San Antonio Breast Cancer Symposium® - December 10-14, 2019 Abstract Number: P2-20-02

# Site of recurrence after neoadjuvant therapy: Clues to biology and impact on endpoints

C. Yau[1], A. DeMichele[2], W. Symmans[3], L. Pusztai[4], D. Yee[5], A. S. Clark[2], C. Hatzis[6], J. B. Matthews[1], J. Carter[7], Y. Chen[1], K. Cole[4], L. Khazai[8], M. Klein[5], D. Kokh[9], G. Krings[1], S. Sahoo[10], K. S. Albain[11], A. Chien[1], K. K. Edmiston[12], A. D. Elias[13], E. D. Ellis[14], D. M. Euhus[15], H. S. Han[8], C. Isaacs[16], Q. J. Khan[17], J. E. Lang[18], J. Lu[18], J. L. Meisel[19], Z. Mitri[20], R. Nanda[21], D. W. Northfelt[22], T. Sanft[4], E. Stringer- Reasor[9], R. K. Viscusi[23], A. M. Wallace[24], R. Yung[25], J. C. Boughey[7], M. E. Melisko[1], J. Perlmutter[26], H. S. Rugo[1], R. Schwab[24], L. J. van' t Veer[1], D. A. Berry[27], N. M. Hylton[1], L. J. Esserman[1]

[1]University of California, San Francisco, CA, [2]University of Pennsylvania, PA, [3]University of Texas, M.D. Anderson Cancer Center, TX, [4]Yale Cancer Center, CT, [5]Masonic Cancer Center, University of Minnesota, MN, [6]Yale University, CT, [7]Mayo Clinic, Rochester, MN, [8]Moffitt Cancer Center, FL, [9]University of Alabama at Birmingham, AL, [10]University of Texas, Southwestern, TX, [11]Loyola University, IL, [12]Inova Health System, VA, [13]University of Colorado, Denver, CO, [14]Swedish Cancer Institute, WA, [15]John Hopkins Medicine, MD, [16]Georgetown University, DC, [17]University of Kansas, KS, [18]University of Southern California, CA, [19]Emory University, GA, [20]Oregon Health & Science University, OR, [21]The University of Chicago Medical Center, IL, [22]Mayo Clinic, Scottsdale, AZ, [23]University of Arizona, AZ, [24]University of California, San Diego, CA, [25]University of Washington, WA, [26]Gemini Group, MI, [27]Berry Consultants, LLC, TX.

## Background

Achieving a pathologic complete response (pCR) has been shown on the patient level to predict excellent long-term event-free survival outcomes. Residual cancer burden (RCB) quantifies the extent of residual disease for patients who did not achieve pCR. A propensity for the central nervous system (CNS), a known chemotherapy sanctuary site, as the site of first relapse was previously observed among the small number of relapses in patients achieving a pCR (Symmans et al 2017), raising the possibility that these CNS events may be independent of response in the breast. In this study, we evaluated the type and sites of recurrences by RCB classes in the I-SPY 2 TRIAL.

## I-SPY 2 TRIAL

**I-SPY 2:** A multicenter, phase 2 platform trial using response-adaptive randomization within biomarker subtypes to evaluate novel agents and combinations in the neoadjuvant setting for women with high-risk primary breast cancer.

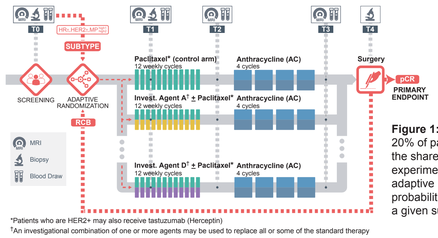
**Inclusion criteria:** Tumor Size ≥ 2.5cm; HR+HER2- MammaPrint (MP) high risk or HR-HER2- or HER2+.

**Primary Endpoint:** Pathologic complete response (pCR).

**Goal:** To identify (graduate) regimens that have ≥ 85% predictive probability of success in a 300-patient phase 3 neoadjuvant trial defined by HR and HER2 status, and MP.

**Regimens may leave the trial for one of four reasons:** Futility (< 10% probability of success) ; Maximum sample size accrual (with probability of success ≥ 10% and < 85%) ; Graduation (≥ 85% predictive probability of success) ; or as recommended by the independent DSMB.

**To date**: 11 experimental regimens have been evaluated for efficacy




*Patients who are HER2+ may also receive tastuzumab (Herceptin)
†An investigational combination of one or more agents may be used to replace all or some of the standard therapy

**Figure 1:** I-SPY2 study schema. 20% of patients are randomized to the shared control arm. Among experimental arms (up to four), adaptive randomization is based on probabilities of achieving pCR within a given subtype for each agent.

## Methods

I-SPY 2 patients enrolled prior to 11/2016 across 9 experimental and control arms, with available RCB and event-free survival (EFS) data were included in this analysis. The median follow-up is 3.8 years. We summarized the EFS event type, further sub-dividing the distant recurrence events by their site of relapse (CNS-only, CNS and other sites, Non-CNS). We estimated the overall and site-specific distant recurrence incidence in each RCB class at 3 years using a competing risk (Fine-Gray) model. In addition, we assessed the association between RCB and distant recurrence free survival including all distant recurrences (DRFS), as well as excluding the CNS-only recurrences (non-CNS DRFS) using a Cox model. Our statistics do not adjust for multiplicities beyond variables evaluated in this study.

## Results

**Among 938 subjects, there were 180 EFS events, including 28 (16%) local recurrences (without distant recurrence and/or death) and 152 DRFS events.**

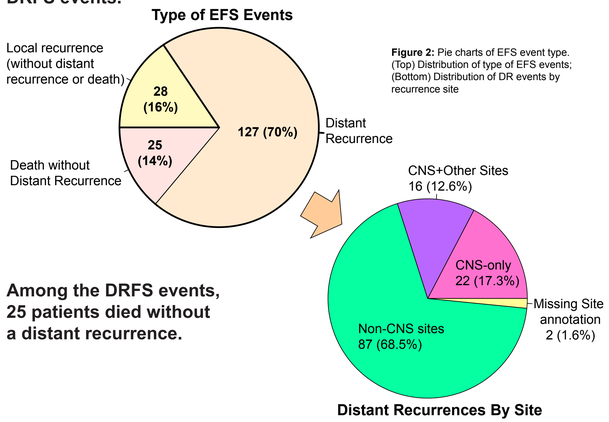



**Figure 2:** Pie charts of EFS event type. (Top) Distribution of type of EFS events; (Bottom) Distribution of DR events by recurrence site

**Among the DRFS events, 25 patients died without a distant recurrence.**

**127 patients experienced distant recurrences, including 22 (17.3%) with CNS-only, 16 (12.6%) with CNS and other sites, and 87 (68.5%) with non-CNS distant recurrence; 2 (1.6%) patients had missing recurrence site information.**

## Results

**Incidence of CNS-only recurrences are low and are similar across RCB classes.**

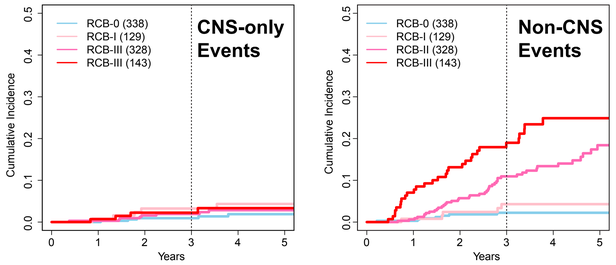



**Figure 3:** Cumulative incidence of CNS-only (right) and Non-CNS (left) events by RCB Class

**In contrast, the incidence of non-CNS recurrences increase with increasing RCB.**

| | Cumulative Incidence at 3 years | |
|---|---|---|
| | CNS-only | Non-CNS |
| pCR (RCB-0) | 1% | 2% |
| RCB-I | 3% | 4% |
| RCB-II | 2% | 11% |
| RCB-III | 2% | 19% |

**DRFS of RCB-I patients do not significantly differ from those achieving a pCR.**

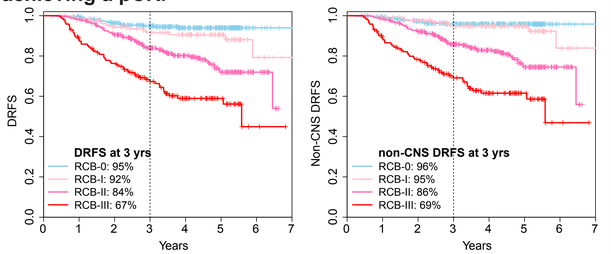
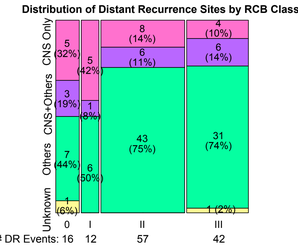



**Figure 4:** Kaplan Meier plots of DRFS (right) and DRFS excluding CNS-only recurrences (Non-CNS DRFS) (left) by RCB Class

**The small numerical difference is further reduced when the CNS-only recurrences are excluded.**

## Results

**CNS recurrences among distant recurrence events are proportionally higher within the pCR and RCB-I than in the RCB-II and RCB-III groups largely because of the relative low frequency of non-CNS recurrence events.**



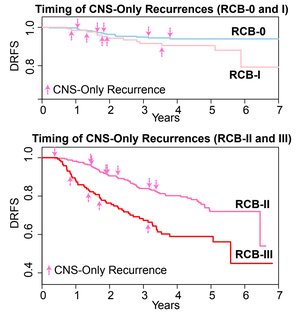




**Figure 5.** A) Mosaic plot of distribution of distant recurrence sites within RCB class; (B-C) Kaplan Meier curves showing DRFS of (B) RCB-0 and RCB-I and (C) RCB-II and RCB-III patients with CNS-only events annotated

## Conclusions

1. CNS-only recurrences are uncommon and similar across RCB groups
2. CNS is likely a sanctuary site and its involvement at first relapse appears independent of response
3. In contrast, non-CNS recurrence rates increase as RCB increases
4. Exclusion of CNS-only recurrences as an outcome event may improve association between neoadjuvant therapy response and DRFS
5. These findings support the use of RCB to identify patients with excellent outcome beyond those achieving pCR

**ACKNOWLEDGEMENTS:**
With support from Quantum Leap Healthcare Collaborative, FNIH, NCI (Grant 28XS197 P-0518835), Safeway, an Albertsons Company, William K. Bowes, Jr. Foundation, Breast Cancer Research Foundation, UCSF, GMU, the Biomarkers Consortium, Salesforce, OpenClinica, Formedix, Natera, Hologic Inc., TGen, Illumina, CCS Associates, Berry Consultants, Breast Cancer Research – Atwater Trust, Stand up to Cancer, California Breast Cancer Research Program, and Give Breast Cancer the Boot, IQVIA, Genentech, Amgen, Pfizer, Merck, Seattle Genetics, Daiichi Sankyo, AstraZeneca, Dynavax Technologies, Puma Biotechnology, AbbVie, Madrigal Pharmaceuticals (formerly Synta Pharmaceuticals), Plexxikon, Regeneron and Agendia. Sincere thanks to our DSMB, Independent Agent Selection Committee, our patients, advocates and investigators.