Impact of Body Mass Index on Pathological Complete Response after Neoadjuvant Chemotherapy: Results from the I-SPY 2 Trial

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BACKGROUND

- Body mass index (BMI) is a risk factor for breast cancer [1].
- Increased BMI is associated with greater disease-specific mortality and overall mortality in breast cancer patients [2, 3].
- Although retrospective studies showed higher BMI was associated with inferior pathological complete response (pCR) after neoadjuvant chemotherapy, it remains unclear if this inferiority was related to obese patients received underdosed chemotherapy in some studies [4, 5, 6].

I-SPY 2 TRIAL OVERVIEW

I-SPY 2 is a multicenter, phase 2 clinical trial using response-adaptive randomization within biomarker subtypes to evaluate novel agents as neoadjuvant therapy for high-risk breast cancer. **Therapy regimens in this trial are dosed based on actual body weight.**

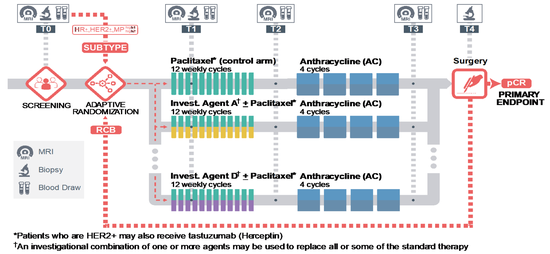
Goal: To identify (graduate) regimens that have ≥85% predictive probability of success in a 300-patient phase 3 neoadjuvant trial defined by hormone receptor and HER2 status, and MammaPrint.

Inclusion criteria:
- Tumor size ≥2.5 cm
- Hormone-receptor positive (HR+)/HER2-, and MammaPrint high-risk
- HR-/HER2-, or HR-/HER2+

Primary Endpoint: pathologic complete response (pCR)

Regimens may leave the trial for one of four reasons:
1. Futility (<10% probability of success)
2. Maximum sample size accrual (probability of success ≥10% and <85%)
3. Graduation (≥85% predictive probability of success)
4. As recommended by the independent Data & Safety Monitoring Board

To date, 11 experimental regimens have been evaluated for efficacy.



I-SPY 2 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.

PURPOSE

We evaluated the association between baseline BMI and response to neoadjuvant chemotherapy (defined by pCR) in the I-SPY 2 trial in which chemotherapy is dosed based on actual body weight without a cap.

METHODS

- 989 patients were enrolled in the I-SPY 2 trial from 3/2010 to 11/2016.
- 978 had a recorded baseline BMI prior to treatment.
- BMI was categorized as obese (BMI ≥30 kg/m^2), overweight (25 ≤ BMI <30 kg/m^2), and normal or underweight (BMI <25 kg/m^2).
- pCR was defined as elimination of detectable invasive cancer in the breast and lymph nodes (ypT0/Tis and ypN0) at time of surgery.
- Logistic regression analysis was used to determine associations between BMI and pCR, and Cox proportional hazards regression was used to examine event-free survival (EFS) and overall survival (OS) by BMI, adjusting for race/ethnicity, age, menopausal status, breast cancer subtype and stage.

RESULTS

- There was no evidence for differences in pCR rates by BMI in either univariate or multivariate analyses.
- There was no evidence for significant interaction between BMI and breast cancer subtype.
- pCR rates differed significantly by tumor subtype and tumor stage. Black patients were more likely to be obese (Table 1).

Table 1: Patient characteristics

	BMI <25 (N=348)	25≤BMI<30 (N=310)	BMI≥30 (N=320)	Total (N=978)	P-value
	# of pts (%)	# of pts (%)	# of pts (%)	# of pts (%)	
Patient Characteristics					
Median age at initial tx	46	49	50	49	<0.0001
Median/Range	25-71	23-77	24-73	23-77	
Race / Ethnicity					
African American / Black	21 (6)	26 (8.4)	71 (22.2)	118 (12.1)	<0.0001
American Indian / Native or Hawaiian / Pacific Islander	4 (1.2)	2 (0.7)	5 (1.6)	11 (1.1)	
Asian	35 (10.1)	27 (8.7)	9 (2.8)	71 (7.3)	
Hispanic	23 (6.6)	44 (14.2)	49 (15.3)	116 (11.9)	
Non-Hispanic White	265 (76.2)	211 (68.1)	186 (58.1)	662 (67.7)	
Diabetes					
No	238 (97.9)	230 (93.9)	212 (89.8)	680 (93.9)	0.001
Yes	5 (2.1)	15 (6.1)	24 (10.2)	44 (6.1)	

Table 2: pCR frequency and rate of each BMI category by breast cancer subtype

Subtype	BMI < 25 Frequency	BMI < 25 %	25 ≤ BMI < 30 Frequency	25 ≤ BMI < 30 %	BMI ≥ 30 Frequency	BMI ≥ 30 %	P-value
HR+ / HER2+	24	38.1	17	38.6	16	33.3	0.83
HR+ / HER2-	25	19.2	14	10.8	25	21.2	0.06
HR- / HER2+	21	75.0	20	64.5	14	48.3	0.11
HR- / HER2-	44	34.7	46	44.2	49	39.2	0.33

Figure 1: pCR rates for 3 BMI categories

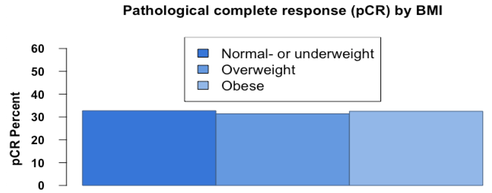


Figure 2: No difference in EFS of 3 BMI categories

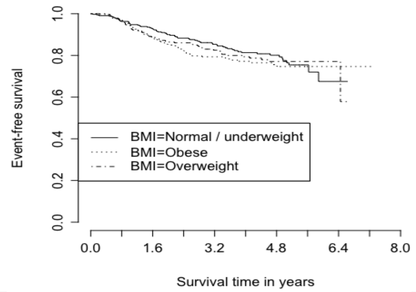


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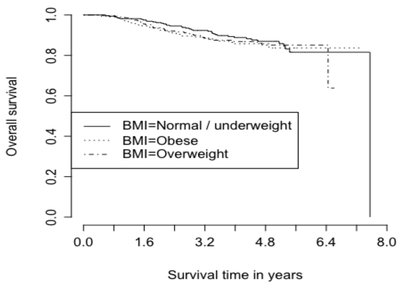
Figure 3: No difference in OS of 3 BMI categories



CONCLUSIONS

- **No difference in pCR rates by baseline BMI in this biologically high-risk breast cancer population receiving actual body weight-based neoadjuvant chemotherapy.**
- **Breast cancer subtype and stage showed predictive value for pCR after neoadjuvant chemotherapy.**
- **These findings suggest that obese patients should be treated with chemotherapy dosage based on actual weight.**

ADVOCATE'S PERSPECTIVE

Many patients struggle with weight issues and worry that being overweight may have contributed to their breast cancer diagnosis and that their subsequent treatment may be impacted. Results of this study are encouraging for such patients. Although previous retrospective studies have shown that higher BMI is associated with lower pCR rates, this was not the case in this study. This difference may be attributed to the fact that I-SPY 2 uses a uniform standard of dosing which is based on each patient's weight with no dosing limitation. In other studies, it is unclear if there was a dose cap as well as other factors causing poorer outcomes.

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