MRI detection of residual disease following neoadjuvant chemotherapy (NAC) in the I-SPY 2 TRIAL

[1]Wen Li, PhD; [1]David C. Newitt, PhD; [1]Bo La Yun, MD; [1]John Kornak, PhD; [1]Bonnie Joe, MD, PhD; [1]Christina Yau, PhD; [2]Hiroyuki Abe; [3]Dulcy Wolverton; [4]Erin Crane; [5]Kathleen Ward; [6]Michael Nelson; [7]Bethany Niell; [7]Jennifer Drukteinis; [8]Karen Oh; [9]Kathy Brandt; [10]Dae Hee Bang; [11]Haydee Ojeda; [11]Mohammad Eghtedari; [12]Pulin Sheth; [13]Wanda Bernreuter; [13]Heidi Umphrey; [14]Mark Rosen; [15]Basak Dogan; [16]Wei Yang; [1]Laura Esserman, MD, MBA; [1]Nola M. Hylton, PhD

[1]University of California, San Francisco, CA; [2]University of Chicago, Chicago, IL; [3]University of Colorado, Denver, CO; [4]Georgetown University, Washington, DC; [5]Loyola University, Maywood, IL; [6]University of Minnesota, Minneapolis, MN; [7]Moffitt Cancer Center, Tampa, FL; [8]Oregon Health Science University, Portland, OR; [9]Rochester Methodist Hospital, Rochester, MN; [10]Swedish Medical Center, Seattle, WA; [11]University of California, San Diego, CA; [12]University of California, Los Angeles, CA; [13]University of Alabama, Birmingham, AL; [14]Univerisity of Pennsylvania, Philadelphia, PA; [15]University of Texas Southwestern, Houston, TX; [16]MD Anderson Cancer Center, Houston, TX

BACKGROUND

The purpose of this study is to determine if the combination of longest diameter (LD) measured by the radiologist and functional tumor volume (FTV) measured automatically by the computer can improve the predictive performance of FTV for assessing treatment response after neoadjuvant therapy in breast cancer patients. I-SPY 2 is a multicenter, phase 2 trial using response-adaptive randomization within biomarker subtypes to evaluate a series of novel agents when added to standard neoadjuvant therapy for women with high-risk stage II/III breast cancer.

PATIENTS

Eligible tumors must meet one of the following criteria: Stage II or III, or T4, any N, M0, including clinical or pathologic inflammatory cancer or Regional Stage IV, where supraclavicular lymph nodes are the only sites metastasis. A sub-cohort of 744 patients (median age: 49; range: 24–77 y/o). from the completed drug arms in I-SPY 2 with all four MRI exams and RCB outcomes were included in this study (Table 1).

Table 1 Patient characteristics

	N	N of breast pCR (rate)	N of pCR (rate)	N of RCB III (rate)
Full cohort	744	301 (41%)	268 (36%)	104 (14%)
HR+/HER2-	295	72 (24%)	58 (20%)	59 (20%)
HR+/HER2+	118	47 (40%)	42 (36%)	16 (14%)
HR-/HER2+	63	42 (67%)	42 (67%)	4 (6%)
HR-/HER2-	268	140 (52%)	126 (47%)	25 (9%)

METHODS

Definition of residual disease

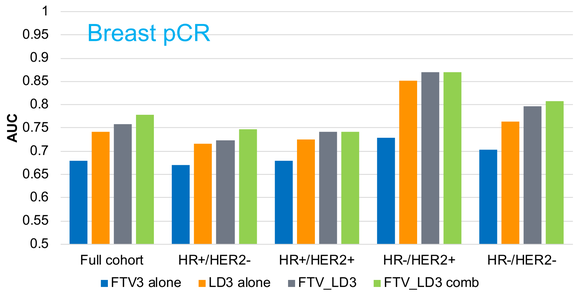
- **Breast pCR:** in-breast RCB=0: yes; in-breast RCB>0: no
- **pCR:** no residual disease in breast or nodes at surger

Statistic analysis

- **Single predictors**: FTV3, LD3 and FTV_LD3 at the pre-surgery
- **Multivariate analysis**: FTV_LD3 comb, a optimized logistic regression model that combines FTV_LD3 with FTV measured at all time points

RESULTS

Figure 2 AUCs of using pre-surgery FTV (FTV3) alone, LD alone (LD3), combined variable (FTV_LD3), and the combination of FTV_LD3 with FTV predictors to predict **breast pCR**



LD AND FTV IN MRI

MRI was acquired at four time points: Baseline (pre-NAC, T0), early (after 3 weeks of NAC, T1), inter-regimen (between two regimens, T2), pre-surgery (post-NAC, T3). Percent changes at T1 to T3 were also calculated (Figure 1).

- **Longest diameter of disease (LD)**

  Measured by radiologist (diameter measurements at treatment time points were required to be along the same axis as baseline)

- **Functional tumor volume (FTV)**

  Calculated by the sum of voxels with enhancement above pre-defined thresholds in the constraining volume of interest (VOI)

- **A linearized variable to combine FTV and LD (FTV_LD)**

$$FTV\_LD = \sqrt{FTV^{1/3} \times LD}$$

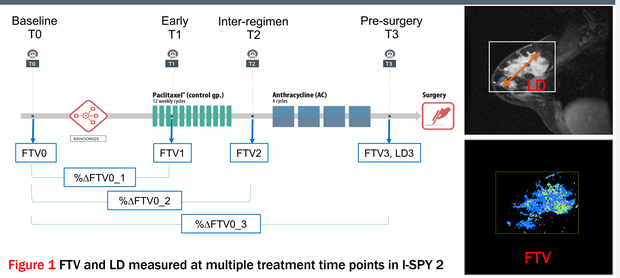


Figure 1 FTV and LD measured at multiple treatment time points in I-SPY 2

Figure 3 AUCs of using pre-surgery FTV (FTV3) alone, LD alone (LD3), combined variable (FTV_LD3), and the combination of FTV_LD3 with FTV predictors to predict **pCR**

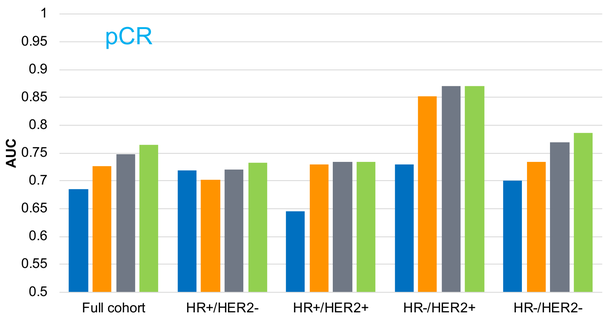
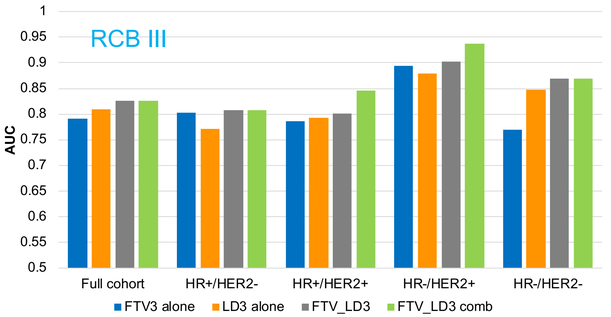


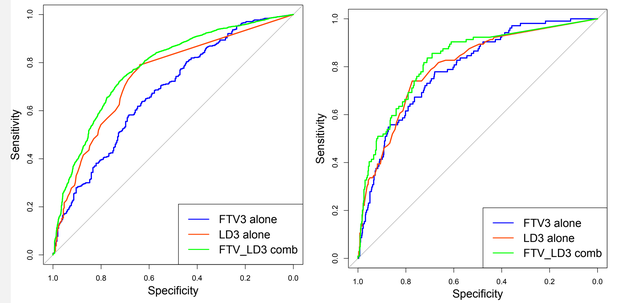
Figure 4 AUCs of using pre-surgery FTV (FTV3) alone, LD alone (LD3), combined variable (FTV_LD3), and the combination of FTV_LD3 with FTV predictors to predict **RCB III**



Summary

- **Fig 2**: the combined variable FTV_LD3 achieved higher AUCs than FTV3 alone to predict breast pCR in the full cohort and in each subtype
- **Fig 3**: very similar to Fig 2, except for the HR+/HER2- subtype
- **Fig 4**: the difference between FTV_LD3 and FTV3 alone becomes smaller, except for the triple negative subtype
- FTV_LD3 plus FTV at all time points (FTV_LD3 comb) increases AUCs in predicting breast pCR or pCR. The increase was varied by subtype

Figure 5 ROC curves of using FTV3 alone, LD3 alone, and FTV_LD3 combined with FTV predictors to predict breast **pCR** (left) and **RCB III** (right)



*FTV_LD3 comb: FTV_LD3 + %ΔFTV0_1 AUCs are **0.68** for FTV3 alone, **0.74** for LD3 alone, and **0.78** for FTV_LD3 comb*

*FTV_LD3 comb: FTV_LD3 AUCs are **0.79** for FTV3 alone, **0.81** for LD3 alone, and **0.83** for FTV_LD3 comb*

DISCUSSION & CONCLUSIONS

- FTV is an automated and 100% reproducible measurement that is used under FDA-IDE approval to adjust randomization and measure response over treatment in I-SPY 2, while LD is measured by the radiologist and is often subjective
- Combined models perform the best in all cases and LD provides the most additive value for prediction of pCR
- MRI, either single or combined measures is better for predicting significant residual disease (i.e. RCB III) than no residual disease (breast pCR)

ACKNOWLEDGEMENTS:

This work is supported in part by NIH R01 CA132870, NIH U01 CA225427 and P01 CA210961.

With support from Quantum Leap Healthcare Collaborative, FNIH, NCI (Grant 28XS197 P-0518835, Safeway Foundation, William K. Bowes, Jr. Foundation, Breast Cancer Research Foundation, UCSF), the Biomarkers Consortium, Salesforce, Novella Clinical, CCS Associates, Berry Consultants, OHSU, and Give Breast Cancer the Boot. Initial support from IQVIA, Johnson & Johnson, Genentech, Amgen, San Francisco Foundation, Eli Lilly, Pfizer, Eisai Company, Side Out Foundation, Harlan Family, Avon Foundation for Women, Alexandria Real Estate Equities and Agendia. Sincere thanks to Anna Barker, our DSMB (Harold Burstein, Elizabeth Frank, Steven Goodman, Clifford Hudis, Robert Mass, Musa Meyer, Janet Wittes, Tiffany Traina and Deborah Laxague), Ken Buetow and CaBIG, our patients, advocates and investigators.