Breast cancer subtype specific association of pCR with MRI assessed tumor volume progression during NAC in the I-SPY 2 TRIAL

Wen Li[1], Natsuko Onishi[1], David C. Newitt[1], Jessica Gibbs[1], Lisa J. Wilmes[1], Ella F. Jones[1], Laura S. Sit[1], Christina Yau[1], Thelma Brown[2], A. Jo Chien[1], Bonnie N. Joe[1], Elissa Price[1], Michelle E. Melisko[1], Anne M. Wallace[3], Richard Schwab[3], Haydee Ojeda-Fornier[3], Mohammad Eghtedari[3], Erica Stringer-Reasor[4], Stefanie Woodard[4], Kathryn W. Zamora[4], Douglas Yee[5], Michael Nelson[5], An Church[5], Patrick Bolan[5], Kathy S. Albain[6], Theresa Kuritza[6], Kevin Morley[6], Anthony D. Elias[7], Dulcy Wolverton[7], Kelly Fountain[7], Dan Lopez Paniagua[7], Judy C. Boughey[8], Kathy Brandt[8], Sadia Choudhery[8], Amy S. Clark[9], Angela DeMichele[9], Mark Rosen[9], Elizabeth S. McDonald[9], Rita Nanda[10], Hiroyuki Abe[10], Deepa Sheth[10], Nick Gruszauskas[10], Claudine Isaacs[11], Erin Crane[11], Julie E. Lang[12], Janice Lu[12], Pulin Sheth[12], Linda Hovanessian-Larsen[12], Erin D. Ellis[13], Dae Hee Bang[13], Christiane D. Mullins[13], Zaha Mitri[14], Karen Y. Oh, Neda[14] Jafarian[14], Alina Tudorica[14], Heather S. Han[15], Bethany Niell[15], Kevin Kalinsky[16], Richard Ha[16], Ralph Wynn[16], Tara Sanft[17], Jane Meisel[18], Mary Newell[18], Michael Cohen[18], Puneet Sharma[18], Donald W. Northfelt[19], Marina Giurescu[19], Kirsten K. Edmiston[20], Elise Berman[20], Rachel Yung[21], Constance Lehman[21], Savannah Partridge[21], Rebecca K. Viscusi[22], Kim Fitzpatrick[22], Marisa H. Borders[22], Debasish Tripathy[23], Wei Yang[23], Basak Dogan[23], W. Fraser Symmans[23], Qamar J. Khan[24], Sally Goudreau[25], David M. Euhus[26], Jane Perlmutter[27], Smita M. Asare[28], Hope S. Rugo[1], Laura J. van't Veer[1], Donald A. Berry[29], Laura J. Esserman[1], Nola M. Hylton[1]

[1]University of California, San Francisco; [2]I-SPY 2 Advocacy Group; [3]University of California, San Diego; [4]University of Alabama at Birmingham; [5]University of Minnesota; [6]Loyola University; [7]University of Colorado; [8]Mayo Clinic, Rochester; [9]University of Pennsylvania; [10]The University of Chicago Medical Center; [11]Georgetown University; [12]University of Southern California; [13]Swedish Cancer Institute; [14]Oregon Health & Science University; [15]Moffitt Cancer Center; [16]Columbia University; [17]Yale Cancer Center; [18]Emory University; [19]Mayo Clinic, Scottsdale; [20]Inova Health System; [21]University of Washington; [22]University of Arizona; [23]University of Texas, M.D. Anderson Cancer Center; [24]University of Kansas; [25]University of Texas, Southwestern; [26]John Hopkins Medicine; [27]Gemini Group; [28]Quantum Leap Healthcare Collaborative; [29]Berry Consultants, LLC

Background

It is important to be able to identify patients who are progressing in an adaptive randomized trial as I-SPY 2 so their treatment can be changed to a different therapeutic regimen.

MRI is an accurate and non-invasive imaging method to monitor treatment response.

Molecularly high risk breast cancer can be very heterogeneous.

Purpose: To study retrospectively the accuracy of identifying patients not achieving pCR using MRI assessed tumor volume at 3 different treatment time points by breast cancer subtype.

I-SPY 2 TRIAL

I-SPY 2: A multicenter, phase 2 trial using response-adaptive randomization within biomarker subtypes to evaluate novel agents as neoadjuvant therapy for high-risk breast cancer

Inclusion criteria: Tumor Size ≥ 2.5cm; hormone-receptor (HR)+HER2- MammaPrint (MP) high risk, 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

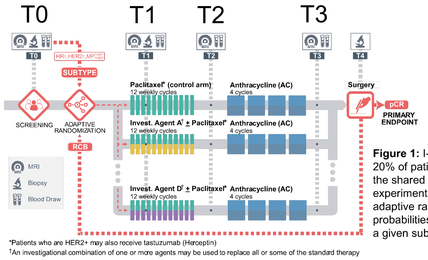


Figure 1: I-SPY2 study schema. 20% of patients are randomized to the shared control arm. Among experimental arms (up to four), adaptive randomization is based on probabilities of achieving pCR within a given subtype for each agent.

*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

Methods

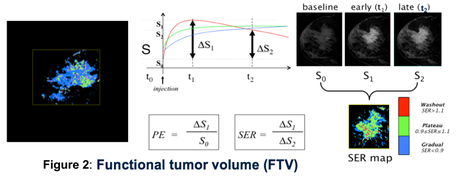


Figure 2: **Functional tumor volume (FTV)**

Patients with any amount of FTV increase at early treatment (after 3 weeks, T1), inter-regimen (T2), and pre-surgery (T3) and visual confirmation to eliminate the possibilities of false progressions due to strong BPE, enhanced vessels, motion, or insufficient image quality.

MRI assessed progression = FTV increase + visual confirmation

MRI assessed progression

- **990** I-SPY 2 patients with pCR outcomes (pCR rate: 33%) were included in this study
- **169/990 (17%)** patients with FTV increase from baseline
- **149/990 (15%)** patients with FTV increase + visual confirmation (MRI assessed progression)

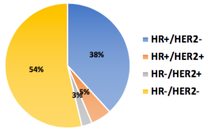


Figure 3: Distribution of progressions by subtype

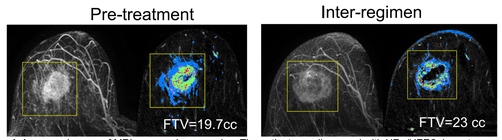


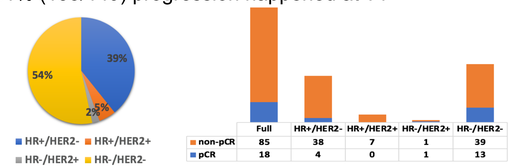
Figure 4: An example case of MRI assessed progression. The patient was diagnosed with HR+/HER2- breast cancer at age 45. Her MRIs at T0 (pre-treatment) and T2 (inter-regimen) were shown here, 2 images for each time point. The image on the left is the subtracted MIP and the image on the right is the SER map overlapping on a subtracted axial slide. FTV increase and visual assessment on the MR images both confirmed that this is a progression at inter-regimen. The patient did not achieve pCR after the treatment.

Progression by treatment time point

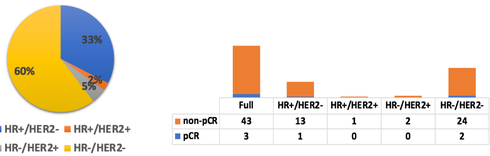
Figure 5: Illustration of treatment time points when progression could happen.

Progression at T1 – is 3 week too early?

- 91% (135/149) progression happened at T1



Progression at T2



Progression at T3

- T1 may be too early for identifying non-pCRs in triple negative disease
- T1 may not be too early for identifying non-pCRs in HR+/HER2+ disease

Summary table

Table 1. MRI assessed progression and number of patients by subtype

	Analysis cohort		MRI assessed progression					
			T1		T2		T3	
	N	Non-pCRs (rate)	N	Non-pCR (%)	N	Non-pCR (%)	N	Non-pCR (%)
Full cohort	990	666 (67%)	135	115 (85)	43	40 (93)	5	5 (100)
HR+/HER2-	380	316 (83%)	53	48 (91)	14	13 (93)	2	2 (100)
HR+/HER2+	156	98 (63%)	7	7 (100)	1	1 (100)	0	NA
HR-/HER2+	89	33 (37%)	3	2 (67)	2	2 (100)	0	NA
HR-/HER2-	363	217 (60%)	72	58 (81)	26	24 (92)	3	3 (100)

- Overall, very few MRI assessed progression found in the analysis cohort
- 100% of MRI assessed progression in HR+/HER2+ were non-pCRs
- over 90% of MRI assessed progression at T2 were non-pCRs

CONCLUSIONS

- Overall, there are very few MRI assessed progression
- MRI assessed disease progression may identify non-responders as early as at T1
- Most progressions are HER2- (HR+/-)
- T1 may be too early for triple negative disease
- MRI assessed progression identifies non-responders more accurately at later time points

ACKNOWLEDGEMENTS:

This study was supported by NIH R01 CA132870, NIH U01 CA225427 and P01 CA210961.

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.