

ORIGINAL ARTICLE

Adaptive Randomization of Veliparib–Carboplatin Treatment in Breast Cancer

H.S. Rugo, O.I. Olopade, A. DeMichele, C. Yau, L.J. van 't Veer, M.B. Buxton, M. Hogarth, N.M. Hylton, M. Paoloni, J. Perlmutter, W.F. Symmans, D. Yee, A.J. Chien, A.M. Wallace, H.G. Kaplan, J.C. Boughey, T.C. Haddad, K.S. Albain, M.C. Liu, C. Isaacs, Q.J. Khan, J.E. Lang, R.K. Viscusi, L. Pusztai, S.L. Moulder, S.Y. Chui, K.A. Kemmer, A.D. Elias, K.K. Edmiston, D.M. Euhus, B.B. Haley, R. Nanda, D.W. Northfelt, D. Tripathy, W.C. Wood, C. Ewing, R. Schwab, J. Lyandres, S.E. Davis, G.L. Hirst, A. Sanil, D.A. Berry, and L.J. Esserman, for the I-SPY 2 Investigators*

ABSTRACT

BACKGROUND

The genetic and clinical heterogeneity of breast cancer makes the identification of effective therapies challenging. We designed I-SPY 2, a phase 2, multicenter, adaptively randomized trial to screen multiple experimental regimens in combination with standard neoadjuvant chemotherapy for breast cancer. The goal is to match experimental regimens with responding cancer subtypes. We report results for veliparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, combined with carboplatin.

METHODS

In this ongoing trial, women are eligible for participation if they have stage II or III breast cancer with a tumor 2.5 cm or larger in diameter; cancers are categorized into eight biomarker subtypes on the basis of status with regard to human epidermal growth factor receptor 2 (HER2), hormone receptors, and a 70-gene assay. Patients undergo adaptive randomization within each biomarker subtype to receive regimens that have better performance than the standard therapy. Regimens are evaluated within 10 biomarker signatures (i.e., prospectively defined combinations of biomarker subtypes). Veliparib–carboplatin plus standard therapy was considered for HER2-negative tumors and was therefore evaluated in 3 signatures. The primary end point is pathological complete response. Tumor volume changes measured by magnetic resonance imaging during treatment are used to predict whether a patient will have a pathological complete response. Regimens move on from phase 2 if and when they have a high Bayesian predictive probability of success in a subsequent phase 3 neoadjuvant trial within the biomarker signature in which they performed well.

RESULTS

With regard to triple-negative breast cancer, veliparib–carboplatin had an 88% predicted probability of success in a phase 3 trial. A total of 72 patients were randomly assigned to receive veliparib–carboplatin, and 44 patients were concurrently assigned to receive control therapy; at the completion of chemotherapy, the estimated rates of pathological complete response in the triple-negative population were 51% (95% Bayesian probability interval [PI], 36 to 66%) in the veliparib–carboplatin group versus 26% (95% PI, 9 to 43%) in the control group. The toxicity of veliparib–carboplatin was greater than that of the control.

CONCLUSIONS

The process used in our trial showed that veliparib–carboplatin added to standard therapy resulted in higher rates of pathological complete response than standard therapy alone specifically in triple-negative breast cancer. (Funded by the QuantumLeap Healthcare Collaborative and others; I-SPY 2 TRIAL ClinicalTrials.gov number, NCT01042379.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Esserman at the UCSF Carol Franc Buck Breast Care Center, University of California, San Francisco, 1600 Divisadero St., Box 1710, San Francisco, CA 94115, or at laura.esserman@ucsf.edu.

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

N Engl J Med 2016;375:23-34.

DOI: 10.1056/NEJMoa1513749

Copyright © 2016 Massachusetts Medical Society.

BREAST CANCER IS GENETICALLY AND clinically heterogeneous, which makes it challenging to identify effective patient-specific therapies. Although mortality due to breast cancer in the United States has decreased, more than 40,000 women in the United States still die from this disease each year.¹ Further decreases in mortality will require therapeutic options that target biologic properties of tumors and can be delivered early enough in the disease course to make a clinical difference.

The neoadjuvant approach facilitates the evaluation of an individual patient's response to treatment and holds promise for the development of experimental therapies for disease while it is still curable.² The long-term outcomes are equivalent to those obtained when the same chemotherapy is given in the context of adjuvant therapy (i.e., therapy given after the entire tumor has been surgically removed and only occult disease is left behind).² Importantly, eradication of the tumor in response to neoadjuvant chemotherapy, designated as pathological complete response in the breast and axillary nodes at the time of surgery, is correlated with event-free and overall survival, depending on the molecular subtype of the cancer, with a particularly strong correlation for triple-negative (i.e., human epidermal growth factor receptor 2 [HER2]-negative, estrogen-receptor-negative, and progesterone-receptor-negative) and HER2-positive disease.³ For this reason, there is intense interest in the neoadjuvant approach.^{4,5}

The I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response through Imaging and Molecular Analysis 2) is a multicenter, randomized, phase 2 "platform" trial (i.e., a trial with a backbone of standard therapy to which multiple investigational regimens can be added and compared with a common control [backbone] regimen) in which patients with high-risk primary breast cancer undergo adaptive randomization for assignment to an experimental group in which they receive new agents or new combinations added to standard neoadjuvant chemotherapy. The primary end point is pathological complete response.⁶ Data on event-free and overall survival, which are secondary end points, are not yet mature.

The goal of the trial from the drug-development perspective is to rapidly identify which disease subtypes (or "signatures"), if any, are suf-

ficiently responsive to treatment with a given regimen to enable a small, focused, and successful phase 3 trial. From the perspective of patients in the trial, they are more likely to be assigned to regimens that are performing well for patients who share their biomarker subtypes, in order to better identify regimens that are effective for such patients.

Preclinical models have shown that veliparib, an oral, potent inhibitor of poly(ADP-ribose) polymerase (PARP), markedly potentiates the antineoplastic effect of carboplatin.⁷ Here we report results from the first experimental regimen to "graduate" — that is, to move on from phase 2 because of a strong efficacy signal: veliparib and carboplatin, added to standard neoadjuvant chemotherapy.

METHODS

STUDY DESIGN

I-SPY 2 is an ongoing, multicenter, open-label, adaptive, phase 2 master protocol or "platform" trial that includes multiple experimental groups for the evaluation of new agents combined with standard neoadjuvant therapy for the treatment of breast cancers that have a high risk of recurrence.⁶ Experimental regimens are compared against a common control regimen consisting of standard neoadjuvant therapy; the primary end point is pathological complete response, which is defined as the absence of residual cancer in the breast or lymph nodes at the time of surgery. Patients who leave the study after starting therapy (with or without withdrawal of consent) or do not undergo surgery for any reason are counted as not having a pathological complete response.

Biomarker assessments (based on status with regard to HER2, hormone [estrogen and progesterone] receptors, and a 70-gene assay [MammaPrint, Agendia], categorized as noted below) are performed at baseline and are used to classify patients into eight prospectively defined disease subtypes for randomization purposes. In addition to standard immunohistochemical and fluorescence in situ hybridization (FISH) assays, the protocol included a microarray-based assay of HER2 expression (TargetPrint, Agendia). This assay has previously shown high concordance with standard immunohistochemical and FISH assays of HER2.⁸ The adaptive-randomization algo-

rithm assigns patients with biomarker subtypes to competing regimens on the basis of current Bayesian probabilities of pathological complete response within that biomarker subtype with the experimental regimen versus with the control, with 20% of patients randomly assigned to control. Adaptive randomization speeds the identification of treatments that perform well within specific disease subtypes and helps avoid exposing patients to therapies that are unlikely to benefit them (Fig. 1A).^{9,10}

To assess efficacy, 10 clinically relevant biomarker “signatures” were defined in the protocol: all (i.e., a group including all enrolled patients regardless of disease subtype), hormone-receptor–positive, hormone-receptor–negative, HER2–positive, HER2–negative, high-risk category 2 on the 70-gene MammaPrint assay (see Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), HER2–positive and hormone-receptor–positive, HER2–positive and hormone-receptor–negative, HER2–negative and hormone-receptor–positive, and triple-negative (HER2–negative, estrogen-receptor–negative, and progesterone-receptor–negative). Experimental regimens are continually evaluated against the control for each of these signatures. The statistical analyses are Bayesian.^{9,11} A regimen leaves the trial when there is an 85% Bayesian predictive probability of success in a simulated 300-patient, equally randomized, phase 3 trial with a traditional statistical design, in which the neoadjuvant therapy is compared with the same control therapy and in which the primary end point — pathological complete response — is the same as that in the current trial (see the protocol, available at NEJM.org). The predictive probabilities of success are power calculations for a 300-patient trial averaged with respect to the probability distributions of pathological complete response rates in the current trial for the experimental group and the control group.^{9,11} The relatively small size of this hypothetical future trial means that a regimen leaves the trial only when there is compelling evidence of efficacy. Enrollment in an experimental group that is being treated with a regimen that achieves this status is halted immediately, but all patients already in the group, as well as its concurrent controls, must complete surgery before the regimen’s status is announced. A regimen is dropped

for futility if its predictive probability of success in a phase 3 trial is lower than 10% for all 10 signatures (or for all 3 signatures in the case of veliparib and carboplatin). The maximum total number of patients assigned to any experimental group is 120.

ELIGIBILITY AND ENROLLMENT

The trial is open to women 18 years of age and older who have a diagnosis of clinical stage II or III breast cancer. Patients must have clinically or radiologically measurable disease in the breast, defined as a tumor larger than 2.5 cm in diameter. If a tumor meets this criterion as assessed in a clinical examination, the tumor must also be larger than 2 cm in diameter as assessed by imaging. Participants must have had no previous cytotoxic treatment for this cancer, must have an Eastern Cooperative Oncology Group performance status score of 0 or 1 (scores range from 0 to 5, with 0 indicating no symptoms and higher numbers reflecting increasing tumor-related disability), and must agree to consent to undergo core biopsy and magnetic resonance imaging (MRI). Patients with hormone-receptor–positive and low-risk tumors as assessed by the 70-gene assay are excluded because the potential benefit of chemotherapy is lower for patients with less proliferative tumors and does not justify the risk of exposure to investigational agents plus chemotherapy.^{6,12} The veliparib–carboplatin regimen was not assigned to patients with HER2–positive tumors, because of the lack of safety data with trastuzumab (used in conjunction with paclitaxel in patients with HER2–positive disease).

All patients provided written informed consent before undergoing screening. If the patient was eligible, a second consent was obtained after random assignment to open-label treatment and before treatment was initiated.

TREATMENT

Participants received weekly paclitaxel at a dose of 80 mg per square meter of body-surface area intravenously for 12 doses, alone (control) or in combination with an experimental regimen (Fig. 1B). Patients who were randomly assigned to receive veliparib–carboplatin received 50 mg of veliparib by mouth twice daily for 12 weeks and carboplatin at a dose aimed to achieve a pharmacologic area under the concentration-versus-time curve

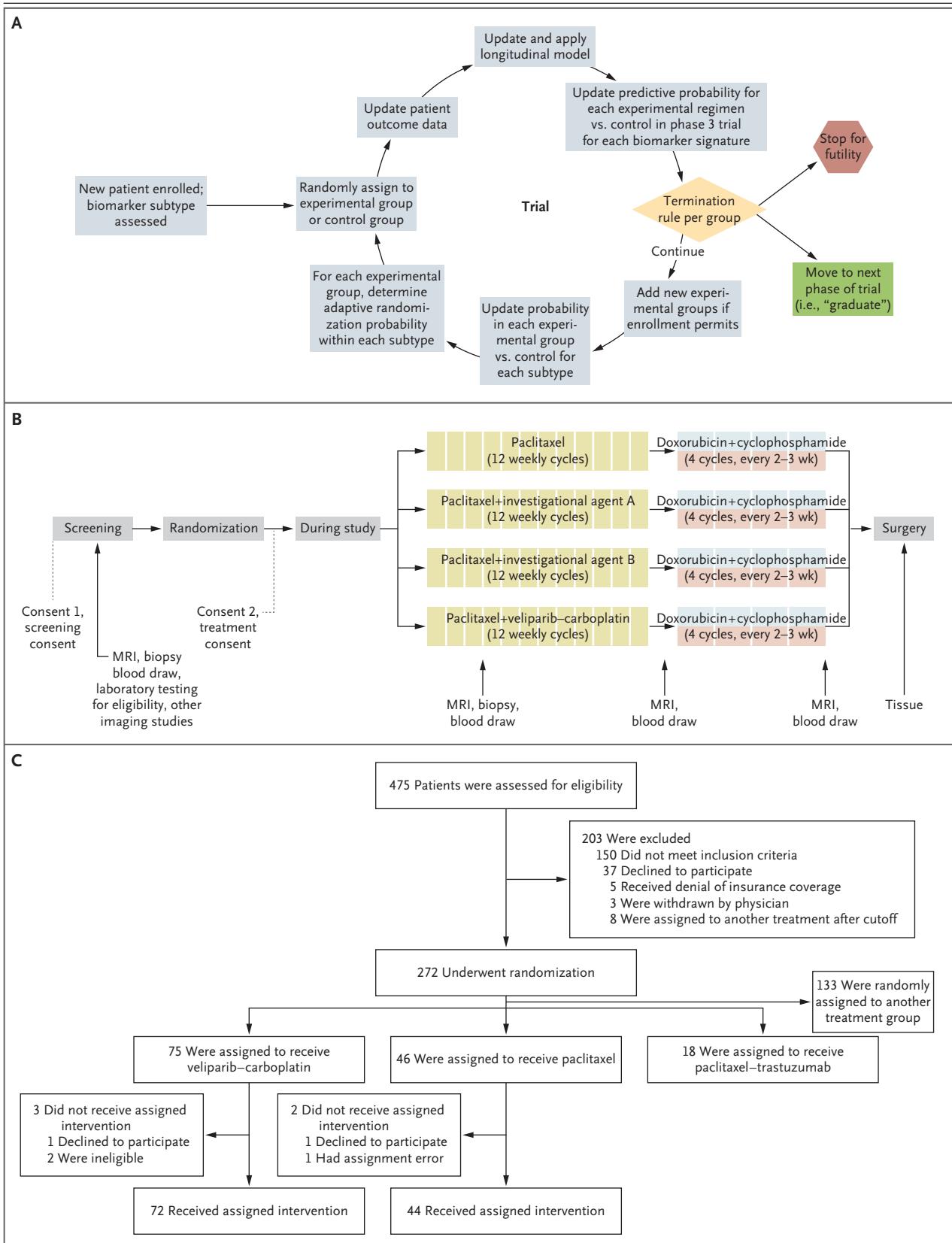


Figure 1 (facing page). Trial Design.

Panel A shows the steps in the adaptive process of the trial. When new patients are enrolled, their cancer subtypes are assessed. As patients undergo randomization, their outcomes are used to update the Bayesian covariate-adjusted model that computes the predictive probability of success in phase 3 with regard to each biomarker signature. Prespecified termination rules are applied for each experimental group to determine whether the regimen should be stopped for futility, moved out of phase 2, or continue, adding on additional experimental groups, as permitted by ongoing patient enrollment. As the trial continues, for each experimental group, the probability of the superiority of each experimental regimen over the control within each subtype is updated, and the randomization probabilities for each subtype into the various experimental groups are adapted (such that new patients entering the trial will be more likely to be randomly assigned to an agent that shows activity within their cancer subtype). Panel B shows the steps involved in the enrollment, randomization, and treatment process. First, patients are screened for eligibility. Eligible patients undergo adaptive randomization and are assigned to 12 weekly cycles of paclitaxel (and trastuzumab, if the patient has human epidermal growth factor receptor 2 [HER2]-positive disease) alone (control) or in combination with one of several experimental agents, followed by four cycles of doxorubicin-cyclophosphamide, with serial biomarkers assessed over the course of their therapy by means of biopsies, blood draws, and magnetic resonance imaging (MRI). Only patients with HER2-negative disease were randomly assigned to the veliparib-carboplatin group. Panel C shows the details regarding the screening, randomization, and treatment of the patients in the veliparib-carboplatin group and its concurrent control group. Only patients with HER2-negative disease were eligible for random assignment to the veliparib-carboplatin group. Patients were categorized as having received the assigned intervention if they received at least one dose of experimental or control therapy.

of 6 mg·hr per liter on weeks 1, 4, 7, and 10, concurrent with weekly paclitaxel. After receiving paclitaxel with or without veliparib-carboplatin, all patients received doxorubicin (60 mg per square meter) and cyclophosphamide (600 mg per square meter) intravenously every 2 to 3 weeks for four doses, with myeloid growth factor support as appropriate, after which they underwent surgery that included axillary node sampling in accordance with National Comprehensive Cancer Network and local practice guidelines. Radiation therapy and endocrine adjuvant therapy after surgery were recommended in accordance with standard guidelines.¹³ Dose modifications for standard

and experimental therapies are listed in Table S3 in the Supplementary Appendix.

ASSESSMENTS

Core biopsy and MRI were performed and blood samples were obtained at baseline and at 3 weeks after treatment initiation. MRI and collection of blood samples were repeated between chemotherapy regimens and before surgery. All surgical specimens were evaluated by pathologists who were trained to assess residual tumor burden.¹⁴ Biomarker assessments included the Agendia 70-gene MammaPrint and TargetPrint HER2 gene-expression assays performed with the Agendia 44K full-genome microarray and reverse-phase phosphoprotein array.^{15,16} The gene assays were purchased at a research rate. Agendia supplied the analysis of the results of the 70-gene assay but had no role in the study design, data collection, data interpretation, or manuscript preparation.

STUDY OVERSIGHT

The study was designed by the principal investigators and the I-SPY 2 investigators. The drug manufacturer supplied veliparib but played no role in the design of the study, the collection or analysis of the data, or the preparation of the manuscript. All participating sites received institutional review board approval. A data and safety monitoring board meets monthly. The manuscript was written entirely by the authors, who vouch for the data and adherence of the trial to the protocol.

STATISTICAL ANALYSIS

Trial participants are categorized into eight subtypes that are based on three biomarkers: hormone-receptor status, HER2 status, and risk level as assessed with the 70-gene assay (high-risk category 1 or 2). The cutoff point between high-risk categories 1 and 2 on the 70-gene assay is the median on a continuous index scale among I-SPY 1 participants who meet the eligibility criteria for I-SPY 2 (Fig. S1 in the Supplementary Appendix).¹⁷

When a Bayesian approach is used,^{10,11} at any given time, the pathological complete response rate for each regimen has a probability distribution within each of the eight biomarker subtypes. This distribution is based on the results for all patients who were previously assigned to the regimen and with the assumption of a covariate-adjusted logistic model with HER2, hormone-receptor,

| Characteristic | Veliparib–Carboplatin (N=72) | Control (N=44) |
|---|------------------------------|----------------|
| Median age (range) — yr | 48.5 (27–70) | 47.5 (24–71) |
| Race — no. (%)† | | |
| White | 54 (75) | 34 (77) |
| Black | 15 (21) | 7 (16) |
| Asian | 3 (4) | 3 (7) |
| Hormone-receptor status — no. (%) | | |
| Positive | 33 (46) | 23 (52) |
| Negative | 39 (54) | 21 (48) |
| BRCA1 and BRCA2 mutation status — no. (%) | | |
| Positive for deleterious mutation | 12 (17) | 2 (5) |
| Genetic variant suspected to be deleterious | 0 | 1 (2) |
| Genetic variant of unknown significance | 2 (3) | 0 |
| Genetic variant, favor polymorphism‡ | 0 | 2 (5) |
| No mutation detected | 56 (78) | 39 (89) |
| Not evaluated§ | 2 (3) | 0 |
| Median tumor size (range) — cm | 5 (0–15) | 5 (0–14) |
| Baseline node status — no. (%) | | |
| Palpable | 31 (43) | 22 (50) |
| Nonpalpable | 41 (57) | 22 (50) |

* There were no significant differences between the two groups. Percentages may not total to 100 because of rounding.

† Race was self-reported.

‡ This test result indicates that a variant has been detected but that it may reflect normal variation and may not be deleterious.

§ Two patients in the veliparib–carboplatin group withdrew consent for the use of their tissue in the analysis.

and 70-gene profile status as covariates. These distributions allow for finding the (Bayesian) probability that each regimen is superior to the control within each subtype. The randomization probabilities are defined in proportion to these probabilities, and therefore they change over time.

A longitudinal statistical model of the tumor volume, as measured by MRI, after 3 weeks and 12 weeks of therapy as compared with the baseline volume improves information about pathological complete response rates through multiple imputation. When all patients receiving the regimen have undergone surgery, tumor volume is no longer required for calculating the probabilities of pathological complete response, but it is used to update the longitudinal model.

We report the final Bayesian probability distributions of rates of pathological complete response for an experimental regimen and its con-

current control for each biomarker signature by providing the estimated rates of pathological complete response (the means of the respective distributions) and 95% Bayesian probability intervals. We do not report the raw data within biomarker subtypes or signatures; our analysis carries greater precision than would a raw-data estimate. We provide, for each biomarker signature, the final probability that the rate of pathological complete response associated with the experimental regimen is greater than that for control, as well as the respective predictive probabilities of success in a future trial as described above.

Additional details regarding the study design are provided in the Supplementary Appendix. The common elements of the I-SPY 2 trial design are also reported by Park et al. in this issue of the *Journal*.¹⁸

RESULTS

PATIENTS

Patients were eligible to be undergo randomization to veliparib-carboplatin from May 2010 through July 2012. During this period, there were three to five groups (veliparib-carboplatin, neratinib, trebananib, ganitumumab, and control) included in the randomization. A total of 72 patients were randomly assigned to receive veliparib-carboplatin and could be evaluated with regard to the primary end point; 44 HER2-negative controls underwent concurrent randomization (Fig. 1C). The characteristics of participants at baseline (Table 1) were similar in the experimental and control groups. More patients in the veliparib-carboplatin group than in the control group carried a mutation that was deleterious or suspected to be deleterious in *BRCA1* or *BRCA2* (17% vs. 7%). Two patients in the veliparib-carboplatin group and 1 patient in the control group did not undergo surgery, and 1 patient in the veliparib-carboplatin group withdrew consent before surgery; all 4 patients were counted as not having had a pathological complete response.

EFFICACY

The veliparib-carboplatin regimen was considered only for HER2-negative tumors and therefore was evaluated with regard to three biomarker signatures: HER2-negative, hormone-receptor-positive and HER2-negative, and triple-negative; it achieved the prespecified efficacy threshold with regard to the triple-negative signature (Fig. 2 and Table 2). Within the group of patients with HER2-negative tumors, the estimated rate of pathological complete response was 33% (95% Bayesian probability interval [PI], 23 to 43%) among those who received veliparib-carboplatin, as compared with 22% (95% PI, 10 to 35%) in the control group (Fig. 2A). This benefit was concentrated in the triple-negative biomarker signature, in which the estimated rate of pathological complete response was 51% (95% PI, 36 to 66%) in the veliparib-carboplatin group versus 26% (95% PI, 9 to 43%) in the control group (Fig. 2B). The estimated rate of pathological complete response among patients with hormone-receptor-positive and HER2-negative breast cancer (Fig. 2C) was 14% (95% PI, 3 to

25%) in the veliparib-carboplatin group and 19% (95% PI, 5 to 33%) in the control group. In the triple-negative signature, the probability that veliparib-carboplatin was superior to control was 99%, and its probability of statistical success in an equally randomized, phase 3 trial including 300 patients was 88% (Fig. 2B and Table 2).

TOXIC EFFECTS

Selected toxic effects according to treatment group are summarized in Table 3; all toxic effects with frequencies higher than 5% are listed in Table S4 in the Supplementary Appendix. The rate of grade 3 or 4 hematologic toxic effects was higher in the veliparib-carboplatin group than in the control group: 71% versus 2% of patients had neutropenia, 1% versus 0% had febrile neutropenia, 21% versus 0% had thrombocytopenia, and 28% versus 0% had anemia. The rate of toxic effects was also higher during doxorubicin-cyclophosphamide treatment among patients who had received veliparib-carboplatin than among those who had received control therapy: 12% versus 5% had febrile neutropenia, and rates of neutropenia, thrombocytopenia, and anemia were also higher in the veliparib-carboplatin group. There were no treatment-related deaths.

DOSE REDUCTIONS AND DISCONTINUATIONS

Dose reductions of paclitaxel occurred in 23 patients (32%) in the veliparib-carboplatin group and in no patients in the control group. Dose reductions of carboplatin occurred in 34 patients (47%). During paclitaxel treatment, 13 patients (18%) in the veliparib-carboplatin group, as compared with 2 patients (5%) in the control group, discontinued therapy early. The reasons for discontinuation of treatment in the veliparib-carboplatin group included toxic effects (10 patients), disease progression (1), and patient preference (2). One patient in the control group discontinued treatment because of toxic effects, and one discontinued because of disease progression. One patient in the veliparib-carboplatin group discontinued doxorubicin-cyclophosphamide treatment after three cycles because of toxic effects, and 3 patients in the control group discontinued doxorubicin-cyclophosphamide early (2 because of toxic effects, and 1 because of disease progression).

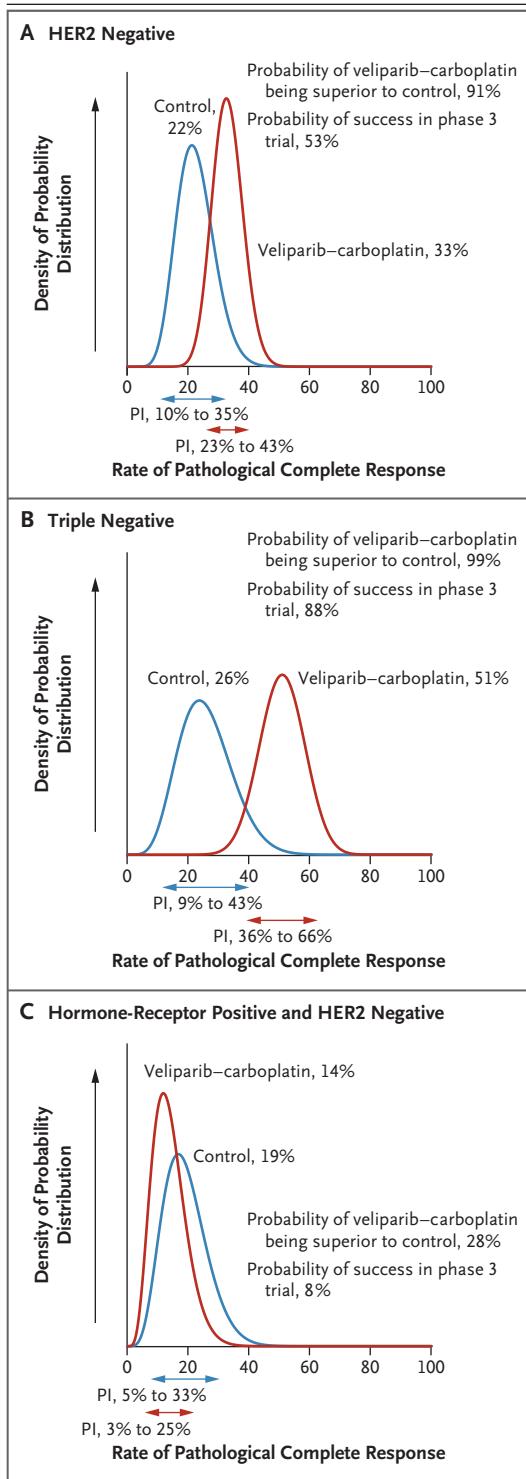


Figure 2. Estimated Rate of Pathological Complete Response with Veliparib-Carboplatin versus the Concurrent HER2-Negative Control.

Panel A shows the probability distribution for all patients with HER2-negative disease, Panel B the probability distribution for patients with hormone-receptor-negative and HER2-negative (triple-negative) disease, and Panel C the probability distribution for patients with hormone-receptor-positive and HER2-negative disease. The red curves represent patients treated with veliparib-carboplatin plus paclitaxel followed by doxorubicin-cyclophosphamide, and the blue curves represent concurrent controls. The corresponding 95% probability intervals (PIs) (represented by the arrows) are shown for each. The mean of each distribution is the estimated rate of pathological complete response.

therapeutics and to identify biomarkers for definitive subsequent study.⁶ A goal of the trial is to provide a framework for more rapidly and efficiently testing promising agents earlier during the course of disease. New agents are added to standard treatment in the context of neoadjuvant therapy for patients who present with tumors that are at high risk for early recurrence. The trial uses adaptive randomization and shared control groups and allows multiple agents and regimens to be tested in a single trial. It is designed to evaluate the response of specific tumor subsets to new agents, with regard to the likelihood of pathological complete response. An important objective is to reduce the number of patients needed to determine the clinical activity of an agent or regimen.^{4,5}

Another goal of the trial is to specifically improve the drug-development process by predicting the potential success of a given regimen in a future phase 3 trial and by accurately assessing the patient population that has a response to the regimen. Predicting outcomes in a future trial that has a substantial chance of being successful establishes a high bar for continued development. Achieving significance in a phase 2 trial is not enough. The target sample size of 300 patients for a future confirmatory trial of neoadjuvant therapy is consistent with our goal of identifying sufficient signal in the current trial (i.e., a rate of pathological complete response approximately 20% higher than that with the control) such that a moderately sized phase 3 trial involving patients with cancer of the biomarker subtype of interest would be successful.

DISCUSSION

I-SPY 2 represents a new clinical trial model that is designed to facilitate rapid evaluation of new

Table 3. Selected Adverse Events and Toxic Effects.

| Event | Veliparib–Carboplatin (N = 72) | | HER2-Negative Control (N = 44) | |
|--|--|--|-----------------------------------|--|
| | Paclitaxel + Veliparib– Carboplatin (N = 72) | Doxorubicin– Cyclophosphamide (N = 66) | Paclitaxel (N = 44) | Doxorubicin– Cyclophosphamide (N = 42) |
| Adverse events of grade 3 or higher | | | | |
| Hematologic events — no. (%) | | | | |
| Febrile neutropenia | 1 (1) | 8 (12) | 0 | 2 (5) |
| Neutropenia | 51 (71) | 16 (24) | 1 (2) | 5 (12) |
| Thrombocytopenia | 15 (21) | 6 (9) | 0 | 0 |
| Anemia | 20 (28) | 20 (30) | 0 | 0 |
| Gastrointestinal events — no. (%) | | | | |
| Stomatitis | 1 (1) | 1 (2) | 0 | 2 (5) |
| Nausea | 0 | 0 | 0 | 0 |
| Vomiting | 1 (1) | 0 | 0 | 0 |
| Diarrhea | 0 | 0 | 2 (5) | 0 |
| Toxic effects | | | | |
| Dose reduction — no. (%) | | | | |
| Paclitaxel | 23 (32) | — | 0 | — |
| Veliparib | 0 | — | — | — |
| Carboplatin | 34 (47) | — | — | — |
| Doxorubicin–cyclophosphamide | — | 6 (9) | — | 3 (7) |
| Early discontinuation — no. (%) | | | | |
| All | 13 (18)* | 1 (2) | 2 (5)† | 3 (7) |
| For toxic effects | 10 (14) | 1 (2) | 1 (2) | 2 (5) |
| For disease progression | 1 (1) | 0 | 1 (2) | 1 (2) |
| Other | 2 (3) | 0 | 0 | 0 |
| Median time from treatment consent to surgery (range) — days | 182 (93–232) | — | 165 (100–248) | — |

* Of the 13 patients who discontinued veliparib–carboplatin early, 7 went on to receive doxorubicin–cyclophosphamide.

† One patient who discontinued early went on to receive doxorubicin–cyclophosphamide.

boplatin group. The use of veliparib–carboplatin was also associated with higher rates of toxic effects during doxorubicin–cyclophosphamide treatment, similar to findings in the CALGB 40603 trial; the higher rates were accounted for by hematologic toxic effects. Despite this, all but one patient completed four cycles of doxorubicin–cyclophosphamide.

A small number of patients in our trial had BRCA mutations. By design, adaptive randomization increased the number of patients with triple-negative disease who were assigned to receive veliparib–carboplatin, as compared with other ex-

perimental regimens. Because of this, the group that underwent adaptive randomization and was assigned to receive veliparib–carboplatin may have been enriched for BRCA mutations. DNA-repair deficiencies were evaluated in all patients but are not reported here.

In summary, patients with triple-negative breast cancer in our trial were found to benefit from veliparib–carboplatin, whereas patients with HER2-negative and hormone-receptor-positive tumors did not. The experience with veliparib–carboplatin in our trial shows the advantage of an adaptively randomized phase 2 platform trial for matching

therapies with biomarker subsets to better inform the design of phase 3 trials so that they can be more focused, smaller, and faster. Future patients stand to benefit, but trial participants benefit, as well, in that exposure to ineffective therapy is minimized.

Presented in part at the San Antonio Breast Cancer Symposium, December 10–14, 2013.

Supported by QuantumLeap Healthcare Collaborative (2013 to present) and the Foundation for the National Institutes of Health (2010 to 2012) and by a grant (28XS197) from the National Cancer Institute Center for Biomedical Informatics and Information Technology. Initial support for the I-SPY 2 TRIAL was provided by the Safeway Foundation, Bill Bowes Founda-

tion, Quintiles Transnational Corporation, Johnson & Johnson, Genentech, Amgen, the San Francisco Foundation, Give Breast Cancer the Boot, Eli Lilly, Pfizer, Eisai Company, Side Out Foundation, Harlan Family, the Avon Foundation for Women, Alexandria Real Estate Equities, and private individuals and family foundations.

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

We thank Anna Barker for leadership in helping to launch the I-SPY 2 TRIAL; the members of the data and safety monitoring committee (Harold Burstein, Elizabeth Frank, Steven Goodman, Clifford Hudis, Robert Mass, Musa Meyer, and Janet Wittes) for meeting monthly to review the safety data; the trial coordinators; Ken Buetow and the staff of caBIG for input with the informatics design; the entire project oversight committee; and our patient advocates, investigators, and all the patients who participated in the trial.

APPENDIX

The authors' full names and academic degrees are as follows: Hope S. Rugo, M.D., Olufunmilayo I. Olopade, M.D., Angela DeMichele, M.D., Christina Yau, Ph.D., Laura J. van 't Veer, Ph.D., Meredith B. Buxton, Ph.D., Michael Hogarth, M.D., Nola M. Hylton, Ph.D., Melissa Paoloni, D.V.M., Jane Perlmutter, Ph.D., W. Fraser Symmans, M.D., Douglas Yee, M.D., A. Jo Chien, M.D., Anne M. Wallace, M.D., Henry G. Kaplan, M.D., Judy C. Boughey, M.D., Tufia C. Haddad, M.D., Kathy S. Albain, M.D., Minetta C. Liu, M.D., Claudine Isaacs, M.D., Qamar J. Khan, M.D., Julie E. Lang, M.D., Rebecca K. Viscusi, M.D., Lajos Pusztai, M.D., D.Phil., Stacy L. Moulder, M.D., Stephen Y. Chui, M.D., Kathleen A. Kemmer, M.D., Anthony D. Elias, M.D., Kirsten K. Edmiston, M.D., David M. Euhus, M.D., Barbara B. Haley, M.D., Rita Nanda, M.D., Donald W. Northfelt, M.D., Debashish Tripathy, M.D., William C. Wood, M.D., Cheryl Ewing, M.D., Richard Schwab, M.D., Julia Lyandres, B.S., Sarah E. Davis, M.S., Gillian L. Hirst, Ph.D., Ashish Sanil, Ph.D., Donald A. Berry, Ph.D., and Laura J. Esserman, M.D., for the I-SPY 2 Investigators

The authors' affiliations are as follows: University of California, San Francisco (UCSF) (H.S.R., C.Y., L.J.V., M.B.B., N.M.H., A.J.C., C.E., J.L., S.E.D., G.L.H., L.J.E.), and QuantumLeap Healthcare Collaborative (M.P.), San Francisco, Buck Institute for Research and Aging, Novato (C.Y.), University of California, Davis, Davis (M.H.), University of California San Diego, San Diego (A.M.W., R.S.), and University of Southern California, Los Angeles (D.T.) — all in California; University of Chicago (O.I.O., R.N.), and Loyola University (K.S.A.), Chicago; University of Pennsylvania, Philadelphia (A.D.); Gemini Group, Ann Arbor, MI (J.P.); University of Texas M.D. Anderson Cancer Center, Houston (W.F.S., L.P., S.L.M., D.A.B.), UT Southwestern Medical Center, Dallas (D.M.E., B.B.H.), and Berry Consultants, Austin (A.S., D.A.B.) — all in Texas; University of Minnesota, Minneapolis (D.Y.), and Mayo Clinic, Rochester (J.C.B., T.C.H.) — both in Minnesota; Swedish Medical Center, Seattle (H.G.K.); Georgetown Lombardi Comprehensive Cancer Center, Washington, DC (M.C.L., C.I.); University of Kansas, Lawrence (Q.J.K.); University of Arizona, Tucson (J.E.L., R.K.V.), and Mayo Clinic, Scottsdale (D.W.N.) — both in Arizona; Oregon Health and Sciences University, Portland (S.Y.C., K.A.K.); University of Denver, Denver (A.D.E.); Inova Fairfax Hospital, Falls Church, VA (K.K.E.); and Emory University, Atlanta (W.C.W.).

REFERENCES

- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015;65:5-29.
- Cortazar P, Geyer CE Jr Pathological complete response in neoadjuvant treatment of breast cancer. *Ann Surg Oncol* 2015;22:1441-6.
- Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet* 2014;384:164-72.
- Yee D, Haddad T, Albain K, et al. Adaptive trials in the neoadjuvant setting: a model to safely tailor care while accelerating drug development. *J Clin Oncol* 2012;30:4584-6, author reply 4588-9.
- DeMichele A, Yee D, Berry DA, et al. The neoadjuvant model is still the future for drug development in breast cancer. *Clin Cancer Res* 2015;21:2911-5.
- Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. *Clin Pharmacol Ther* 2009;86:97-100.
- Donawho CK, Luo Y, Luo Y, et al. ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models. *Clin Cancer Res* 2007;13:2728-37.
- Viale G, Slaets L, Bogaerts J, et al. High concordance of protein (by IHC), gene (by FISH; HER2 only), and microarray readout (by TargetPrint) of ER, PgR, and HER2: results from the EORTC 10041/BIG 03-04 MINDACT trial. *Ann Oncol* 2014;25:816-23.
- Berry DA. Adaptive clinical trials in oncology. *Nat Rev Clin Oncol* 2012;9:199-207.
- Berry DA. The brave new world of clinical cancer research: adaptive biomarker-driven trials integrating clinical practice with clinical research. *Mol Oncol* 2015;9:951-9.
- Berry DA. Bayesian clinical trials. *Nat Rev Drug Discov* 2006;5:27-36.
- Prowell TM, Pazdur R. Pathological complete response and accelerated drug approval in early breast cancer. *N Engl J Med* 2012;366:2438-41.
- Gradishar WJ, Anderson BO, Balassanian R, et al. Breast cancer, version 1.2016. *J Natl Compr Canc Netw* 2015;13:1475-85.
- Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol* 2007;25:4414-22.
- Glas AM, Floore A, Delahaye LJ, et al. Converting a breast cancer microarray signature into a high-throughput diagnostic test. *BMC Genomics* 2006;7:278-88.
- Roepman P, Horlings HM, Krijgsman O, et al. Microarray-based determination of estrogen receptor, progesterone receptor, and HER2 receptor status in breast cancer. *Clin Cancer Res* 2009;15:7003-11.
- Wolff D, Daemon A, Yau C, et al.

MammaPrint ultra-high risk score is associated with response to neoadjuvant chemotherapy in the I-SPY1 trial (CALGB 150007/150012; ACRIN 6657). *Cancer Res* 2014;73:24 Suppl. abstract (http://cancerres.aacrjournals.org/content/73/24_Supplement/P1-08-01?cited-by=yes&legid=canres;73/24_Supplement/P1-08-01).

18. Park JW, Liu MC, Yee D, et al. Adaptive

randomization of neratinib in early breast cancer. *N Engl J Med* 2016;375:11-22.

19. von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. *Lancet Oncol* 2014;15:747-56.

20. Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/

or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). *J Clin Oncol* 2015;33:13-21.

Copyright © 2016 Massachusetts Medical Society.

AN NEJM APP FOR IPHONE

The NEJM Image Challenge app brings a popular online feature to the smartphone. Optimized for viewing on the iPhone and iPod Touch, the Image Challenge app lets you test your diagnostic skills anytime, anywhere. The Image Challenge app randomly selects from 300 challenging clinical photos published in NEJM, with a new image added each week. View an image, choose your answer, get immediate feedback, and see how others answered. The Image Challenge app is available at the iTunes App Store.