



Please review the Supplemental Files folder to review documents not compiled in the PDF.

## I-SPY 2 TRIAL Adaptive Randomization of Veliparib/Carboplatin in Breast Cancer

Journal:	<i>New England Journal of Medicine</i>
Manuscript ID	15-13749.R2
Article Type:	Original Article
Date Submitted by the Author:	29-Feb-2016
Complete List of Authors:	Rugo, Hope; University of California San Francisco, Comprehensive Cancer Center Olopade, Olufunmilayo; University of Chicago, DeMichele, Angela; University of Pennsylvania School of Medicine, Yau, Christina; UCSF, Department of Surgery; Buck Institute for Research and Aging van 't Veer, Laura; UCSF Buxton, Meredith; University of California, San Francisco, Hogarth, Michael; UCSF, Department of Surgery Hylton, Nola; University of California San Francisco, Comprehensive Cancer Center Paoloni, Melissa; QuantumLeap Healthcare Collaborative Perlmutter, Jane; Gemini Group, Symmans, W.; The University of Texas M.D. Anderson Cancer Center, Department of Pathology Yee, Douglas; University of Minnesota Cancer Center Chien, A. Jo; University of California, San Francisco, Wallace, Anne; University of California, San Diego, Moores Cancer Center Kaplan, Henry; Swedish Cancer Institute, Oncology Boughey, Judy; Mayo Clinic Haddad, Tufia; Mayo Clinic Albain, Kathy; Loyola University Chicago Stritch School of Medicine, Cardinal Bernardin Cancer Center; Liu, Minetta; Georgetown Lombardi Comprehensive Cancer Center Isaacs, Claudine; Georgetown University, Khan, Qamar; University of Kansas Lang, Julie; University of Arizona Viscusi, Rebecca; University of Arizona Pusztai, Lajos; The University of Texas MD Anderson Cancer Center, Breast Medical Oncology Moulder, Stacy; University of Texas, M.D. Anderson Cancer Center, Chui, Stephen; Oregon Health & Sciences University Kemmer, Kathleen; Oregon Health & Sciences University Elias, Anthony; University of Colorado, Department of Medicine; Edmiston, Kirsten; Inova Fairfax Hospital Euhus, David; UT Southwestern Medical Center Haley, Barbara; UT Southwestern School of Medicine, Hematology

1	Oncology
2	Nanda, Rita; University of Chicago, Department of Medicine, Section of Hematology/Oncology
3	Northfelt, Donald; Mayo Clinic Arizona, Hematology-Medical Oncology
4	Tripathy, Debasish; The University of Texas MD Anderson Cancer Center,
5	Wood, William; University of Southern California, Surgery
6	Ewing, Cheryl; UCSF Medical Center at Mount Zion, Surgery
7	Schwab, Richard; UCSD, Medicine
8	Lyandres Clennell, Julia; University of California San Francisco, Comprehensive Cancer Center
9	Davis, Sarah; University of California San Francisco, Comprehensive Cancer Center
10	Hirst, Gillian; University of California San Francisco, Comprehensive Cancer Center
11	Sanil, Ashish; Berry Consultants
12	Berry, Donald; University of Texas M.D. Anderson Cancer Center, Division of Quantitative Sciences
13	Esserman, Laura; UCSF, Department of Surgery;
14	Background
15	I-SPY 2 is a phase 2 standing multicenter platform trial designed to screen multiple experimental regimens in combination with standard neoadjuvant chemotherapy for breast cancer. The goal is to match experimental regimens with responding patient subtypes. We report results for veliparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, combined with carboplatin (VC).
16	Methods
17	Eligible women had >2.5 cm stage II/III breast cancer, categorized into 8 biomarker subtypes based on HER2, hormone-receptor status (HR) and MammaPrint. Patients are adaptively randomized within subtype to better performing regimens compared to standard therapy (control). Regimens are evaluated within 10 signatures, prospectively defined combinations of subtypes. VC plus standard therapy was considered for HER2-negative tumors and therefore evaluated in 3 signatures. The primary endpoint of I- SPY 2 is pathologic complete response (pCR). MR volume changes during treatment inform the likelihood that a patient will achieve pCR. Regimens graduate if and when they have a high (Bayesian) predictive probability of success in a subsequent phase 3 neoadjuvant trial within the graduating signature.
18	Results
19	VC graduated in triple-negative breast cancer with 88% predicted probability of phase 3 success. A total of 72 patients were randomized to VC and 44 to concurrent controls. Respective pCR estimates (95% probability intervals) were 51% (35%-69%) vs 26% (11%-40%). Greater toxicity of VC was manageable.
20	Conclusion
21	The design of I-SPY 2 has the potential to efficiently identify responding tumor subtypes for the various therapies being evaluated. VC added to standard therapy improves pCR rates specifically in triple-negative breast cancer.
22	Abstract:
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
60	

**I-SPY 2 TRIAL Adaptive Randomization of Veliparib/Carboplatin in Breast Cancer**

Hope S. Rugo, M.D.<sup>1</sup>, Olufunmilayo I. Olopade, M.D.<sup>2</sup>, Angela DeMichele, M.D.<sup>3</sup>, Christina Yau, Ph.D.,<sup>1,4</sup> Laura J. van 't Veer, Ph.D.<sup>1</sup>, Meredith B. Buxton, Ph.D.<sup>1</sup>, Michael Hogarth, M.D.<sup>5</sup>, Nola M. Hylton, Ph.D.<sup>1</sup>, Melissa Paoloni, D.V.M.<sup>6</sup>, Jane Perlmutter, Ph.D.<sup>7</sup>, W. Fraser Symmans, M.D.<sup>8</sup>, Douglas Yee, M.D.<sup>9</sup>, A. Jo Chien, M.D.<sup>1</sup>, Anne M. Wallace, M.D.<sup>10</sup>, Henry G. Kaplan, M.D.<sup>11</sup>, Judy C. Boughey, M.D.<sup>12</sup>, Tufia C. Haddad, M.D.<sup>12</sup>, Kathy S. Albain, M.D.<sup>13</sup>, Minetta C. Liu, M.D.<sup>14</sup>, Claudine Isaacs, M.D.,<sup>14</sup> Qamar J. Khan, M.D.<sup>15</sup>, Julie E. Lang, M.D.<sup>16</sup>, Rebecca K. Viscusi, M.D.<sup>16</sup>, Lajos Pusztai, M.D., D.Phil.,<sup>8</sup>, Stacy L. Moulder, Ph.D.<sup>8</sup>, Stephen Y. Chui, M.D.<sup>17</sup>, Kathleen A. Kemmer, M.D.<sup>17</sup>, Anthony D. Elias, M.D.<sup>18</sup>, Kirsten K. Edmiston, M.D.<sup>19</sup>, David M. Euhus, M.D.<sup>20</sup>, Barbara B. Haley, M.D.<sup>20</sup>, Rita Nanda, M.D.<sup>2</sup>, Donald W. Northfelt, M.D.<sup>21</sup>, Debasish Tripathy, M.D.<sup>22</sup>, William C. Wood, M.D.<sup>22</sup>, Cheryl Ewing, M.D.<sup>1</sup>, Richard Schwab, M.D.<sup>10</sup>, Julia Lyandres, B.S.<sup>1</sup>, Sarah E. Davis, M.S.<sup>1</sup>, Gillian L. Hirst, Ph.D.<sup>1</sup>, Ashish Sanil, Ph.D.<sup>24</sup>, Donald A. Berry, Ph.D.<sup>8,24</sup> and Laura J. Esserman, M.D., M.B.A.<sup>1</sup> on behalf of the I-SPY2 Investigators

**Institution Information**

<sup>1</sup>UCSF, San Francisco, CA; <sup>2</sup>University of Chicago, Chicago, IL; <sup>3</sup>University of Pennsylvania, Philadelphia, PA; <sup>4</sup>Buck Institute for Research and Aging; <sup>5</sup>University of California, Davis; <sup>6</sup>QuantumLeap Healthcare Collaborative, San Francisco, California; <sup>7</sup>Gemini Group, Ann Arbor, MI; <sup>8</sup>University of Texas MD Anderson Cancer Center, Houston, TX; <sup>9</sup>University of Minnesota, Minneapolis, MN; <sup>10</sup>University of California San Diego, San Diego, CA; <sup>11</sup>Swedish Medical Center, Seattle, WA; <sup>12</sup>Mayo Clinic, Rochester, Minnesota; <sup>13</sup>Loyola University, Chicago, IL; <sup>14</sup>Georgetown Lombardi Comprehensive Cancer Center, Washington, DC; <sup>15</sup>University of Kansas, Lawrence, KS; <sup>16</sup>University of Arizona, AZ; <sup>17</sup>Oregon Health & Sciences University, Portland, OR; <sup>18</sup>University of Denver, Denver, CO; <sup>19</sup>Inova Fairfax Hospital, Falls Church, VA;

1  
2  
3       <sup>20</sup>UT Southwestern Medical Center, Dallas, TX; <sup>21</sup>Mayo Clinic, Scottsdale, AZ , <sup>22</sup>University of  
4  
5       Southern California, CA; <sup>23</sup>Emory University, Atlanta, GA; <sup>24</sup>Berry Consultants, Austin, TX  
6  
7  
8

9       **Correspondence to:**

10      Laura Esserman, M.D., M.B.A.

11      Director, UCSF Carol Franc Buck Breast Care Center

12      Professor of Surgery and Radiology, UCSF

13      1600 Divisadero Box 1710

14      San Francisco, CA 94115

15      Office 415 885 7691

16      laura.esserman@ucsf.edu

27      Presented in part at the San Antonio Breast Cancer Symposium in December, 2013

## ABSTRACT

**Background:** I-SPY 2 is a phase 2 multicenter platform trial designed to screen multiple experimental regimens in combination with standard neoadjuvant chemotherapy for breast cancer. The goal is to match experimental regimens with responding patient subtypes. We report results for veliparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, combined with carboplatin (VC).

**Methods:** Eligible women had  $\geq 2.5$  cm stage II/III breast cancer, categorized into 8 biomarker subtypes based on HER2, hormone-receptor status and MammaPrint. Patients are adaptively randomized within subtype to better performing regimens compared to standard therapy. Regimens are evaluated within 10 signatures, prospectively defined combinations of subtypes. VC plus standard therapy was considered for HER2-negative tumors and therefore evaluated in 3 signatures. The primary endpoint of I-SPY 2 is pathologic complete response. Magnetic resonance imaging volume changes during treatment inform the likelihood that a patient will achieve pathologic complete response. Regimens “graduate” (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 tumor signature in which they performed well.

**Results:** VC graduated in triple-negative breast cancer with 88% predicted probability of phase 3 success. A total of 72 patients were randomized to VC and 44 to concurrent controls with measured respective pathological complete response estimates (95% probability intervals) of 51% (35%-69%) vs 26% (11%-40%) at the completion of chemotherapy. Toxicity of VC was greater than control.

**Conclusion:** The I-SPY 2 TRIAL process demonstrated that VC added to standard therapy improves pathologic complete response rates specifically in triple-negative breast cancer.  
(ClinicalTrials.gov number, NCT01042379)

1  
2  
3 Breast cancer is genetically and clinically heterogeneous, making it challenging to identify  
4 optimal therapies. Although breast cancer mortality in the United States has decreased, over  
5 40,000 women in the U.S. still die of this disease yearly.<sup>1</sup> Further decreases in mortality will  
6 require therapeutic options that target tumor biology and can be delivered early enough in the  
7 disease course to make a clinical difference.

8  
9  
10  
11  
12  
13  
14  
15 The neoadjuvant approach facilitates evaluating an individual patient's response to treatment  
16 and holds promise for developing experimental therapies for disease while it is still curable.<sup>2</sup>  
17  
18 Long-term outcomes are equivalent to those when the same chemotherapy is given in the  
19 adjuvant setting (therapy given after all the tumor has been surgically removed leaving only  
20 occult disease behind).<sup>2</sup> Importantly, eradication of tumor in response to neoadjuvant  
21 chemotherapy, designated as pathologic complete response in breast and axillary nodes at  
22 surgery, correlates with event-free and overall survival depending on molecular subtype, with  
23 particularly strong correlation for triple-negative (HER2-/HR-) and HER2+ diseases.<sup>3</sup> For these  
24 reasons there is intense interest in the neoadjuvant approach.<sup>4,5</sup>

25  
26  
27  
28  
29  
30  
31  
32  
33 The I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response  
34  
35 Through Imaging and Molecular Analysis 2, I-SPY 2) is a multicenter, randomized phase 2  
36 'platform' trial in which experimental arms consisting of novel agents or novel combinations  
37 added to standard neoadjuvant chemotherapy are adaptively randomized in patients with high-  
38 risk primary breast cancer. The primary endpoint is pathologic complete remission.<sup>6</sup> Event-free  
39 and overall survival are not yet mature but are secondary endpoints.

40  
41  
42  
43  
44  
45  
46  
47  
48  
49 The trial goal from the drug development perspective is to rapidly identify which patient  
50 subtypes (or 'signature'), if any, are sufficiently responsive to enable a small, focused and  
51 successful phase 3 trial. From the perspective of patients in the trial, they are assigned with  
52  
53  
54  
55  
56  
57  
58  
59  
60

higher probability to regimens that are performing better for patients who share their biomarker subtypes and to better identify regimens that are more effective for such patients.

Preclinical models have demonstrated that veliparib, an oral, potent inhibitor of poly(ADP-ribose)polymerase (PARP), markedly potentiates the anti-neoplastic effect of carboplatin.<sup>7</sup> We report results from the first experimental regimen to “graduate,” i.e., leave the trial due to 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 with multiple experimental arms that evaluate novel agents combined with standard neoadjuvant therapy in breast cancers at high risk of recurrence.<sup>6</sup> Experimental treatments are compared against a common control arm of standard neoadjuvant therapy, with the primary endpoint being pathologic complete response, which is defined as no residual cancer in either breast or lymph nodes at time of surgery. Patients who dropout after starting therapy (with or without withdrawal of consent) or do not undergo surgery for any reason are counted as non-pathologic complete responders.

Biomarker assessments (HER2, HR, MammaPrint, categorized as noted below) performed at baseline are used to classify patients into  $2 \times 2 \times 2 = 8$  prospectively defined subtypes for randomization purposes. In addition to standard IHC and FISH assays, the protocol included a microarray-based assay of HER2 expression (TargetPrint<sup>TM</sup>). This assay has previously shown high concordance with standard IHC and FISH assays of HER2<sup>8</sup>. The adaptive randomization algorithm assigns patients with biomarker subtypes to competing drugs/arms based on current

1  
2  
3 Bayesian probabilities of achieving pathologic complete remission within that subtype vs control  
4 with 20% of patients assigned to control. Adaptive randomization speeds the identification of  
5 treatments that perform better within specific patient subtypes and helps avoid exposing  
6 patients to therapies that are unlikely to benefit them (Figure 1A).<sup>9,10</sup>  
7  
8  
9  
10  
11  
12  
13

14 To assess efficacy, ten clinically relevant biomarker ‘signatures’ were defined in the protocol:  
15 All; hormone receptor (HR)+; HR-; HER2+; HER2-; MammaPrint Hi-2; HER2+/HR+; HER2+/HR-  
16 ; HER2-/HR+; HER2-/HR-. Experimental arms are continually evaluated against control for each  
17 of these signatures and “graduate” when and if they demonstrate statistical superiority in  
18 pathologic complete response rate. Statistical analyses are Bayesian.<sup>9,11</sup> Graduation requires an  
19 85% Bayesian predictive probability of success in a 300-patient equally randomized  
20 neoadjuvant phase 3 trial with a traditional statistical design comparing to the same control arm  
21 and primary endpoint, pathologic complete response, as in I-SPY 2 (see Supplementary  
22 Information). Predictive probabilities of success are power calculations for a 300-patient trial  
23 averaged with respect to the current probability distributions of pathologic complete response  
24 rates for the experimental arm and control.<sup>9,11</sup> The modest size of this hypothetical future trial  
25 means that graduation occurs only when there is compelling evidence of an arm’s efficacy.  
26  
27 Accrual to a graduating arm halts enrollment in that arm immediately, but all patients already on  
28 the arm and its concurrent controls must complete surgery before graduation is announced. An  
29 experimental arm is dropped for futility if its predictive probability of success in a phase 3 trial is  
30 <10% for all ten signatures. The maximum total number of patients assigned to any  
31 experimental arm is 120.  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

### I-SPY 2 Eligibility & Enrollment

I-SPY 2 is open to women aged 18 and over, diagnosed with clinical stage II-III disease.

1  
2  
3 Patients must have clinically or radiologically measureable disease in the breast, defined as >  
4  
5 2.5 cm. If a tumor meets this criterion by clinical exam, the tumor must also be >2 cm by  
6  
7 imaging. Participants must have no prior cytotoxic treatment for this malignancy, have ECOG  
8  
9 performance status of 0-1 (a scale from 0 to 5 where 0 is asymptomatic and higher numbers  
10  
11 reflect increasing tumor-related disability), and agree to consent to core biopsy and MRI.  
12  
13

14 Patients with HR+/MammaPrint-low-risk tumors are excluded because the potential benefit of  
15  
16 chemotherapy is lower in patients with lower proliferative tumors and does not justify the risk of  
17  
18 exposure to investigational agents plus chemotherapy.<sup>6,12</sup>  
19

20  
21  
22 The veliparib/carboplatin (VC) regimen was not assigned to patients with HER2+ tumors due to  
23  
24 the lack of safety data with trastuzumab.  
25  
26

27  
28 All patients provided written, informed consent before initiating I-SPY2 screening. If eligible, a  
29  
30 second consent was obtained after randomized open-label treatment assignment and before  
31  
32 treatment.  
33  
34

### 35 36 Treatment

37  
38

39 Participants received weekly paclitaxel at 80 mg/m<sup>2</sup> (T) IV for 12 doses alone (control), or in  
40  
41 combination with an experimental regimen (Figure 1B). Patients randomized to VC received 50  
42  
43 mg of veliparib by mouth twice daily for 12 weeks, and carboplatin at a dose aimed to achieve a  
44  
45 pharmacologic area under the concentration versus time curve of 6 mg.hr/L (AUC 6) on weeks  
46  
47 1, 4, 7, and 10, concurrent with weekly paclitaxel. Following paclitaxel +/- VC, all patients  
48  
49 received doxorubicin 60 mg/m<sup>2</sup> and cyclophosphamide 600 mg/m<sup>2</sup> (AC) IV every 2 to 3 weeks  
50  
51 for 4 doses, with myeloid growth factor support as appropriate, followed by surgery that included  
52  
53 axillary node sampling per National Comprehensive Cancer Network (NCCN) and local practice  
54  
55 guidelines. Radiation and endocrine adjuvant therapy was recommended following surgery  
56  
57  
58

1  
2  
3 using standard guidelines.<sup>13</sup> Dose modifications for standard and experimental therapies are  
4 listed in Supplemental Table 4.  
5  
6  
7  
8  
9

## 10 Assessments

11  
12 Core biopsy, blood draws and MRI were performed at baseline and 3 weeks after treatment  
13 began. MRI and blood draws were repeated between chemotherapy regimens and before  
14 surgery. All surgical specimens were evaluated by pathologists trained to assess residual tumor  
15 burden.<sup>14</sup> Biomarker assessments include the Agenda 70-gene MammaPrint and TargetPrint  
16 HER2 gene expression using the Agenda 44K full genome microarray and reverse phase  
17 phosphoprotein array.<sup>15,16</sup>  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27

## 28 Study Oversight

29  
30 The study was designed by the principal investigators and the I-SPY2 investigators. The study  
31 was sponsored by the Foundation for the National Cancer Institute and the Quantum Leap  
32 Healthcare Collaborative. The drug manufacturer supplied the agent that was administered in  
33 an outpatient setting but played no role in the study design, data accrual, data analysis, or  
34 manuscript preparation. All participating sites received institutional review approval. A data  
35 safety monitoring board meets monthly. The manuscript was written entirely by the authors, who  
36 vouch for the data and adherence to the protocol, which is available at NEJM.org.  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

## 48 Statistical Considerations

49  
50 Trial participants are categorized into 8 subtypes based on three biomarkers: HR status, HER2  
51 status and MammaPrint High 1 (MP1) or High 2 (MP2) (supplemental Figure 1). The cutpoint  
52 between MP1 and MP2 is the median (-0.154) of I-SPY 1 participants who fit the eligibility  
53 criteria for I-SPY 2. (see Supplemental Figure 1)<sup>17</sup>  
54  
55  
56  
57  
58  
59  
60

Following a Bayesian approach,<sup>10,11</sup> at any given time each regimen's pathologic complete response rate has a probability distribution within each of the 8 biomarker subtypes. This distribution is based on the results for all patients previously assigned to the regimen and assumes a covariate-adjusted logistic model with covariates HER2, HR, and MammaPrint statuses. These distributions allow for finding the (Bayesian) probability that each regimen is superior to 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 MRI volume after 3 and 12 weeks of therapy in comparison with baseline improves information about pathologic complete response rates via multiple imputation. When all patients on the regimen have had surgery, MRI volumes are no longer required for calculating probabilities of pathologic complete response, but they are used to update the longitudinal model.

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

Additional study design details are in the Supplemental appendix; the common elements of the I-SPY2 study design are also reported in the neratinib manuscript in the same volume of this journal (ref Park et al).

## RESULTS

### Patients and disease characteristics

Patients were eligible to be randomized to VC from May 2010 to July 2012. During this period there were 3 to 5 arms (VC, neratinib, trebananib, ganitumumab, control) being randomized. A total of 72 patients were randomized to VC and evaluable for the primary endpoint; there were 44 concurrently randomized HER2- controls (Figure 1C). Baseline characteristics of participants (Table 1) were similar between the experimental and control arms. More VC patients (17% vs. 7%) carried a deleterious mutation in BRCA1/2 (see discussion). Two VC patients and one control patient did not have surgery; one VC patient withdrew consent before surgery; all 4 patients were counted as non-pathologic complete responders.

### Efficacy

VC was eligible to graduate in 3 signatures: HER2-negative, HR-positive/HER2-negative, and triple-negative. It graduated in the triple-negative signature (Figure 2, Table 2). Within HER2-tumors treated with VC, its estimated pathologic complete response rate was 33% (95% probability interval (PI) 23-43%), compared to 22% (95% PI 10-35%) in the control arm (Figure 2A). This benefit was concentrated in the graduating signature, triple-negative, where the estimated pathologic complete response rate was 51% (95% PI 36-66%) for those receiving VC vs 26% (95% PI 9-43%) in control patients (Figure 2B). The estimated pathologic complete response rate in patients with HR+/HER2- breast cancer (Figure 2C) was 14% (95% PI 3-25%) for VC compared to 19% (95% PI 5-33%) for control.

In the triple-negative subtype, the probability that VC is superior to control is 99%, and its probability of statistical success in an equally randomized, phase 3 trial including 300 patients is 88% (Table 2, Figure 2B).

## Toxicity

Selected toxicities by treatment arm are summarized in Table 3; all toxicities >5% are listed in Supplemental Table 5. Grade 3/4 hematologic toxicity was increased in VC relative to control, with 71 vs 2% of patients experiencing neutropenia, 1 vs 0% febrile neutropenia, 21 vs 0% thrombocytopenia, and 28 vs 0% anemia. Toxicity was also increased during AC in those who had received VC, with 12 vs 5% febrile neutropenia, as well as an increase in neutropenia, thrombocytopenia, and anemia. There was no treatment-related mortality.

## Dose reductions and discontinuations

Dose reductions in paclitaxel, although absent in the control arm, occurred in 23 (32%) VC patients. Dose reductions of carboplatin occurred in 34 (48%) patients. During paclitaxel, 13 patients (18%) discontinued therapy early in the VC arm compared to 2 patients (5%) in the control arm. Reasons for discontinuation in the VC arm included toxicity (10), progression (1), and patient preference (2). One patient in the control arm discontinued for toxicity, and one for progression. One patient discontinued AC after 3 cycles for toxicity in the VC arm, and 3 patients discontinued AC early in the control arm (toxicity (2), progression (1)).

## DISCUSSION

I-SPY 2 is a new clinical trial model designed to facilitate rapid evaluation of novel therapeutics with identification of biomarkers for definitive subsequent study.<sup>6</sup> A goal of I-SPY 2 is to provide

a framework for more rapidly and efficiently testing promising agents earlier in the course of disease. Novel agents are added to standard treatment in the neoadjuvant setting for patients who present with tumors at high risk for early recurrence. I-SPY 2 uses adaptive randomization, shared control arms, and allows multiple agents and regimens to be tested in a single trial. It is designed to evaluate tumor subsets for improvement in the likelihood of pathologic complete response. An important objective is to reduce the number of patients needed to determine clinical activity of an agent or regimen.<sup>4,5</sup>

Another goal of I-SPY 2 is to specifically improve the drug development process by establishing a link to the potential success of a future phase 3 trial. Predicting outcomes in a future trial that has a substantial chance of being successful establishes a high bar for continued development. Achieving statistical significance in a phase II trial is not enough. The target sample size of 300 for a future confirmatory neoadjuvant trial is consistent with our goal of identifying sufficient signal in I-SPY 2 (improvement in pathologic complete response rate in the range of 20% over control) such that a moderately sized phase 3 trial in the subtype of interest would be successful. However, there is no requirement in I-SPY 2 for a future trial.

Triple-negative breast cancer is aggressive, putting women at risk for early recurrence and death. Those with stage II-III disease who achieve pathologic complete response have a marked improvement in outcome compared to women with residual disease.<sup>3</sup> For example, the advantage in 3-year event-free survival is about 30%. Identifying promising combinations that have the potential to improve long-term outcomes in this tumor subset is a high priority and is consistent with the I-SPY 2 goal of accelerating the pace of getting successful therapies to patients.

Two recent randomized neoadjuvant trials have demonstrated improved pathologic complete response rates with the addition of carboplatin in patients with triple-negative disease. The GeparSixto trial randomized 315 patients to receive paclitaxel, non-pegylated liposomal doxorubicin and bevacizumab, with or without carboplatin.<sup>18</sup> Significantly more patients receiving carboplatin achieved pathologic complete response (53% versus 37%, p=0.005). CALGB 40603 randomized 443 patients to receive paclitaxel with carboplatin and/or bevacizumab, followed by AC<sup>19</sup>. Similar to GeparSixto, the addition of carboplatin significantly increased pathologic complete response rate (54% versus 41%; p = .0029).

The combination of veliparib plus carboplatin graduated with a signature of triple-negative breast cancer, with an estimated probability of pathologic complete response 52% vs. an estimated control rate of 26%. Importantly, our trial showed no improvement in the pathologic complete remission rate in HR+/HER2- disease. Our design did not evaluate the individual contributions of veliparib and carboplatin, but instead it evaluated a combination of agents that might have maximum effect. Based on these data, an ongoing phase 3 neoadjuvant trial is comparing the efficacy of standard chemotherapy alone, with carboplatin or with veliparib plus carboplatin in triple-negative breast cancer (NCT02032277).

In both GeparSixto<sup>18</sup> and CALGB 40603,<sup>19</sup> hematologic and nonhematologic toxicity, dose modifications and early discontinuation were increased with carboplatin. In the I-SPY 2 VC arm we observed rates of toxicities comparable to those observed with carboplatin in CALGB 40603. However, we have no ability to ascribe the higher rates in the VC arm to either carboplatin or veliparib. In the VC arm, despite increased dose reductions and early discontinuation compared to control, estimated pathologic complete response rates were higher. The use of VC also increased toxicity during AC, similar to CALGB 40603, with increased hematologic toxicity. Despite this, all but one patient completed 4 cycles of AC.

1  
2  
3  
4 A small number of patients had BRCA mutations in I-SPY 2. By design, adaptive randomization  
5 increased the number of triple-negative patients assigned to VC in comparison with other  
6 experimental arms. This may have enriched the group adaptively randomized to VC for BRCA  
7 mutations. DNA repair deficiencies were evaluated in all patients and are not reported here.  
8  
9  
10  
11  
12  
13  
14

15 In summary triple-negative breast cancer patients benefit from VC while patients with HER2-  
16 /HR+ tumors do not. The experience of VC in I-SPY2 demonstrates the advantage of an  
17 adaptively randomized phase 2 platform trial for matching therapies with biomarker subsets to  
18 better inform the design of phase 3 trials so they can be more focused, smaller, and faster.  
19 Future patients stand to benefit but trial participants benefit as well by minimizing exposure to  
20 ineffective therapy.  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Disclosure:**

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

**Funding:**

The FNIH (2010-2012) and Quantum Leap (2013-present) were the study sponsors of the I-SPY2 TRIAL which operates as a precompetitive consortia model.

We acknowledge the initial support for the I-SPY 2 TRIAL by the following: The Safeway Foundation, Bill Bowes Foundation, Quintiles Transnational Corporation, Johnson & Johnson, Genentech, Amgen, Inc., The San Francisco Foundation, Give Breast Cancer the Boot, Eli Lilly and Company, Pfizer, Inc., Eisai Company Ltd., Side Out Foundation, Harlan Family, The Avon Foundation for Women, Alexandria Real Estate Equities, Inc., and private individuals and family foundations.

### References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics 2015. CA: a cancer journal for clinicians  
2015;65:5-29.
2. Cortazar P, Geyer CE, Jr. Pathological complete response in neoadjuvant treatment of  
breast cancer. Annals of surgical oncology 2015;22:1441-6.
3. 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.
4. 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 8-9.
5. 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.
6. 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. Clinical  
pharmacology and therapeutics 2009;86:97-100.
7. 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.
8. 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.
9. Berry DA. Adaptive clinical trials in oncology. Nature reviews Clinical oncology  
2012;9:199-207.
10. Berry DA. The Brave New World of clinical cancer research: Adaptive biomarker-driven  
trials integrating clinical practice with clinical research. Molecular oncology 2015;9:951-9.
11. Berry DA. Bayesian clinical trials. Nature reviews Drug discovery 2006;5:27-36.

- 1  
2  
3 12. Prowell TM, Pazdur R. Pathological complete response and accelerated drug approval  
4 in early breast cancer. *The New England journal of medicine* 2012;366:2438-41.  
5  
6 13. Gradishar WJ, Anderson BO, Balassanian R, et al. Breast Cancer, Version 1.2016. J  
7 Natl Compr Canc Netw 2015;13:1475-1485.  
8  
9 14. Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer  
10 burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol* 2007;25:4414-22.  
11  
12 15. Glas AM, Floore A, Delahaye LJ, et al. Converting a breast cancer microarray signature  
13 into a high-throughput diagnostic test. *BMC Genomics* 2006;7:278-288.  
14  
15 16. Roepman P, Horlings HM, Krijgsman O, et al. Microarray-based determination of  
16 estrogen receptor, progesterone receptor, and HER2 receptor status in breast cancer. Clin  
17 Cancer Res 2009;15:7003-7011.  
18  
19 17. Wolff D, Daemon A, Yau C, al e. MammaPrint ultra-high risk score is associated with  
20 response to neoadjuvant chemotherapy in the I-SPY1 trial (CALGB 150007/150012; ACRIN  
21 6657). *Cancer Res* 2014;73 (24 Suppl):P1-08-1.  
22  
23 18. von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with  
24 triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised  
25 phase 2 trial. *Lancet Oncol* 2014;15:747-56.  
26  
27 19. Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/or  
28 bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and  
29 cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast  
30 cancer: CALGB 40603 (Alliance). *J Clin Oncol* 2015;33:13-21.  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Figure Legends****Figure 1****A: I-SPY 2 Adaptive Design**

Figure 1A illustrates the steps within the I-SPY 2 adaptive process. When new patients are enrolled, their subtypes are assessed. As patients are randomized, their outcomes are used to update the Bayesian co-variate adjusted model which computes the predictive probability of success in phase 3 for each signature. Pre-defined termination rules are applied for each experimental arm to determine whether it should stop for futility, graduate, or continue, adding on additional experimental arms if accrual permitting. As the trial continues, for each experimental arm, the probability of superiority over control within each subtype is updated; and the randomization probabilities for each subtype into the various experimental arms are adapted (such that new patients entering the trial will be more likely to be randomized to an agent showing activity within their subtype).

**B: I-SPY 2 Study Design**

Patients are screened for I-SPY 2 eligibility. Eligible patients are adaptively randomized to 12 weekly paclitaxel (and trastuzumab if HER2+) cycles (control) or in combination with one of several experimental agents followed by doxorubicin/cyclophosphamide (AC) x 4, with serial biomarkers (biopsies, blood draw and MRI scans) assessed over the course of their therapy. Only patients with HER2- disease were randomized to the veliparib/carboplatin arm.

**C. I-SPY 2 Consort Diagram for veliparib/carboplatin arm and its concurrent control.**

Only patients with HER2-negative disease were eligible for randomization to the VC arm. Patients were categorized as received allocated invention if they received at least one dose of experimental (or control) therapy.

1  
2  
3  
4 **Figure 2. Estimated pathologic complete remission rate for the signatures evaluated for**  
5 **V/C vs. concurrent HER2-negative control.**

6  
7 **2A.** Probability distribution for all patients with HER2-negative disease; **2B.** Probability  
8 distribution for patients with TNBC (HR-negative/HER2-negative); **2C.** Probability distribution for  
9 patients with HR-positive, HER2-negative disease. The red curves represent patients treated  
10 with V/C plus paclitaxel followed by AC, and the blue curves represent concurrent controls. The  
11 corresponding 95% probability distributions (represented by the width of the curve) are shown  
12 for each. The mean of each distribution is the estimated pathologic complete remission rate.  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

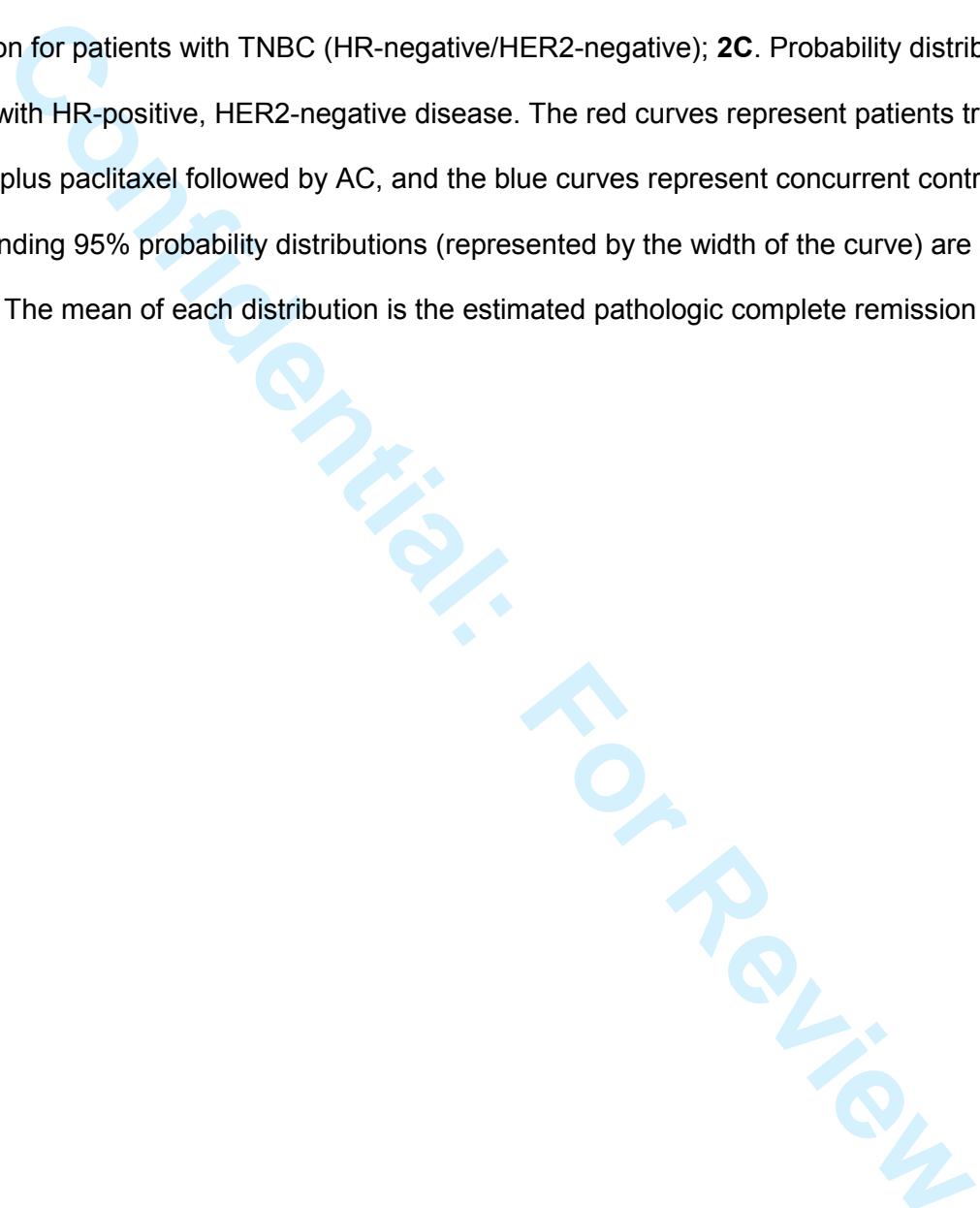


Table 1. Demographics

	V/C (n=72)	Control (n=44)
<b>Age (years)</b>		
Median (Range)	48.5 (27 - 70)	47.5 (24-71)
<b>Ethnicity, n(%)</b>		
White	54 (75%)	34 (77%)
African American	15 (21%)	7 (16%)
Asian	3 (4%)	3 (7%)
<b>HR Status, n (%)</b>		
Positive	33 (46%)	23 (52%)
Negative	39 (54%)	21 (48%)
<b>BRCA1/2 Mutation Status, n(%)</b>		
Positive for Deleterious Mutation	12 (17%)	2 (5%)
Genetic Variant, Suspected Deleterious	0 (0%)	1 (2%)
Genetic Variant, Unknown significance	2 (3%)	0 (0%)
Genetic Variant, Favor Polymorphism	0 (0%)	2 (5%)
No mutation detected	56 (78%)	39 (89%)
Not Evaluated*	2 (3%)	0
<b>Clinical Tumor Size (cm)</b>		
Median (Range)	5 (0-15)	5 (0-14)
<b>Baseline node status , n (%)</b>		
Palpable	31 (43%)	22 (50%)
Non-palpable	41 (57%)	22 (50%)

\* 2 patients in the V/C arm withdrew consent for use of tissue for analysis

**Table 2: Final predictive probabilities**

Signature	Estimated Pathologic Complete Remission Rate (95% Probability Interval) [Equivalent Sample Size N*]		Probability VC is Superior to Control	Predictive Probability of Success in Phase 3 Trial
	VC	Control		
All HER2-negative	33% (23-43%) [72]	22% (10-35%) [44]	91%	53%
HR-positive/HER2-negative	14% (3-25%) [38.1]	19% (5-33%) [29.4]	28%	8%
HR-negative/HER2-negative (triple-negative)	51% (36-66%) [45.9]	26% (9-43%) [24.9]	99%	88%

**Table 3. Selected Toxicities**

	VC (n=72)		HER2-negative Control (n=44)	
	Paclitaxel + VC (n=72)	AC (n=66)	Paclitaxel (n=44)	AC (n=42)
<b>ADVERSE EVENTS</b>				
<b>Hematologic, ≥Grade 3, n (%)</b>				
Febrile neutropenia	1 (1%)	8 (12%)	0 (0)	2 (5%)
Neutropenia	51 (71%)	16 (24%)	1 (2%)	5 (12%)
Thrombocytopenia	15 (21%)	6 (9%)	0 (0)	0 (0)
Anemia	20 (28%)	20 (30%)	0 (0)	0 (0)
<b>Gastrointestinal, ≥Grade 3, n (%)</b>				
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
<b>TOXICITY</b>				
<b>Dose reductions, n (%)</b>				
	paclitaxel: 23 (32%) V: 0 C: 34 (47%)	A/C: 6 (9%)	paclitaxel: 0	A/C: 3 (7%)
<b>Early discontinuation, n (%)</b>				
All	13 (18%)*	1 (2%)	2 (5%) **	3 (7%)
Toxicity	10 (14%)	1 (2%)	1 (2%)	2(5%)
Progression	1 (1%)	0	1 (2%)	1 (2%)
Other	2 (3%)	0	0	0
<b>Time from Treatment Consent to Surgery (days)</b>				
Median (range)	182 (93 - 232)		165 (100 - 248)	

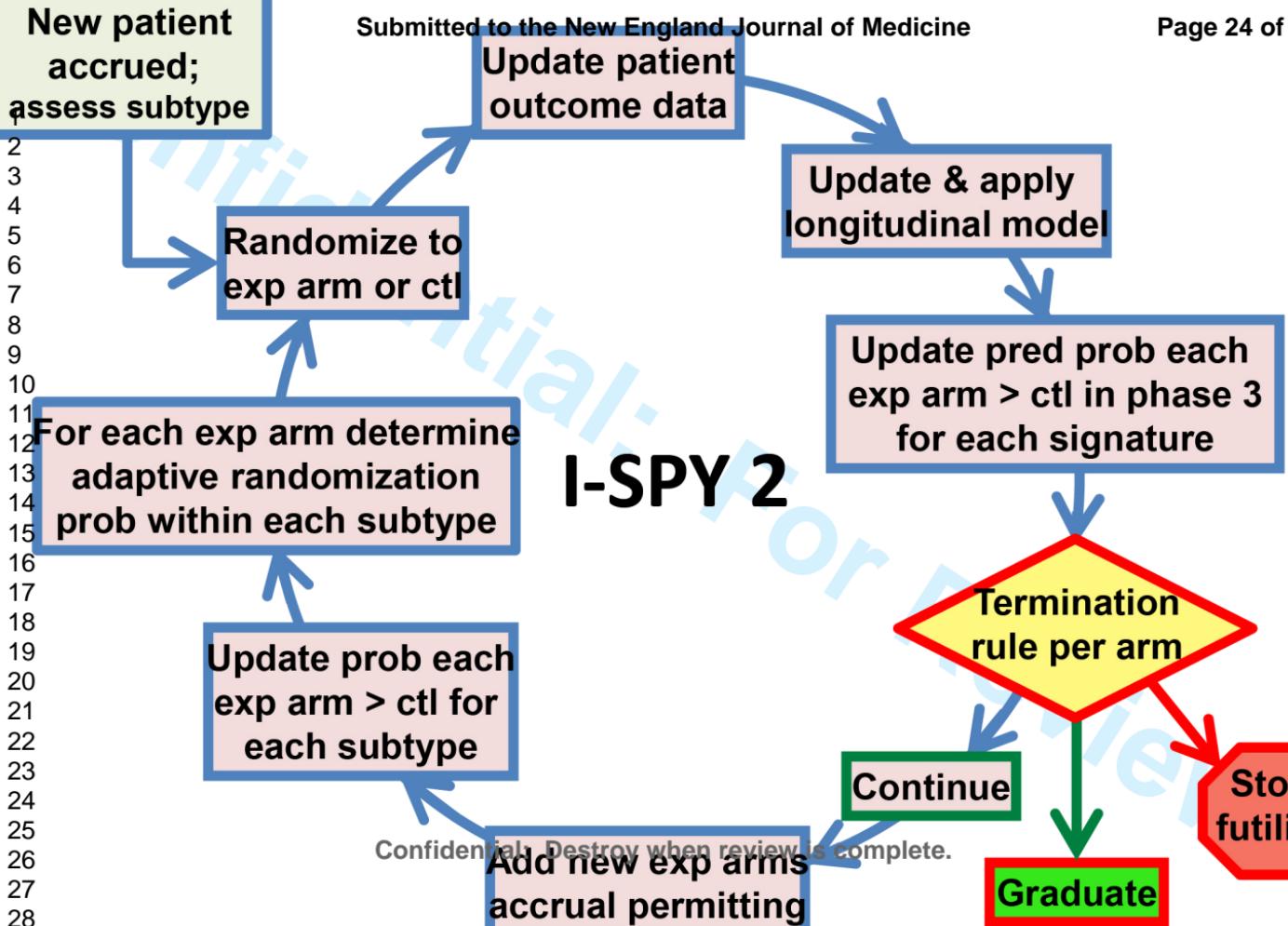
V: veliparib

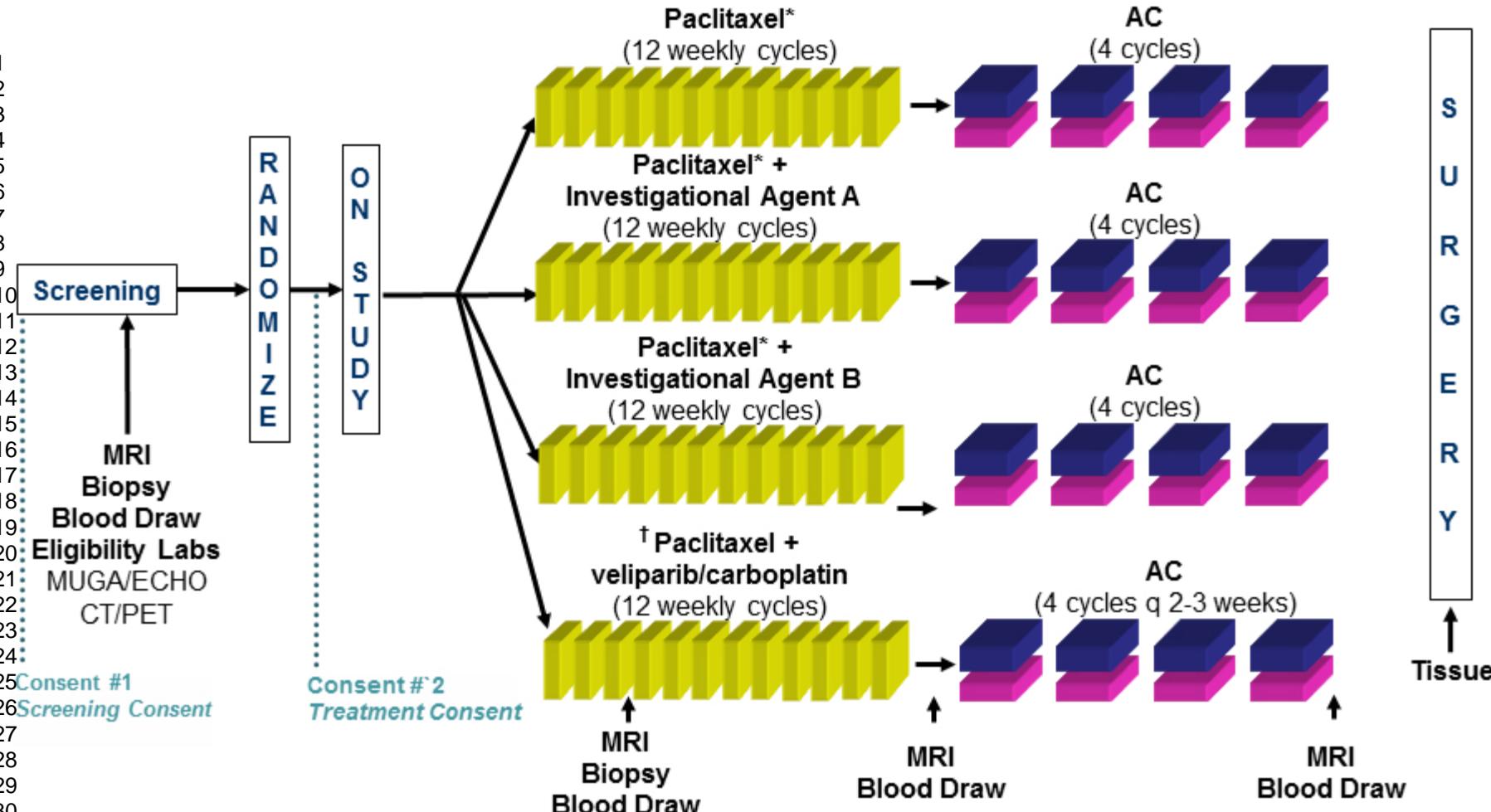
C: carboplatin

AC: doxorubicin and cyclophosphamide

\* 7 of the 13 patients who discontinued VC early continued to AC

\*\* 1 patient who discontinued early continued to AC





\* HER2 positive participants also receive Trastuzumab. An investigational agent may be used instead of Trastuzumab.

† The veliparib/carboplatin arm is only open to HER2 negative patients.

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

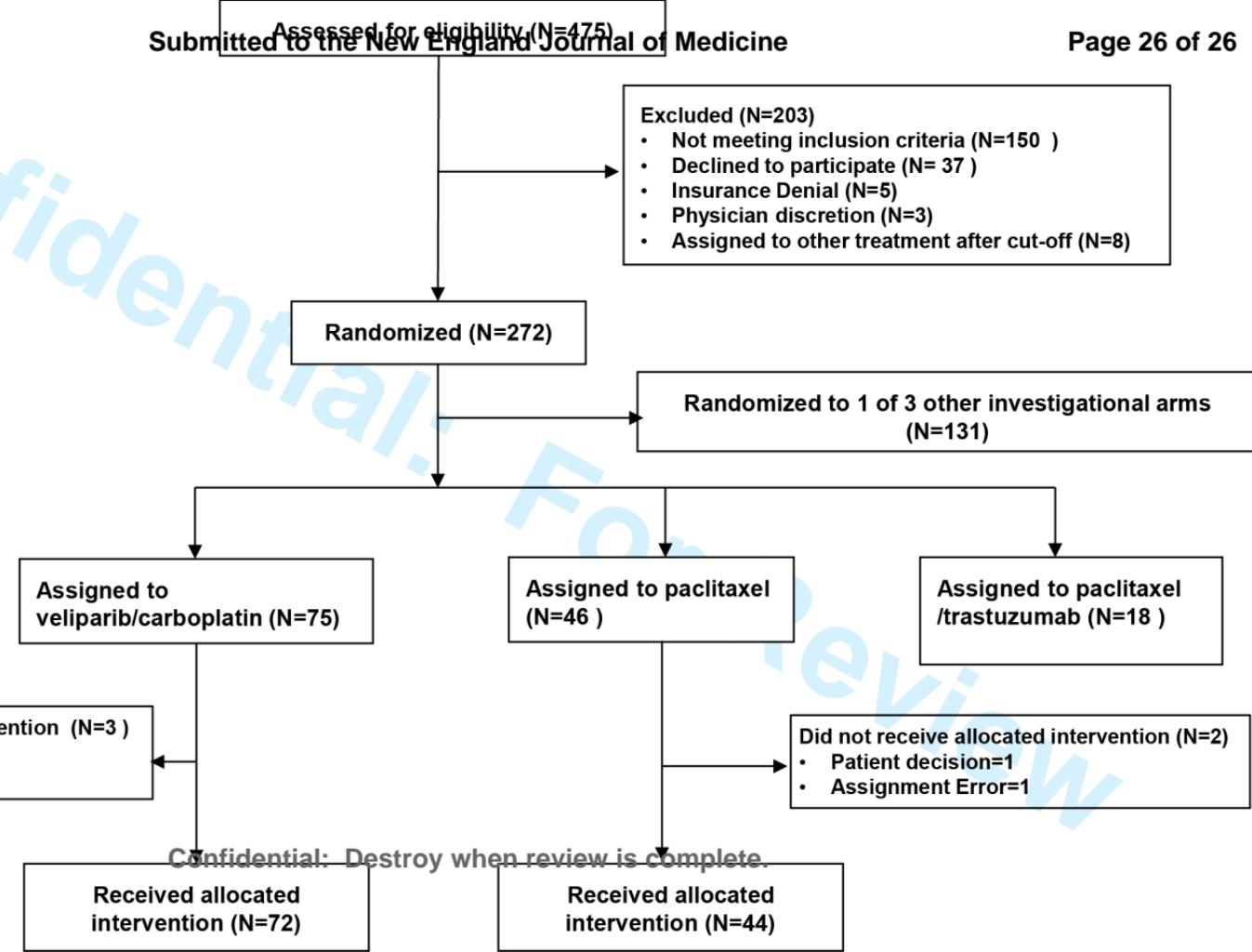
23

24

25

26

27



Confidential: Destroy when review is complete.

**HER2-****HR+HER2-**