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# Association of Residual Ductal Carcinoma In Situ With Breast Cancer Recurrence in the Neoadjuvant I-SPY2 Trial

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**IMPORTANCE** Pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) in breast cancer strongly correlates with overall survival and has become the standard end point in neoadjuvant trials. However, there is controversy regarding whether the definition of pCR should exclude or permit the presence of residual ductal carcinoma in situ (DCIS).

**OBJECTIVE** To examine the association of residual DCIS in surgical specimens after neoadjuvant chemotherapy for breast cancer with survival end points to inform standards for the assessment of pathologic complete response.

**DESIGN, SETTING, AND PARTICIPANTS** The study team analyzed the association of residual DCIS after NAC with 3-year event-free survival (EFS), distant recurrence-free survival (DRFS), and local-regional recurrence (LRR) in the I-SPY2 trial, an adaptive neoadjuvant platform trial for patients with breast cancer at high risk of recurrence. This is a retrospective analysis of clinical specimens and data from the ongoing I-SPY2 adaptive platform trial of novel therapeutics on a background of standard of care for early breast cancer. I-SPY2 participants are adult women diagnosed with stage II/III breast cancer at high risk of recurrence.

**INTERVENTIONS** Participants were randomized to receive taxane and anthracycline-based neoadjuvant therapy with or without 1 of 10 investigational agents, followed by definitive surgery.

**MAIN OUTCOMES AND MEASURES** The presence of DCIS and EFS, DRFS, and LRR.

**RESULTS** The study team identified 933 I-SPY2 participants (aged 24 to 77 years) with complete pathology and follow-up data. Median follow-up time was 3.9 years; 337 participants (36%) had no residual invasive disease (residual cancer burden 0, or pCR). Of the 337 participants with pCR, 70 (21%) had residual DCIS, which varied significantly by tumor-receptor subtype; residual DCIS was present in 8.5% of triple negative tumors, 15.6% of hormone-receptor positive tumors, and 36.6% of ERBB2-positive tumors. Among those participants with pCR, there was no significant difference in EFS, DRFS, or LRR based on presence or absence of residual DCIS.

**CONCLUSIONS AND RELEVANCE** The analysis supports the definition of pCR as the absence of invasive disease after NAC regardless of the presence or absence of DCIS.

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Many studies have demonstrated that pathological complete response (pCR) following neoadjuvant chemotherapy (NAC) for breast cancer strongly correlates with overall survival.[1-7] As such, the US Food and Drug Administration now accepts pCR as an end point for accelerated drug approval in neoadjuvant breast cancer trials.[8] While the recommended definition of pCR requires only the absence of invasive disease,[9] there remains some controversy regarding whether the presence of residual ductal carcinoma in situ (DCIS) is associated with outcomes after pCR. Some studies[10-15] suggest that residual DCIS after NAC could be associated with recurrence rates and therefore define pCR as the absence of both invasive and in situ disease (eg, Brenner et al,[10] Von Minckwitz et al[13]), resulting in lower pCR rates, although data are limited and contradictory. Importantly, the significance of residual DCIS can be confounded by the method of pathology assessment and whether standardized tools for evaluation are used.[16]

Here we examine the association of residual DCIS after NAC with event-free survival (EFS), distant recurrence-free survival (DRFS), and local-regional recurrence (LRR) in the I-SPY2 trial. I-SPY2 is an adaptive, neoadjuvant platform trial evaluating novel investigational regimens added to standard chemotherapy in women with stage II/III breast cancer at high risk of recurrence. I-SPY2 uses the residual cancer burden (RCB) method for pathology assessment,[16] standardized across all sites, with pathologists trained and certified in the methods.

### Key Points

**Question** To examine residual ductal carcinoma in situ (DCIS) in surgical specimens after neoadjuvant chemotherapy for breast cancer to evaluate whether the definition of pathologic complete response should exclude or permit the presence of DCIS.

**Findings** There was no association between residual DCIS and recurrence end points after neoadjuvant chemotherapy.

**Meaning** This analysis supports a definition of pathologic complete response as the absence of invasive disease after neoadjuvant therapy regardless of the presence or absence of DCIS.

## Methods

### Patients

Detailed information on the I-SPY2 design has been published previously.[17,18] It is an ongoing adaptive neoadjuvant platform trial conducted across 20 clinical sites in the US. Eligible patients are at least 18 years of age with stage II or III breast cancer and no previous history of breast cancer treatment. At baseline, histological grade is assessed according to the Elston-Ellis modification of the Scarff-Bloom-Richardson grading system,[19] with hormone-receptor and ERBB2 status determined locally according to international recommendations,[20,21] and 70-gene signature assessed by Mammaprint.[22] Patients are grouped into the following categories based on tumor receptor subtypes; ERBB2-positive (defined as ERBB2 overexpressing with any hormone receptor status), hormone receptor –positive (defined as estrogen receptor– or progesterone receptor-positive and ERBB2 negative), and triple negative (defined as hormone receptor-negative and ERBB2 negative). Participants in I-SPY2 are treated with neoadjuvant paclitaxel with or without an experimental agent/combination, followed by anthracycline-based chemotherapy and definitive surgery. The institutional review boards of all participating sites approved the I-SPY2 protocol (NCT01042379) and all patients provided written informed consent at screening and again prior to treatment; only patients who agreed in writing to research use of their data and specimens are reported in this article. An independent data and safety monitoring board meets regularly to review progress. Race and ethnicity were self-reported by study participants into investigator-defined categories, with data included in the article for completeness. Patient-level data supporting the results of this study are available on request from the corresponding author. This article follows EQUATOR reporting guidelines.

From September 2010 to November 2016, 1038 patients enrolled in the I-SPY2 trial received treatment on 1 of 10 arms, including control. The present analysis included all participants for whom surgical pathology (including complete RCB) and follow-up data were available and who had documented assessment of presence or absence of DCIS in surgical specimens.

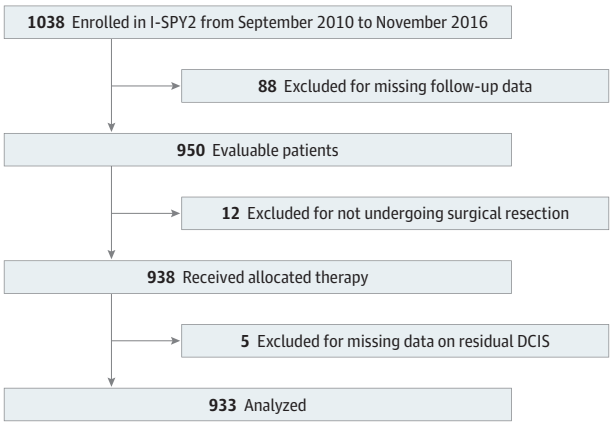
### Pathology Assessments

Pathology assessment of specimens collected at the time of definitive surgical resection used the RCB method,[16] assessed by pathologists at each participating site who were trained in the method and required to demonstrate agreement with centrally read reference specimens prior to evaluating study specimens. RCB includes both a standard for gross specimen processing and evaluation of the primary tumor bed and excised lymph nodes. RCB is a composite of several individual pathology measures: bidimensional measure of the primary tumor bed, overall invasive cancer cellularity, the percentage of DCIS in the primary tumor bed, the number of positive lymph nodes, and the diameter of largest lymph node metastasis. We used the percentage of DCIS in the primary tumor bed from the RCB assessment to define presence or absence of residual DCIS, with a percentage of 0 meaning no residual DCIS was present, and a percentage more than 0 meaning that residual DCIS was present. An RCB of 0 is equivalent to pCR as defined by the absence of invasive disease in the breast and nodes.

### Survival Assessments

Event-free survival and distant relapse-free survival are secondary end points in I-SPY2, evaluated according to the standard definitions for efficacy end points criteria.[23] For EFS, any locoregional or distant recurrence or death from any cause was considered as an event. LRR was also assessed, defined as the presence of invasive disease in the ipsilateral breast and/or axilla or presence of invasive disease in regional lymph nodes, chest wall, or skin of the ipsilateral breast. DRFS was defined as any recurrence except LRR or contralateral breast cancer.

Figure 1. CONSORT Diagram




DCIS indicates ductal carcinoma in situ.

All survival rates were calculated from the date of treatment consent. Patients without an event were censored at the date of last follow-up.

### Statistical Methods

We first analyzed the cohort as 2 groups (with or without pCR), stratified by presence or absence of residual DCIS. In each group, EFS, DRFS, and LRR at 3 years were evaluated using the Kaplan-Meier method. Cox proportional hazards model was used to determine hazard ratios (HRs) for each end point in each group, using the presence or absence of residual DCIS as the predictor.

The entire cohort (both those with and without pCR) was also evaluated using a multivariate Cox proportional hazards model using pCR and residual DCIS as predictors, for each of the 3 end points (EFS, DRFS, and LRR). We compared the rate of residual DCIS across tumor receptor subtypes in those with pCR using the $\chi^2$ test. *P* values were 2-tailed. Statistical analysis was performed using R software.

## Results

### Patient Characteristics

Of the 1038 patients enrolled in the I-SPY2 trial, a total of 950 patients had complete follow-up data, including 938 women who underwent surgical resection. Five patients were missing DCIS data, leaving 933 cases with complete pathology data available (**Figure 1**). Follow-up times range from 0.4 to 7.6 years, with median follow-up time of 3.9 years. Baseline characteristics at diagnosis and after NAC are reported in **Table 1**. In the study population, 56.4% of patients (n = 526) were hormone receptor positive and Mammaprint high risk, 27.8% (n = 259) were ERBB2 positive, and 34.3% (n = 320) had triple negative (TN) breast cancer.

Overall, 337 patients achieved pCR after NAC, of whom 70 (20.8%) had residual DCIS. Among the 596 patients with residual invasive disease (non-pCR), 296 (49.6%) also had residual DCIS in addition to the invasive disease.

### Patients With pCR

Among the patients who achieved pCR, those with DCIS trended toward worse EFS and DRFS, although statistical significance was not achieved. Three-year EFS for patients with no residual DCIS was 95.6% vs 89.2% for those with residual DCIS (**Figure 2**A), resulting in an HR of 2.08 (95% CI, 0.83-5.20; *P* = .12). Similarly, DRFS at 3 years was 96.0% vs 90.6% for patients achieving pCR without residual DCIS vs with residual DCIS (Figure 2C), with an associated HR of 1.91 (95% CI, 0.72-5.08; *P* = .20). The LRR rate at 3 years in those with or without residual DCIS was 97.7% vs 97.0% (Figure 2E) with HR of 1.27 (95% CI, 0.26-6.28; *P* = .77).

### Patients Without pCR

Among the 596 patients who did not have a pCR, the presence or absence of residual DCIS had no association with EFS, DRFS, or LRR (Figure 2B, D, and F, **Table 2**). At 3 years, EFS was 78.7% for patients without residual DCIS vs 77.8% for patients with residual DCIS (HR, 1.03; 95% CI, 0.76-1.41; *P* = .83). DRFS at 3 years was similar regardless of the presence of residual DCIS: 80.1% for patients without residual DCIS vs 82.6% for patients with residual DCIS (HR, 0.92; 95% CI, 0.65-1.29; *P* = .63). Additionally, LRR at 3 years was 90.1% in those without residual DCIS and of 89.1% in those with residual DCIS (HR, 1.11; 95% CI, 0.7-1.78; *P* = .65).

### Multivariate Analyses

In multivariate models for each end point that included all 933 patients using both presence/absence of pCR and presence/absence of residual DCIS as predictors, only pCR was significantly associated with EFS, DRFS, and LRR. Having a pCR was associated with significantly improved EFS (HR, 0.21; 95% CI, 0.13-0.33; *P* < .001), DRFS (HR, 0.22; 95% CI, 0.13-0.36; *P* < .001), and LRR (HR, 0.2; 95% CI, 0.09-0.42; *P* < .001). The presence or absence of residual DCIS was not associated with EFS, DRFS, or LRR in these models.

### Residual DCIS and Tumor Receptor Subtype

Considering the 337 patients with pCR, tumor receptor subtype was TN in 41.8% (n = 141), ERBB2 positive in 39.2% (n = 132), and hormone receptor positive in 19.0% (n = 64). Overall, this corresponds to a pCR rate of 44.2% in TN tumors, 50.9% in ERBB2-positive tumors, and 18.0% in hormone receptor-positive tumors. The presence of residual DCIS in these cases with pCR varied significantly by tumor receptor subtype, being most common in those with ERBB2-positive disease and least common in those with TN tumors. Residual DCIS was present in 36.6% of ERBB2-positive tumors (n = 48), 15.6% of hormone receptor-positive tumors (n = 10), and 8.5% of TN tumors (n = 12).

## Discussion

Neoadjuvant therapy is increasingly being used in the setting of early-stage breast cancer. It has several advantages, including the ability to downstage tumors prior to surgery and allowing short-term assessment of treatment response. Patho-

Table 1. Patient Characteristics

| Characteristic | No. (%) | | | | |
|---|---|---|---|---|---|
| | Overall (n = 933) | RCB-0 + no DCIS (n = 267) | RCB-0 + DCIS (n = 70) | RCB>0 + no DCIS (n = 300) | RCB>0 + DCIS (n = 296) |
| Age, median (range), y | NA | 49 (25-73) | 46.5 (27-70) | 50 (23 – 77) | 47 (24-71) |
| Race[a] | | | | | |
| American Indian or Alaska Native | 4 (0.43) | 1 (0.37) | 0 | 2 (0.67) | 1 (0.34) |
| Asian | 67 (7.18) | 16 (5.99) | 7 (10) | 16 (5.33) | 28 (9.46) |
| Black or African American | 105 (11.25) | 28 (10.49) | 7 (10) | 38 (12.67) | 32 (10.81) |
| Mixed race | 7 (0.75) | 2 (0.75) | 1 (1.43) | 2 (0.67) | 2 (0.68) |
| Native Hawaiian or Pacific Islander | 5 (0.54) | 1 (0.37) | 1 (1.43) | 0 | 3 (1.01) |
| White | 745 (79.85) | 219 (82.02) | 54 (77.14) | 242 (80.67) | 230 (77.70) |
| Ethnicity[a] | | | | | |
| Hispanic or Latino | 100 (10.72) | 40 (14.98) | 7 (10) | 33 (11) | 20 (6.76) |
| Not Hispanic or Latino | 833 (89.28) | 227 (85.02) | 63 (90) | 267 (89) | 276 (93.24) |
| Tumor characteristics | | | | | |
| MRI longest diameter, median (range) | NA | 3.3 (1.2-14.7) | 3.25 (0.44-11) | 3.85 (0.8-22) | 4.15 (1.4-14) |
| Hormone receptor status | | | | | |
| HR+ | 526 (56.38) | 93 (34.83) | 42 (60) | 171 (57) | 220 (74.32) |
| HR- | 407 (43.62) | 174 (65.17) | 28 (40) | 129 (43) | 76 (25.68) |
| ERBB2 status | | | | | |
| ERBB2+ | 259 (27.56) | 84 (31.46) | 48 (68.57) | 47 (15.67) | 80 (27.03) |
| ERBB2- | 674 (72.24) | 183 (68.54) | 22 (31.42) | 253 (84.33) | 216 (72.97) |
| Receptor subtypes | | | | | |
| HR+ERBB2- | 355 (38.05) | 54 (20.22) | 10 (14.29) | 139 (46.33) | 152 (51.35) |
| HR+ERBB2+ | 171 (18.33) | 39 (14.61) | 32 (45.71) | 32 (10.67) | 68 (22.97) |
| HR-ERBB2+ | 88 (9.43) | 45 (16.85) | 16 (22.86) | 15 (5) | 12 (4.05) |
| HR-ERBB2- | 319 (34.19) | 129 (48.31) | 12 (17.14) | 114 (38) | 64 (21.62) |
| Clinical T category | | | | | |
| T0 | 3 (0.32) | 1 (0.37) | 1 (1.43) | 0 | 1 (0.34) |
| T1 | 28 (3) | 9 (3.37) | 2 (2.85) | 6 (2) | 11 (3.72) |
| T2 | 519 (55.63) | 156 (58.43) | 47 (67.14) | 166 (55.33) | 150 (50.68) |
| T3 | 193 (20.69) | 42 (15.73) | 6 (8.57) | 72 (24) | 73 (24.66) |
| T4 | 34 (3.64) | 7 (2.62) | 0 | 11 (3.67) | 16 (5.41) |
| Missing | 156 (16.72) | 52 (19.48) | 14 (20) | 45 (15) | 45 (15.2) |
| Clinical N category | | | | | |
| N0 | 393 (42.12) | 119 (44.57) | 35 (50) | 126 (42) | 113 (38.18) |
| N1 | 289 (30.98) | 68 (25.47) | 14 (20) | 102 (34) | 105 (35.47) |
| N2 | 49 (5.25) | 14 (5.24) | 2 (2.86) | 12 (4) | 21 (7.09) |
| N3 | 21 (2.25) | 4 (1.5) | 4 (5.71) | 7 (2.33) | 6 (2.03) |
| Missing | 181 (19.4) | 62 (23.22) | 15 (21.43) | 53 (17.67) | 51 (17.23) |
| SBR grade | | | | | |
| I | 8 (0.86) | 1 (0.37) | 0 | 2 (0.67) | 5 (1.69) |
| II | 186 (19.93) | 32 (11.98) | 18 (25.71) | 63 (21) | 73 (24.66) |
| III | 445 (47.7) | 152 (56.93) | 36 (51.43) | 136 (45.33) | 121 (40.88) |
| Missing | 294 (31.51) | 82 (30.71) | 16 (22.86) | 99 (33) | 97 (32.77) |

Abbreviations: DCIS, ductal carcinoma in situ; HR, hormone receptor; MRI, magnetic resonance imaging; NA, not applicable; RCB, residual cancer burden; SBR, Scarff-Bloom-Richardson.

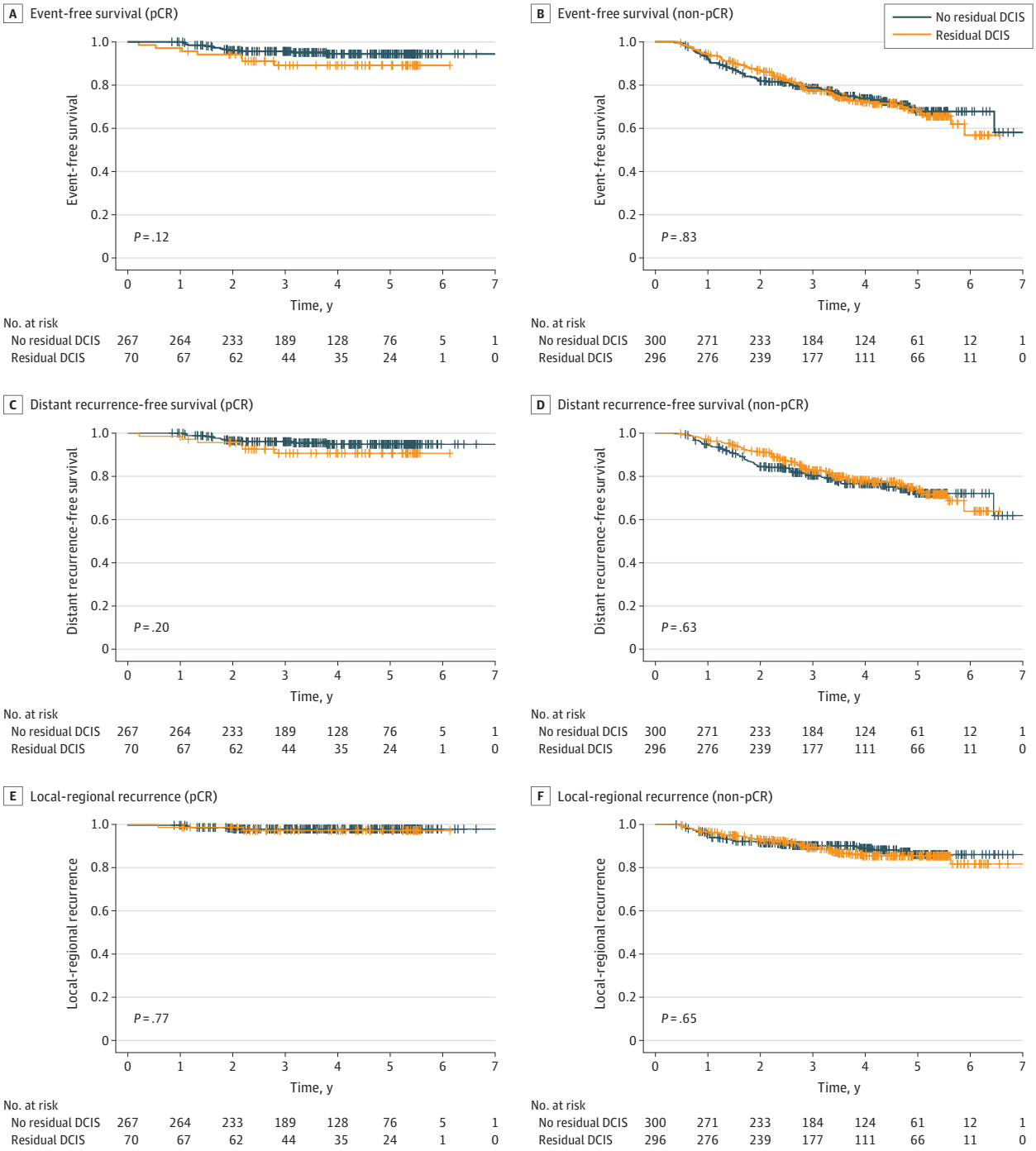
[a] Race and ethnicity were self-reported by study participants into investigator-defined categories.

logic complete response is strongly prognostic for survival and has become the end point of choice for neoadjuvant trials.[24]

Increasingly, pCR is also becoming the clinical goal of NAC treatment. It is therefore important to have a clear, consistent definition of pCR and its association with long-term outcomes. While there is consensus that it should include the absence of disease in both the primary site and lymph nodes, the question of whether the definition of pCR should also require the absence of residual DCIS, and how its presence may affect outcomes, is subject to debate.

Here, as demonstrated in multiple studies, pCR after NAC was associated with significantly improved EFS compared with

Figure 2. Kaplan-Meier Curves Showing Survival Outcomes at Median 3-Year Follow-up Time by Pathologic Complete Response (pCR) Status With or Without Residual Ductal Carcinoma In Situ (DCIS)




There were no significant differences within pathologic complete response or nonpathologic complete response groups by presence of residual DCIS.

the absence of pCR. However, no statistically significant association was observed between the presence of DCIS and 3-year survival outcomes, regardless of whether pCR was achieved.

We did find, however, that among patients with no residual invasive disease, having residual DCIS was associated with increased hazard for recurrence, with HRs of 2.1 and 2.0 for EFS and DRFS, respectively, although this did not reach statistical significance. In contrast, the German Breast Group (GBG) reported a pooled analysis of over 6000 patients from 7 trials showing a significant association between residual DCIS (in those without invasive disease) and worsening DRFS (HR,

Table 2. Prognostic Association of Residual DCIS With EFS, DRFS and LRR

| | All patients, No. (%) | No. of patients with event | EFS at 3 y | | | No. of patients with event | DRFS at 3 y | | | No. of patients with event | LRR at 3 y | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | EFS rate, % | Hazard ratio (95% CI) | *P* value | | DRFS rate, % | Hazard ratio (95% CI) | *P* value | | LRR rate, % | Hazard ratio (95% CI) | *P* value |
| pCR, - no DCIS | 267 (28.6) | 13 | 4.4 | 1 [Reference] | NA | 12 | 4 | 1 [Reference] | NA | 6 | 2.3 | 1 [Reference] | NA |
| pCR, + DCIS | 70 (7.5) | 7 | 10.8 | 2.08 (0.83-5.22) | .12 | 6 | 9.4 | 1.91 (0.72-5.08) | .20 | 2 | 3 | 1.27 (0.26-6.28) | .77 |
| No pCR, - no DCIS | 300 (32.1) | 79 | 21.3 | 1 [Reference] | NA | 69 | 19.9 | 1 [Reference] | NA | 33 | 9.9 | 1 [Reference] | NA |
| No pCR, + DCIS | 296 (31.7) | 81 | 22.2 | 1.03 (0.76-1.41) | .83 | 65 | 17.4 | 0.92 (0.65-1.29) | .63 | 37 | 10.9 | 1.11 (0.70-1.78) | .65 |

Abbreviations: DCIS, ductal carcinoma in situ; DRFS, distant recurrence-free survival; EFS, event-free survival; LRR, local-regional recurrence; NA, not applicable; pCR, pathologic complete response; RCB, residual cancer burden.

1.74; $P < .001$).[13] An important consideration when comparing our findings with those of the GBG include treatment factors that could influence overall response rates; for example, the overall rate of pCR reported was lower in the GBG pooled analysis compared with our current study (19.8% vs 36.1%, respectively). The impact of novel therapeutic strategies in the I-SPY2 study could influence the rate of pCR, the presence of residual DCIS, and outcomes, thus affecting the associations between these factors. However, a number of other studies have reported similar findings to ours, also showing no association between residual DCIS and outcomes following NAC. In an analysis from Mazouni et al,[12] 5-year overall survival rates were identical for those with pCR in the presence or absence of residual DCIS; similarly at 10 years, overall survival was 92% vs 92.5%, respectively. Cortazar and colleagues' analysis[6] of 11 955 patients yielded similar results, with no difference in overall survival or EFS regardless of the presence of residual DCIS in the breast, in both the overall population and in the analysis by receptor subtypes. Recently, an evaluation of patients with ERBB2-positive breast cancer also found that residual DCIS after NAC was not associated with shorter DRFS.[15]

While our findings are consistent with the studies showing no impact of residual DCIS on the prognostic significance of having a pCR, important considerations include differences in sample sizes between studies (with our current study being much smaller than the GBG report), differences in the sensitivity of pathology evaluation from study to study, as well as the potential for a subtype-specific impact of residual DCIS that requires even larger sample sizes to identify. Less rigorous methods for pathology evaluation can result in falsely elevated rates of pCR (because of lower sensitivity for minimal residual invasive disease), which would lead to worse outcomes than expected for patients classified as having pCR. These worse outcomes could be driven by undetected invasive disease, rather than the associated residual DCIS. In the GBG analysis, the RCB method was not used, potentially reducing the sensitivity for identifying minimal residual invasive disease. If minimal residual invasive disease is reported as pCR with residual DCIS, we would expect to find an association between residual DCIS and worse outcomes. These issues represent some of the challenges in comparing trials with differing methods of pathology ascertainment, and the importance of rigorous specimen evaluation.

Of note, our findings reflect a lack of association between residual DCIS and early recurrence, with 3-year end points reported in this analysis. Given prior work showing that molecularly high-risk tumors, such as those in the I-SPY2 trial, are at risk for such early recurrences, evaluation at this time point remains of interest.[25] However, our findings do not eliminate the possibility that residual DCIS could be associated with late recurrences in this high-risk patient population. Should subsequent analyses bear this out, this would provide insight into factors associated with early vs late events.[26]

### Strengths and Limitations

A strength of the I-SPY2 trial is the emphasis on thorough, consistent RCB assessment, which allows us to specifically determine the percentage of residual DCIS. Some limitations of our analysis include the smaller sample size compared with reported pooled analyses, and the potential impact of including high-risk subtypes only (although most patients undergoing NAC and having pCR will likely be high risk).

## Conclusions

In summary, our findings are consistent with other studies that support the definition of pCR as the absence of invasive disease after NAC, regardless of the presence of DCIS. The finding that the prevalence of residual DCIS varied significantly by receptor subtype is intriguing and raises the possibility that a residual in situ component could have different prognostic significance in subtype specific analyses. Such an evaluation would require an even larger data set but should be explored.

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## REFERENCES

1. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol*. 1998;16(8):2672-2685. doi:10.1200/JCO.1998.16.8.2672

2. Kuerer HM, Newman LA, Smith TL, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol*. 1999;17(2):460-469. doi:10.1200/JCO.1999.17.2.460

3. Rouzier R, Extra JM, Klijanienko J, et al. Incidence and prognostic significance of complete axillary downstaging after primary chemotherapy in breast cancer patients with T1 to T3 tumors and cytologically proven axillary metastatic lymph nodes. *J Clin Oncol*. 2002;20(5):1304-1310. doi:10.1200/JCO.2002.20.5.1304

4. Carey LA, Metzger R, Dees EC, et al. American Joint Committee on Cancer tumor-node-metastasis stage after neoadjuvant chemotherapy and breast cancer outcome. *J Natl Cancer Inst*. 2005;97(15):1137-1142. doi:10.1093/jnci/dji206

5. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol*. 2008;26(5):778-785. doi:10.1200/JCO.2007.15.0235

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(9938):164-172. doi:10.1016/S0140-6736(13)62422-8

7. Spring L, Greenup R, Niemierko A, et al. Pathologic complete response after neoadjuvant chemotherapy and long-term outcomes among young women with breast cancer. *J Natl Compr Canc Netw*. 2017;15(10):1216-1223. doi:10.6004/jnccn.2017.0158

8. US Food and Drug Administration. Guidance for industry: pathological complete response in neoadjuvant treatment of high-risk early-stage breast cancer: use as an endpoint to support accelerated approval. Accessed August 2, 2021. https://www.fda.gov/downloads/drugs/guidances/ucm305501.pdf has been redirected to https://www.fda.gov/media/83507/download

9. Provenzano E, Bossuyt V, Viale G, et al. Standardization of pathologic evaluation and reporting of postneoadjuvant specimens in clinical trials of breast cancer: recommendations from an international working group. *Mod Pathol*.

2015;28(9):1185-1201. doi:10.1038/modpathol.2015.74

**10**. Brenner B, Siris N, Rakowsky E, Fenig E, Sulkes A, Lurie H. Prediction of outcome in locally advanced breast cancer by post-chemotherapy nodal status and baseline serum tumour markers. *Br J Cancer*. 2002;87(12):1404-1410. doi:10.1038/sj.bjc.6600616

**11**. Jones RL, Lakhani SR, Ring AE, Ashley S, Walsh G, Smith IE. Pathological complete response and residual DCIS following neoadjuvant chemotherapy for breast carcinoma. *Br J Cancer*. 2006;94(3):358-362. doi:10.1038/sj.bjc.6602950

**12**. Mazouni C, Peintinger F, Wan-Kau S, et al. Residual ductal carcinoma in situ in patients with complete eradication of invasive breast cancer after neoadjuvant chemotherapy does not adversely affect patient outcome. *J Clin Oncol*. 2007;25(19):2650-2655. doi:10.1200/JCO.2006.08.2271

**13**. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol*. 2012;30(15):1796-1804. doi:10.1200/JCO.2011.38.8595

**14**. Kuroi K, Toi M, Ohno S, et al. Comparison of different definitions of pathologic complete response in operable breast cancer: a pooled analysis of three prospective neoadjuvant studies of JBCRG. *Breast Cancer*. 2015;22(6):586-595. doi:10.1007/s12282-014-0524-4

**15**. Hamy AS, Belin L, Bonsang-Kitzis H, et al. Pathological complete response and prognosis after neoadjuvant chemotherapy for HER2-positive breast cancers before and after trastuzumab era: results from a real-life cohort. *Br J Cancer*. 2016;114(1):44-52. doi:10.1038/bjc.2015.426

**16**. 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(28):4414-4422. doi:10.1200/JCO.2007.10.6823

**17**. Park JW, Liu MC, Yee D, et al; I-SPY 2 Investigators. Adaptive randomization of neratinib in early breast cancer. *N Engl J Med*. 2016;375(1):11-22. doi:10.1056/NEJMoa1513750

**18**. Rugo HS, Olopade OI, DeMichele A, et al; I-SPY 2 Investigators. Adaptive randomization of veliparib-carboplatin treatment in breast cancer. *N Engl J Med*. 2016;375(1):23-34. doi:10.1056/NEJMoa1513749

**19**. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. the value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology*. 1991;19(5):403-410. doi:10.1111/j.1365-2559.1991.tb00229.x

**20**. Remmele W, Schicketanz KH. Immunohistochemical determination of estrogen and progesterone receptor content in human breast cancer. computer-assisted image analysis (QIC score) vs. subjective grading (IRS). *Pathol Res Pract*. 1993;189(8):862-866. doi:10.1016/S0344-0338(11)81095-2

**21**. Wolff AC, Hammond MEH, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol*. 2013;31(31):3997-4013. doi:10.1200/JCO.2013.50.9984

**22**. Cardoso F, van't Veer LJ, Bogaerts J, et al; MINDACT Investigators. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med*. 2016;375(8):717-729. doi:10.1056/NEJMoa1602253

**23**. Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *J Clin Oncol*. 2007;25(15):2127-2132. doi:10.1200/JCO.2006.10.3523

**24**. LeVasseur N, Sun J, Gondara L, et al. Impact of pathologic complete response on survival after neoadjuvant chemotherapy in early-stage breast cancer: a population-based analysis. *J Cancer Res Clin Oncol*. 2020;146(2):529-536. doi:10.1007/s00432-019-03083-y

**25**. Ribelles N, Perez-Villa L, Jerez JM, et al. Pattern of recurrence of early breast cancer is different according to intrinsic subtype and proliferation index. *Breast Cancer Res*. 2013;15(5):R98-R98. doi:10.1186/bcr3559

**26**. Pedersen RN, Mellemkjær L, Ejlertsen B, Nørgaard M, Cronin-Fenton DP. Mortality after late breast cancer recurrence in Denmark. *J Clin Oncol*. 2022;40(13):1450-1463. doi:10.1200/JCO.21.02062