Residual cancer burden (RCB) is prognostic in the I-SPY 2 TRIAL

W. Fraser Symmans[1], Christina Yau[2], Yunn-Yi Chen[2], Brian Datnow[3], Shi Wei[4], Michael D Feldman[5], Jon Ritter[6], Xiuzhen Duan[7], Beiyun Chen[8], Ronald Tickman[9], Husain Sattar[10], Anthony Martin Magliocco[11], Bhaskar Kallakury[12], Megan Troxell[13], Smita Asare[14], Minetta C. Liu[8], Angela DeMichele[5], Douglas Yee[6], Donald A. Berry[1], Laura Esserman[2] on behalf of I-SPY 2 TRIAL Investigators and Pathologists

[1]Unversity of Texas, MD Anderson Cancer Center; [2]Univeristy of California, San Francisco; [3]University of California, San Diego; [4]University of Alabama at Birmingham [5]University of Pennsylvania; [6]University of Minnesota; [7]Loyola University; [8]Mayo Clinic, Rochester; [9]Swedish Cancer Institute; [10]University of Chicago; [11]Moffitt Cancer Center; [12]Georgetown University; [13]Oregon Health and Science University; [14]Quantum Leap Health Care Collaborative

BACKGROUND

Residual cancer burden (RCB) is a secondary response endpoint in the I-SPY2 trial that is measured and reported by the pathologists at each treatment site after reviewing training materials on the RCB website. I-SPY2 is a multicenter phase 2 trial in high risk stage II/III breast cancer (BC) using adaptive randomization to evaluate novel treatment agents added to standard neoadjuvant chemotherapy (NAC) within subsets of breast cancer.

Residual Cancer Burden (RCB)

RCB Index: Continuous measure of extent of residual disease based on:

- Primary tumor bed dimensions ($d_{prim}=\sqrt{d_1 d_2}$)
- Cellularity of fraction of invasive cancer (f_{inv})
- Size of largest metastasis (d_{met})
- Number of positive lymph nodes (LN)

www.mdanderson.org/breastcancer_RCB

I-SPY 2 TRIAL

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 increased pCR rate if tested in a neoadjuvant 300-patient phase 3 trial within a (graduating) signature defined by HR, HER2 and MP.

To date: 10 experimental regimens have been evaluated for efficacy.

- 6 regimens graduated (Veliparib/Carboplatin and Pembrolizumab in HR-HER2-; Pembrolizumab in HR+HER2-; Neratinib, MK2206, TDM-1/Pertuzumab and Pertuzumab/Trastuzumab in HER2+)

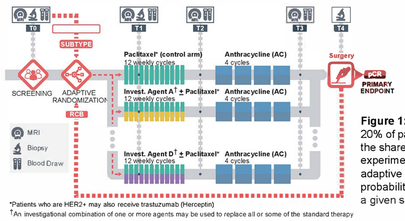


Figure 1: I-SPY2 study schema. 20% of patients are randomized to the shared control arm. Among experimental arms (up to four), adaptive randomization is based on probabilities of achieving pCR within a given subtype for each agent.

Secondary Endpoints: RCB and Event-free Survival (EFS).

We evaluated the association between RCB and EFS and compared the distributions of RCB index between experimental and control arms.

Methods

Local site pathologists reported RCB in case report forms.

- We assessed the prognosis (EFS) related to RCB index (continuous) and RCB classes using Cox proportional hazard modeling in all patients and in subtypes defined by hormone receptor (HR) and HER2 status.
- We compared the distributions of RCB index in the first six regimens that graduated, versus matching controls, using the Wilcoxon rank sum test.

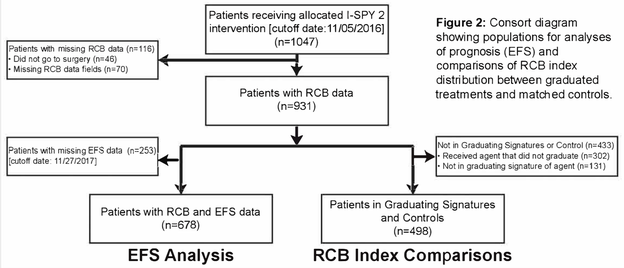


Figure 2: Consort diagram showing populations for analyses of prognosis (EFS) and comparisons of RCB index distribution between graduated treatments and matched controls.

Association Between RCB and EFS

RCB index and RCB class were prognostic overall

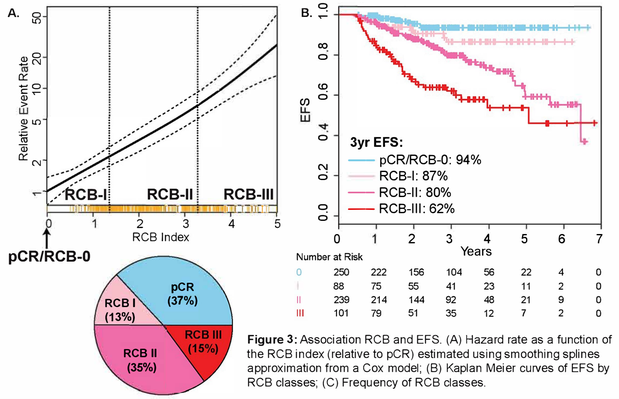


Figure 3: Association RCB and EFS. (A) Hazard rate as a function of the RCB index (relative to pCR) estimated using smoothing splines approximation from a Cox model; (B) Kaplan Meier curves of EFS by RCB classes; (C) Frequency of RCB classes.

RCB and EFS Within Subtypes

Although the distribution of RCB index differs between subtypes, RCB is prognostic within each subtype

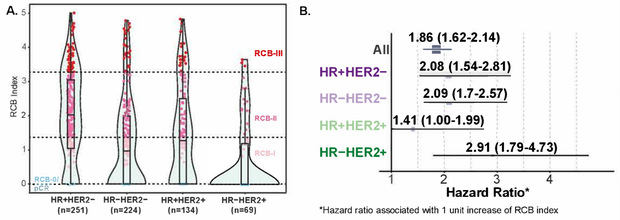


Figure 4: RCB and EFS Within Subtypes. (A) RCB index distribution within subtypes. (B) Forest plot showing hazard ratio associated with RCB index overall and within subtypes.

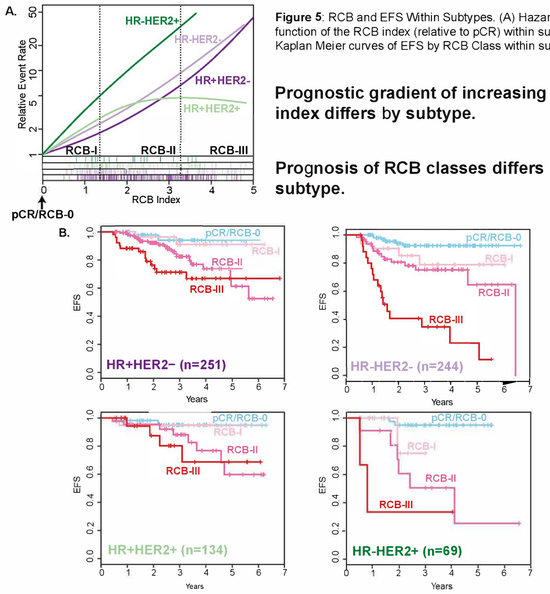


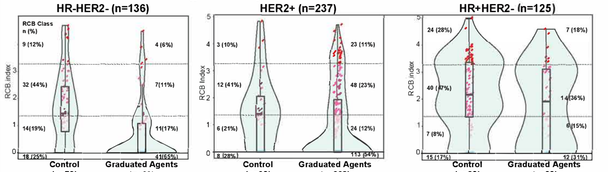
Figure 5: RCB and EFS Within Subtypes. (A) Hazard rate as a function of the RCB index (relative to pCR) within subtype; (B) Kaplan Meier curves of EFS by RCB Class within subtype.

Prognostic gradient of increasing RCB index differs by subtype.

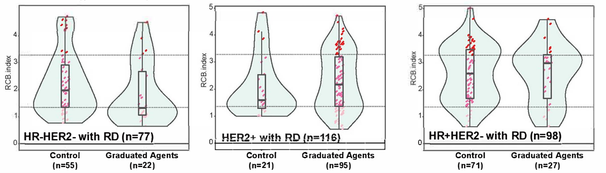
Prognosis of RCB classes differs by subtype.

Comparing RCB Index: Graduated vs Control Rx

The distribution of RCB index was lowered with graduating treatments, relative to control therapy, in HR-HER2- (p < 0.001) and HER2+ (p = 0.03), but not in HR+/HER2- (p = 0.21).



In those with residual disease (excluding pCR), there was a trend for decreased RCB index with graduating treatments, relative to control therapy, in HR-HER2- (p = 0.08), but not in HER2+ (p = 0.43) or HR+/HER2- cancers (p = 0.94).



Conclusions

RCB was independently validated by local site pathologists as a prognostic surrogate in all subtypes of breast cancer.

Randomized treatments (predicted to increase pCR rate) variably affected RCB index according to subtype. Comparisons of RCB distributions might describe patterns of efficacy from new treatments, e.g. generalized or idiosyncratic.

ACKNOWLEDGEMENTS:

I-SPY2 operates as a precompetitive consortia, with study sponsors FNIH (2010-2012) and QuantumLeap Healthcare Collaborative (2013-present).

I-SPY2 has received the gracious support of: William K Bowes Jr. Foundation, Give Breast Cancer the Boot, UCSF, The Biomarkers Consortium, Quintiles, The Breast Cancer Research Foundation, Safeway, an Albertsons Company, Seattle Genetics, AstraZeneca, Daiichi-Sankyo, Merck, Pfizer, Genentech, Amgen, Synta Pharmaceuticals, Plexxikon, Puma Biotechnology, AbbVie, Berry and Associates, CCS Associates, Salesforce, Agendia, and Novella Clinical.