Pathologic Complete Response Predicts Recurrence-Free Survival More Effectively by Cancer Subset: Results From the I-SPY 1 TRIAL—CALGB 150007/150012, ACRIN 6657

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ABSTRACT

Purpose
Neoadjuvant chemotherapy for breast cancer provides critical information about tumor response; how best to leverage this for predicting recurrence-free survival (RFS) is not established. The I-SPY 1 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis) was a multicenter breast cancer study integrating clinical, imaging, and genomic data to evaluate pathologic response, RFS, and their relationship and predictability based on tumor biomarkers.

Patients and Methods
Eligible patients had tumors ≥ 3 cm and received neoadjuvant chemotherapy. We determined associations between pathologic complete response (pCR; defined as the absence of invasive cancer in breast and nodes) and RFS, overall and within receptor subsets.

Results
In 221 evaluable patients (median tumor size, 6.0 cm; median age, 49 years; 91% classified as poor risk on the basis of the 70-gene prognosis profile), 41% were hormone receptor (HR) negative, and 31% were human epidermal growth factor receptor 2 (HER2) positive. For 190 patients treated without neoadjuvant trastuzumab, pCR was highest for HR-negative/HER2-positive patients (45%) and lowest for HR-positive/HER2-negative patients (9%). Achieving pCR predicted favorable RFS. For 172 patients treated without trastuzumab, the hazard ratio for RFS of pCR versus no pCR was 0.29 (95% CI, 0.07 to 0.82). pCR was more predictive of RFS by multivariate analysis when subtype was taken into account, and point estimates of hazard ratios within the HR-positive/HER2-negative (hazard ratio, 0.00; 95% CI, 0.00 to 0.93), HR-negative/HER2-negative (hazard ratio, 0.25; 95% CI, 0.04 to 0.97), and HER2-positive (hazard ratio, 0.14; 95% CI, 0.01 to 1.0) subtypes are lower. Ki67 further improved the prediction of pCR within subsets.

Conclusion
In this biologically high-risk group, pCR differs by receptor subset. pCR is more highly predictive of RFS within every established receptor subset than overall, demonstrating that the extent of outcome advantage conferred by pCR is specific to tumor biology.

INTRODUCTION

Advances in adjuvant therapy as well as screening have helped reduce breast cancer mortality, but approximately 20% of patients with breast cancer in the United States still die of their disease. Mortality is highest among women who present with larger, palpable tumors and in whom the absolute incidence has not decreased much. Thus, better treatments are needed.

Breast cancer is a heterogeneous disease that varies widely in outcomes and response to standard therapies. Neoadjuvant or preoperative chemotherapy yields outcomes equivalent to adjuvant therapy but has the benefit of downstaging tumors and increasing breast conservation rates, and it permits assessment of individual tumor response to treatment.

The I-SPY 1 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis) is a multicenter neoadjuvant breast cancer study designed to establish standards for collecting molecular and imaging data over the course of care. Primary objectives were...
to evaluate whether response to therapy—as measured by imaging (magnetic resonance imaging [MRI] volume) response and pathologic complete response (pCR)—would predict recurrence-free survival (RFS), overall and within biologic and imaging subsets. Secondary objectives were to develop a resource of clinical, molecular, genetic, and imaging biomarker data and a multicenter network to support high-quality real-time biomarker evaluation for future trials of tailored therapy. This first report describes the ability of short-term response to therapy, as measured by pCR, to predict RFS, both overall and within receptor subsets.

**PATIENTS AND METHODS**

The I-SPY 1 TRIAL was a collaboration of the American College of Radiology Imaging Network (ACRIN), Cancer and Leukemia Group B (CALGB), and the National Cancer Institute (NCI)’s Specialized Programs of Research Excellence (SPORE). It consisted of two protocols developed to identify markers of response to conventional neoadjuvant chemotherapy: CALGB 150007 (molecular marker component) and ACRIN 6657/CALGB 150012 (imaging component). The protocol (schema is shown in Fig 1) was approved by institutional review boards at all participating institutions. Patients signed one combined informed consent form before joining the study, which allowed them to simultaneously enroll onto the CALGB and ACRIN protocols. Details of accrual have been published previously.10

The primary end point for the trial was RFS according to the STEEP (Standardization of Events and End Points) criteria.11 RFS was calculated from the date of chemotherapy initiation. An estimated target sample size of 244 patients with 15% drop rate was needed to be able to detect (with 90% power and 0.05 type I error) a hazard ratio of 0.5 between two biomarker-defined groups (eg, MRI volume change in response to neoadjuvant chemotherapy or risk groups defined by molecular signatures). Defining the relationship of biomarkers to RFS were secondary aims of the trial. All sites tested for estrogen receptor (ER) status, progesterone receptor (PR) status, and human epidermal growth factor receptor 2 (HER2) overexpression and assessed pCR. pCR was defined as the absence of invasive tumor in both breast and axillary lymph nodes after neoadjuvant therapy.

**Patient Eligibility**

Eligible patients had histologically confirmed invasive breast cancers measuring at least 3 cm by clinical examination or imaging, with no evidence of distant metastatic disease, and were candidates for neoadjuvant chemotherapy with an anthracycline-based regimen. Patients with T4 or inflammatory disease were eligible. Patients were considered evaluable if they completed neoadjuvant chemotherapy.

**Study Treatment and Procedures**

After four cycles of anthracycline-based therapy, patients could either undergo surgical excision or receive a taxane before surgery. Treatment after surgery, including chemotherapy, radiation, and hormone therapy, was at the physician’s discretion.

Biopsies and imaging studies were conducted at four time points during neoadjuvant chemotherapy (Fig 1). Details of the imaging component (ACRIN 6657/CALGB 150012) are described elsewhere.12 Trastuzumab treatment was not dictated by the protocol and was not used as neoadjuvant therapy until April 2005.

**Standard Clinical Biomarkers**

Hormone receptor (HR) status (ER positive or PR positive) and HER2 overexpression were measured from diagnostic samples obtained by a standard method in Clinical Laboratory Improvement Amendments (CLIA)—approved laboratories at local sites on formalin-fixed, paraffin-embedded core biopsies obtained at diagnosis.

Both ER and PR status were determined by immunohistochemistry (IHC) and were considered positive if the Allred score was ≥ 312; HER2 status was determined by IHC and/or fluorescent in situ hybridization assays locally and centrally at the University of North Carolina.14 HER2 status was regarded as positive if there was 3+ staining and/or fluorescent in situ hybridization positivity (positive defined as HER2/CEP17 ratio ≥ 2.2) locally or centrally.

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**Results From the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657)**

Fig 1. I-SPY 1 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis) schema. Sixteen-gauge core-needle biopsies were performed at four time points: T1, before treatment; T2, between 24 and 96 hours after starting treatment; T3, after completing the regimen that contained doxorubicin (if a taxane was to be given); and T4, at the time of surgical resection. Blood was drawn to obtain serum and plasma before chemotherapy, between anthracycline and taxane regimens, if applicable, and before surgery. Magnetic resonance (MR) images were obtained before chemotherapy, approximately 2 weeks after the first dose of anthracycline, at the end of anthracycline treatment (if the patient went on to receive a taxane), and again before surgical resection. The goal of the trial was to relate early and late outcomes. Early outcome measures included MR volume change and rates of pathologic complete response (pCR). Late outcomes were measured by recurrence-free survival (RFS), which was measured as the proportion of patients who did not experience an invasive breast cancer recurrence in the ipsilateral breast or regional nodes, distant organ sites, or death from any cause for the specified time period. MRI, magnetic resonance imaging. (*) Twenty-four to 96 hours after the start of anthracycline. (†) Two weeks after the start of anthracycline.

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Ki67 IHC staining was performed centrally at the University of North Carolina by using standard avidin-biotin complex technique. Tumors were categorized as low, intermediate, or high proliferation index for less than 10%, 10% to 25%, and more than 25% of tumor cell nuclei staining positive, respectively, and were interpreted by a single pathologist (C.L.). Molecular assays and analyses are described in detail elsewhere. 

**Data Collection and Platform Integration for Analysis**

The NCI Center for Bioinformatics developed a Web-based system, caINTEGRATOR, to support centralized reporting of results across disparate sources and platforms and provided a common platform for accessing data (https://caintegrator-stage.nci.nih.gov/ispy/index2.jsp). I-SPY 1 data dated February 2011 was used for the analyses in this article.

**Statistical Analysis**

Rates of pCR were calculated for each combination of HR and HER2 status. Kaplan-Meier survival curves were generated for patients who achieved pCR versus those who did not, overall and within each receptor subset. The RFS hazard ratios and \( p \)-values for comparisons of patients who achieved pCR versus those who did not were based on multivariate Cox proportional hazards models, adjusting for age and clinical stage. These analyses were conducted by using JMP Version 8.0.1 (SAS Institute, Cary, NC).

**Patients**

Between May 2002 and March 2006, 237 patients were enrolled. Figure 1 shows the protocol schema; Figure 2 shows the number of patients accrued and reasons for exclusions. The remaining 221 patients received neoadjuvant chemotherapy and were evaluable. Of these, 215 (97%) underwent surgical resection and had pCR information available (Fig 2). HER2 and HR information was available for 210 of the 215 patients (HER2 status was missing for four, and HR information was missing for one).

The characteristics of patients who participated in the trial are provided in Table 1. Average baseline tumor size was 6.0 cm (range, 0 to 25 cm) clinically and 6.8 cm (range, 0 to 18.4 cm) by MRI. Most patients (65%) had clinically or pathologically confirmed axillary lymph node involvement at diagnosis; 90% had tumors of intermediate or high histologic grade. Overall, 59% of patients were HR positive (n = 131), and 31% were HER2 positive (n = 67); 29% (n = 55) were scored as Ki67 low, 33% (n = 63) as Ki67 medium, and 38% (n = 71) as Ki67 high.

All patients received doxorubicin plus cyclophosphamide as initial chemotherapy (54% on a dose-dense [every 2 weeks] schedule, 34% on a standard [every 3 weeks] schedule, and 12% on a modified schedule), and 95% subsequently received a taxane (55%, every 2 weeks; 26%, every 3 weeks; and 19%, once per week). Among the 66 patients with HER2-positive tumors, 46 (69%) were treated before trastuzumab was approved for adjuvant breast cancer in 2005 and therefore did not receive concurrent neoadjuvant trastuzumab. Of the 46 HER2-positive patients who did not receive neoadjuvant trastuzumab, 17 HER2-positive patients (36%) received adjuvant trastuzumab (plus one HER2-negative patient). A total of 172 received the same chemotherapy regimen without any trastuzumab (Fig 2). The median follow-up time was 3.9 years (range 3.0 to 7.5 years).

**RESULTS**

**Tumor Receptors and Rates of pCR**

Of the 210 patients with receptor status and surgery results, 56 (27%) experienced a pCR. Of the 190 patients who did not receive neoadjuvant trastuzumab, 44 (23%) experienced a pCR. The pCR rate was lowest (9%) in the HR-positive/HER2-negative receptor subset and highest (45%) in the HR-negative/HER2-positive receptor subset. The incremental effect of being HR negative versus HR positive resulted in an estimated 24% increase in the rate of pCR; the incremental increase in the likelihood of pCR in HER2-negative versus HER2-positive patients was 21% (Table 2).

The impact of Ki67 is best appreciated within the receptor subsets. Ki67 staining was available for 166 of the 190 patients who did not receive neoadjuvant trastuzumab (Table 3). The pCR rate was significantly higher within the high Ki67 group (34% vs 11% in the low/medium group) overall, and Ki67 remained a significant predictor of pCR when HR and HER2 status were taken into account (multivariate logistic regression \( P = .02 \)). When the impact of Ki67 on pCR was assessed within receptor subsets (Table 3), high Ki67 was significantly associated with increased responsiveness only in the HER2-negative subsets. In addition, the incremental impact of HER2 positivity on pCR rate was observed only within the low/medium Ki67 (+31%) but not the high Ki67 (−7%) subset. These findings suggest that adding Ki67 to standard receptor subtyping may further improve the prediction of pCR.

**Relationship of pCR to RFS**

RFS for all patients (excluding those treated with trastuzumab) and the receptor subsets are shown in Figure 3, stratified by whether a pCR was achieved (solid line) or not (dotted line). Table 4 details the...
Table 1. Characteristics of Patients in the I-SPY 1 TRIAL

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>I-SPY 1 Trial Evaluable* (n = 221)</th>
<th>Patients Without Trastuzumab Treatment† (n = 172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>49 48</td>
<td>26-68 27-68</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>106 48</td>
<td>82 48</td>
</tr>
<tr>
<td>Race</td>
<td>White 165 75</td>
<td>African American 42 19</td>
</tr>
<tr>
<td></td>
<td>Asian 9 4</td>
<td>Other 5 2</td>
</tr>
<tr>
<td>Clinical tumor size, cm</td>
<td>6.0 6.0</td>
<td>Range 0-25 0-18</td>
</tr>
<tr>
<td>Tumor longest diameter on baseline MRI, cm</td>
<td>6.8 6.8</td>
<td>Range 0-18-4 2.0-16.8</td>
</tr>
<tr>
<td>Clinically node positive at diagnosis</td>
<td>143 65</td>
<td>107 62</td>
</tr>
<tr>
<td>Histologic grade (baseline)</td>
<td>Low 18 8</td>
<td>Intermediate 96 46</td>
</tr>
<tr>
<td></td>
<td>High 103 47</td>
<td>Indeterminate 4 2</td>
</tr>
<tr>
<td>Clinical stage (baseline)</td>
<td>I 3 1</td>
<td>II 96 46</td>
</tr>
<tr>
<td></td>
<td>IIA 43 19</td>
<td>IIIB 11 5</td>
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<tr>
<td></td>
<td>IIIC 78 35</td>
<td>IIC 7 3</td>
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<tr>
<td></td>
<td>Inflammatory 17 8</td>
<td>Indeterminate 1 &lt; 1</td>
</tr>
<tr>
<td></td>
<td>Low hormone receptor status</td>
<td>Negative 8/24 33</td>
</tr>
<tr>
<td></td>
<td>ER positive 125 57</td>
<td>HR positive (ER or PR) 104 47</td>
</tr>
<tr>
<td></td>
<td>PR positive 47 88</td>
<td>HER2 positive (ER or PR) 131 59</td>
</tr>
<tr>
<td></td>
<td>HR negative/HER2 negative</td>
<td>HER2 positive (baseline) 67 30</td>
</tr>
<tr>
<td></td>
<td>Neoadjuvant trastuzumab</td>
<td>Neoadjuvant trastuzumab 53 24</td>
</tr>
<tr>
<td></td>
<td>Anthracycline only 11 5</td>
<td>Anthracycline + taxane 187 85</td>
</tr>
<tr>
<td></td>
<td>Anthracycline + taxane + trastuzumab</td>
<td>20 9 0</td>
</tr>
<tr>
<td></td>
<td>Anthracycline + taxane + other 3 1 2</td>
<td>1 2 1</td>
</tr>
<tr>
<td>Surgery type</td>
<td>Mastectomy 123 56</td>
<td>Lumpectomy 92 41</td>
</tr>
<tr>
<td></td>
<td>No surgery 6 3</td>
<td></td>
</tr>
<tr>
<td>Postoperative adjuvant therapy</td>
<td>Any hormonal therapy 128 58</td>
<td>Tamoxifen 75 34</td>
</tr>
<tr>
<td></td>
<td>Ovarian suppression 29 9</td>
<td>Aromatase inhibitor 95 43</td>
</tr>
<tr>
<td></td>
<td>Ovarian ablation 7 3</td>
<td>Ovarian suppression 29 9</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab 35 16</td>
<td>Ovarian ablation 7 3</td>
</tr>
</tbody>
</table>

Table 2. Rates of pCR by Receptor Subset for Patients Who Did Not Receive Neoadjuvant Trastuzumab (n = 190)

<table>
<thead>
<tr>
<th>Receptor Subset</th>
<th>HR Positive</th>
<th>HR Negative</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. pCR/No.</td>
<td>%</td>
<td>No. pCR/No.</td>
</tr>
<tr>
<td>HER2 status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive*</td>
<td>8/24</td>
<td>33</td>
<td>10/22</td>
</tr>
<tr>
<td>Negative</td>
<td>8/93</td>
<td>9</td>
<td>18/51</td>
</tr>
<tr>
<td>Overall</td>
<td>16/117</td>
<td>14</td>
<td>28/73</td>
</tr>
</tbody>
</table>

NOTE. Rates of pCR are shown for the receptor subsets and include patients for whom pathologic evaluation and receptor status were available and exclude the 20 patients who received trastuzumab as neoadjuvant therapy. The Overall (%) column shows that being HR negative v HER2 positive results in a 24% higher probability of achieving a pCR (P < .01). The bottom row (Overall) shows that being HER2 positive v HER2 negative results in a 21% higher probability of achieving a pCR (P < .01). Overall data appear in bold. Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; pCR, pathologic complete response.

*For the 20 patients who received neoadjuvant trastuzumab, the pCR rate was 60%. These 20 patients are not included in the table.
estimated hazard ratios is smaller than the overall hazard ratio (eg, 0.00, 0.25, 0.14 are all less than 0.29). This is an instance of Simpson’s paradox.\(^{18}\) However, the parameters of which these are estimates are not precisely known and so they may not have the same relationships.

### DISCUSSION

The I-SPY 1 population had clinical and biologic high-risk features: median age 49 years, 41% HR negative, 90% intermediate or high grade, and 91% high risk by the 70-gene profile.\(^{18}\) For patients with biologically high-risk invasive breast cancers, 3-year RFS is better for those who experience a pCR after neoadjuvant chemotherapy than for those who do not.

The observation of Simpson’s paradox based on the estimated hazard ratios in Figure 3 is associated with well-known characteristics of breast cancer. Of the three tumor subtypes in Figure 3, the tumors that are least sensitive to either adjuvant or neoadjuvant chemotherapy are those that are HR positive/HER2 negative.\(^{5,19,20}\) However, these tumors have the best prognosis in the absence of chemotherapy. Despite the fact that these tumors have the lowest rate of pCR (9% v 36% and 41%), patients with these tumors tend to have a better RFS than patients with triple-negative or HER2-positive tumors, both overall and within pCR and no pCR categories. So although our relatively small study is not sufficient by itself to conclude that the population parameters have the same relationship as their estimates, this observation is consistent with what we understand about the biology of breast cancer and is to be expected. Other researchers should categorize tumors by molecular and receptor characteristics in relating pCR and longer-term end points such as RFS and overall survival.

These results provide additional insights into previous neoadjuvant trials that have examined the relationship between pCR and RFS.\(^ {21}\) For example, although most neoadjuvant chemotherapy trials have shown that pCR is associated with favorable outcome, this was not seen in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 neoadjuvant trial. In that trial, although pCR improved significantly when paclitaxel was added to a doxorubicin-based chemotherapy regimen, the improvement was not of the same magnitude as that for RFS or overall survival.\(^7\) The possibility of a Simpson’s paradox relationship suggests that analyzing only overall pCR and survival rates may have underestimated the true predictive effect of pCR in NSABP B-27.

The rate of pCR in the HR-positive/HER2-positive subset was lower than in the HR-negative/HER2-positive subset in the I-SPY TRIAL (in the absence of neoadjuvant trastuzumab). The sample sizes in our study were small, but this effect has also been observed consistently in three large randomized phase III neoadjuvant trials: NeoALTTO (Neoadjuvant Lapatinib or Trastuzumab Optimization Study),\(^ {22}\) GeparQuinto,\(^ {23}\) and NEOSPHERE (Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation)\(^ {24}\); the effect was less than that mentioned in a personal communication with G. von Minckwitz on August 19, 2011, and more than that mentioned in the CHER-LOB (Preoperative Chemotherapy Plus Trastuzumab, Lapatinib or Both in HER2-Positive Operable Breast Cancer) phase II trial.\(^ {25}\) In the nonrandomized MD Anderson Cancer Center neoadjuvant series,\(^ {26}\) pCR rates were also lower in the HR-positive/HER2-positive subset than in the HR-negative/HER2-positive subset, and the subsequent RFS rates were also lower in this group. Our trial results are limited by the small number of patients who received neoadjuvant trastuzumab. Ongoing and future trials will help us better understand whether different treatment approaches will be needed to improve outcome for HER2-positive disease on the basis of HR status.

High rates of proliferation, as measured by Ki67, increased the likelihood of pCR. However, Ki67 is highly correlated with receptor subsets and appears to improve the ability to predict response within all subsets except HER2 positive.

Clinical trials for breast cancer have historically contained a mix of receptor subsets. Given our findings and those of others that tumor biology is different for these subsets, comparisons should be anchored within molecular subsets rather than across whole trial populations. Sufficiently powered analyses of subsets on the basis of receptor status or molecular profiles (which are highly correlated with receptor status) should be a planned feature of future trials if we hope to extract the maximal value from them.\(^{10}\) Molecular profiles at baseline may provide the opportunity to identify, beyond HR positivity alone, patients likely to have a good survival outcome as shown by I-SPY 1 molecular analyses.\(^ {10}\)

Getting a drug approved for marketing is estimated to take more than 10 years and $1 billion.\(^ {27,28}\) To shorten the period of time for drug development (what has been referred to as knowledge turns\(^ {29}\)), a new approach is needed. The neoadjuvant approach gives us the opportunity to use response to therapy as an early evaluation end point. Fortunately, whether chemotherapy is...
given before surgery or after does not influence RFS and overall survival, but giving chemotherapy before surgery offers an opportunity both to evaluate response to therapy and to alter subsequent treatment if the tumor is downstaged. More importantly, it informs us about the success of standard and experimental therapies. For example, in the MD Anderson Cancer Center neoadjuvant trial, in which HER2-positive patients were randomly assigned to receive paclitaxel followed by fluorouracil, epirubicin, and cyclophosphamide plus or minus trastuzumab, the significant increase in pCR in the trastuzumab arm (65.2% vs 26% for patients who did not receive trastuzumab) in just 34 patients foreshadowed the results of the adjuvant trastuzumab trials, which accrued more than 9,000 patients and were completed 1 year later. Several trials are now evaluating novel agents in the neoadjuvant setting, including poly (ADP-ribose) polymerase inhibitors, CALGB 40601, NEOSPHERE, and GeparQuinto. Our results support this approach and further emphasize that evaluation should be performed by receptor or molecular subset.

Despite optimal therapy, many patients still remain at substantial risk for disease progression. To make more rapid progress in finding agents that may reduce risk for these women, we have incorporated the observations from I-SPY 1 TRIAL into the design of the I-SPY 2 TRIAL. That trial uses pCR as an end point and focuses on women with biologically higher risk disease—in the context of either standard marker subsets or molecular subsets of breast cancer—and uses an adaptive design to screen phase II agents in combination with the taxane portion of chemotherapy.

The goal is to test these novel agents for their ability to improve pCR rates for 10 subsets of breast cancer defined by both standard and molecular markers.
focusing on high-risk patients and analyzing data by subsets, the neoadjuvant setting can provide a unique opportunity to accelerate learning.

In an effort to develop a noninvasive measure of pCR, I-SPY 1 also included multiple imaging parameters\(^2\) and demonstrated that change in MR volume is the imaging marker that best predicts pCR, has the potential to serve as a noninvasive measure of response to therapy, and may further accelerate evaluation of novel agents in combination with standard treatments. In I-SPY 2, MR volume is being used to provide information about response to chemotherapy between regimens, information that cannot otherwise be obtained without surgical resection.

The conclusions of our study are limited by the short follow-up time. It is well known that the HR-positive patients remain at risk for recurrence for many years, and early recurrence data may not reflect the overall outcome. However, the Oxford Overview Analysis\(^36\) of early breast cancer trials strongly suggests that the benefit of chemotherapy is reflected by the distant disease-free survival at 5 years; that is, the survival curves diverge during the first 5 years, but after year 5, they are parallel, suggesting that the survival benefit from chemotherapy is likely to be manifest in the first 5 years. With the median follow-up for the I-SPY 1 TRIAL currently at 3.9 years, current rates of RFS are likely to reflect primarily the benefit from chemotherapy.

The outcomes for patients in I-SPY 1 is also affected by hormonal therapy given adjuvantly, although molecular predictors of sensitivity to endocrine therapy have been described and will likely further refine our ability to focus on patients most at risk for disease progression at the time of diagnosis.\(^37,38\)

### Table 4. pCR Paradox

<table>
<thead>
<tr>
<th>Population</th>
<th>Relative Hazard Ratio (95% CI)</th>
<th>Absolute Difference in RFS at 3 Years (%)</th>
<th>Absolute Difference in RFS at 5 Years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n = 172)</td>
<td>0.29 (0.07 to 0.82)</td>
<td>16 (P = 0.04)</td>
<td>23 (P = 0.07)</td>
</tr>
<tr>
<td>HR positive/HER2 negative (n = 93)</td>
<td>0.00 (0.00 to 0.94)</td>
<td>14 (P = 0.05)</td>
<td>22 (P = 0.06)</td>
</tr>
<tr>
<td>HR negative/HER2 negative (n = 50)</td>
<td>0.25 (0.04 to 0.97)</td>
<td>34 (P = 0.03)</td>
<td>39 (P = 0.02)</td>
</tr>
<tr>
<td>HER2 positive (n = 29)</td>
<td>0.14 (0.01 to 1.0)</td>
<td>26 (P = 0.07)</td>
<td>42 (P = 0.007)</td>
</tr>
</tbody>
</table>

**NOTE.** The hazard ratios for pCR are shown for the 172 patients who had both pathologic information and receptor status available. Patients who received neoadjuvant (n = 20) or adjuvant (n = 18) trastuzumab were excluded (n = 38). Abbreviation: HR, hormone receptor; pCR, pathologic complete response; RFS, recurrence-free survival.

*Based on whether pCR was achieved or not.

In conclusion, the I-SPY 1 TRIAL shows that the ability of pCR to predict outcome is substantially improved when analyzed within tumor subsets. This predictive power is sufficiently strong that pCR can be used as an early indicator of RFS. Indeed, pCR is the primary end point of the next generation study, the I-SPY 2 TRIAL, which is designed to identify agents early in the drug development cycle that improve the rates of pCR and for which molecular subsets this is so.

### AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author’s immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

**Employment or Leadership Position:** Laura van ‘t Veer, Agenda (C) Consultant or Advisory Role: Donald A. Berry, Berry Consultants (C); Constance Lehman, Philips Healthcare (C), General Electric (C), Bayer Pharmaceuticals (C) Stock Ownership: Laura van ‘t Veer, Agenda

**Honoraria:** Baljit Singh, Genentech Research Funding: Constance Lehman, General Electric; Nola Hylton, National Cancer Institute American College of Radiology Imaging Network (ACRIN) Expert Testimony: None Other Remuneration: None

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**Manuscript writing:** All authors

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### REFERENCES


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**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Although all authors completed the disclosure declaration, the following author(s) and/or an author’s immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

**Employment or Leadership Position:** Laura van ‘t Veer, Agenda (C) Consultant or Advisory Role: Donald A. Berry, Berry Consultants (C); Constance Lehman, Philips Healthcare (C), General Electric (C), Bayer Pharmaceuticals (C) Stock Ownership: Laura van ‘t Veer, Agenda

**Honoraria:** Baljit Singh, Genentech Research Funding: Constance Lehman, General Electric; Nola Hylton, National Cancer Institute American College of Radiology Imaging Network (ACRIN) Expert Testimony: None Other Remuneration: None

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**FINANCIAL SUPPORT:** Debasis Tripathy

**ADMINISTRATIVE SUPPORT:** Sarah E. Davis, Meredith Buxton, Clif Hudis

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**MANUSCRIPT WRITING:** All authors

**FINAL APPROVAL OF MANUSCRIPT:** All authors
Results From the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657)

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16. Reference deleted


24. Gianni L, Pienkowski T, Im Y-H, et al: Neoad- juvant pertuzumab (P) and trastuzumab (H): Antitu- mor and safety analysis of a randomized phase II study (‘NeoSphere’). Cancer Res 70, 2010 (suppl 2; abst S3-3)


