events — pneumonitis in one patient in the control group and dehydration in two patients in the neratinib group — were reported by the investigator as being probably or definitely attributable to the protocol-directed therapy. No case of symptomatic congestive heart failure occurred during the trial. One patient had a grade 3 decline in the left ventricular ejection fraction. No deaths were considered by the investigators to be related to treatment.

Dose reductions or interruptions in the neratinib group occurred in 64% of the patients for neratinib and in 39% for paclitaxel. In the control group, dose reduction or interruptions occurred in 12% of the patients. A total of 11% of patients in the neratinib group, as compared with 1% of the patients in the control group, discontinued the treatment early (i.e., during the taxane phase) owing to toxic effects (Table 3).

DISCUSSION

In this article, we describe the efficacy, leading to continuation to phase 3 testing, of an experimental therapy consisting of paclitaxel plus neratinib followed by doxorubicin and cyclophosphamide in patients with high-risk breast cancer that was characterized by a HER2-positive, hormone-receptor-negative biomarker signature. With regard to this molecular subtype, neratinib was shown to be superior to the current standard of care, trastuzumab, with a high degree of probability (95%), as measured by the estimated mean rate of pathological complete response of 56% in the neratinib group versus 33% in the control group. In terms of the primary goal of the trial, which was to facilitate the rapid identification of pairs of agents and biomarker profiles that are likely to succeed in subsequent phase 3 trials, the neratinib regimen was estimated to have a 79% probability of statistical success in a focused phase 3 trial of neoadjuvant therapy on the basis of results observed in an experimental-therapy group that included 115 participants.

Although patients with HER2-positive cancer who were randomly assigned to the experimental-therapy group did not receive trastuzumab in the context of neoadjuvant therapy, these patients

Table 3. Adverse Events and Early Discontinuation of Treatment.

| Variable | Neratinib (N=115) | | Control (N=78) | |
|--|-------------------------------------|--------------------|--------------------|--------------------|
| | Grade 1 or 2 Event | Grade 3 or 4 Event | Grade 1 or 2 Event | Grade 3 or 4 Event |
| | <i>number of patients (percent)</i> | | | |
| Adverse event | | | | |
| Hematologic event | | | | |
| Febrile neutropenia | 0 | 7 (6) | 0 | 5 (6) |
| Neutropenia | 16 (14) | 18 (16) | 8 (10) | 9 (12) |
| Thrombocytopenia | 6 (5) | 1 (1) | 2 (3) | 0 |
| Anemia | 34 (30) | 3 (3) | 16 (21) | 0 |
| Gastrointestinal event | | | | |
| Diarrhea | 110 (96) | 44 (38) | 39 (50) | 3 (4) |
| Nausea | 94 (82) | 3 (3) | 65 (83) | 0 |
| Vomiting | 46 (40) | 2 (2) | 20 (26) | 0 |
| Stomatitis* | 52 (45) | 2 (2) | 31 (40) | 2 (3) |
| Abnormal aspartate aminotransferase level† | 30 (26) | 5 (4) | 5 (6) | 1 (1) |
| Abnormal alanine aminotransferase level† | 42 (37) | 13 (11) | 9 (12) | 1 (1) |
| Early discontinuation of treatment‡ | 21 (18) | — | 3 (4) | — |
| Toxic effect | 13 (11) | — | 1 (1) | — |
| Disease progression | 6 (5) | — | 0 | — |
| Other reason | 2 (2) | — | 2 (3) | — |

* Stomatitis included the terms “oral pain,” “oral hemorrhage,” and “mucositis oral” from the Common Terminology Criteria for Adverse Events, version 4.

† An abnormality in the aspartate or alanine aminotransferase level was defined as a level above the upper limit of the normal range on laboratory testing.

‡ Early discontinuation of treatment was evaluated during the taxane phase only and did not include patients who discontinued treatment during the phase of receiving doxorubicin and cyclophosphamide. These values for early discontinuation include patients who continued on to receive doxorubicin and cyclophosphamide.

received a full year of adjuvant trastuzumab (after surgery) as dictated by standard of care. Since moving out of phase 2 in this adaptive randomization trial, neratinib has shown benefit as an extended or secondary adjuvant therapy in patients with early-stage, high-risk HER2-positive breast cancer, after standard trastuzumab-based adjuvant therapy.²¹

The efficacy threshold of 85% that was specified in the trial protocol was reached before all the patients completed neoadjuvant therapy and had an assessment of the primary end point (i.e., had surgery completed). Once all the additional data points regarding pathological complete response were accumulated, the probabilities were updated, and there was a slight reduction in the probability to 79%. This possibility had been anticipated in the design of the trial, and thus a

particularly high threshold of 85% had been selected for this reason.

The finding of the superiority of neratinib over trastuzumab in this tumor biomarker signature is notable given the experience in a number of trials that sought to improve on the efficacy of the current standard of care. Among these are several phase 3 trials of lapatinib, an ErbB–HER tyrosine kinase inhibitor that is similar to neratinib, which has not shown superiority over trastuzumab in trials when it has been evaluated in patients with metastatic cancer²² or in those receiving adjuvant therapy²³ or neoadjuvant therapy.²⁴ In the last of these, some higher rates of pathological complete response were noted with the use of a triple combination of lapatinib, trastuzumab, and paclitaxel than with trastuzumab and paclitaxel. In the current trial, we observed that the rate of

pathological complete response was higher with neratinib plus paclitaxel than with trastuzumab plus paclitaxel.

A recent meta-analysis of trials of neoadjuvant therapy in participants with HER2-positive breast cancer showed an overall rate of pathological complete response of 39% with single HER2-targeted agents that were combined with anthracycline–taxane-based chemotherapy.²⁵ In our trial, the rate of pathological complete response among participants with HER2-positive cancer in the control group (which received trastuzumab plus paclitaxel) was 23% (Table 2); the rate was 33% among patients with HER2-positive, hormone-receptor–negative cancer and 17% among those with HER2-positive, hormone-receptor–positive cancer. These rates are lower than those observed with trastuzumab-based therapy in previous trials of neoadjuvant therapy in participants with HER2-positive breast cancer.²⁶ There were no obvious differences with regard to the characteristics of the patients in our trial versus those in other trials of neoadjuvant therapy. The method used in our trial, including the standardized stringent analysis of tissue after neoadjuvant therapy,²⁷ may have contributed to lower rates of pathological complete response than were observed in other trials.

As expected,^{6,28–30} diarrhea was the most problematic adverse effect with neratinib, warranting aggressive supportive care. In this regard, an intensive mandatory regimen for diarrhea prophylaxis with the use of high-dose loperamide at the initiation of the trial and subsequent tapering was evaluated in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-7 phase 1 trial, in which patients had frequent diarrhea that was limited to grade 2.³⁰ Prophylactic high-dose loperamide with neratinib is being further evaluated in an ongoing trial of adjuvant therapy (ClinicalTrials.gov number, NCT02400476).

On the basis of our trial results and other clinical data, phase 3 testing of neratinib as neoadjuvant therapy is moving forward in the successor I-SPY 3 program, which is aimed at generating accelerated approval following guidance from the Food and Drug Administration.^{31,32} Although the results of our trial predict a 79% probability of success of neratinib in a phase 3 trial of neoadjuvant treatment in patients with HER2-positive, hormone-receptor–negative cancer, a modified design is required in order to reflect the cur-

rent standard of dual HER-targeting (regimens containing pertuzumab and trastuzumab) that has already received accelerated approval.^{33,34} The updated phase 3 design will test the combination of neratinib, pertuzumab, trastuzumab, and taxane with the combination of pertuzumab, trastuzumab, and taxane and the combination of neratinib, trastuzumab, and taxane, all followed by doxorubicin and cyclophosphamide. The I-SPY 3 trial will include patients with HER2-positive, hormone-receptor–negative and patients with HER2-positive, hormone-receptor–positive cancer, as appropriate.

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

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APPENDIX

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