Pertuzumab/Trastuzumab/Paclitaxel Versus Standard Trastuzumab/Paclitaxel Therapy for HER2+ Breast Cancer: Results from the Neoadjuvant I-SPY 2 TRIAL

Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis 2

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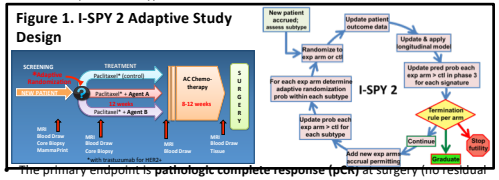
Background and Rationale: I-SPY 2

- 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 **(FIG.1)**
  - 20% of patients are assigned to control.
  - Within each patient subtype the other 80% are assigned to experimental therapy based on the relative performances of the various therapies in the trial.
  - Randomization probabilities are in proportion to the current probabilities that the respective therapies have a higher pCR rate than the control rate in the respective subtypes.

Figure 1. I-SPY 2 Adaptive Study Design



- The primary endpoint is **pathologic complete response (pCR)** at surgery (no residual invasive disease in breast or nodes).
- The goal is to identify/graduate regimens that have ≥85% Bayesian predictive probability of success (statistical significance) in a 300-patient phase 3 neoadjuvant trial defined by hormone-receptor (HR) & HER2 status & MammaPrint (MP).
- Regimens may leave the trial for one of four reasons:
  - Graduate (as described above)
  - Drop for futility (< 10% probability of success)
  - Following accrual of maximum sample size, n = 75 (10% probability of success < 85%)
  - Safety Issues
- I-SPY 2 has evaluated or is presently evaluating 10 experimental arms from 7 pharmaceutical companies. To date 3 of the 10 have graduated to phase 3.
- Here, we report the results for experimental arm: **Pertuzumab + Trastuzumab + Paclitaxel** vs. Trastuzumab+ Paclitaxel to improve pCR

Investigational Agent Evaluation: Pertuzumab/Trastuzumab/Paclitaxel (THP)

- Pertuzumab (rhuMAb 2C4), is a fully humanized monoclonal antibody, that acts by blocking the association of HER2 with other HER family members, including EGFR, HER3, and HER4, to form HER2 heterodimers
- Pertuzumab (P) has established survival benefit in the metastatic setting, and received accelerated approval in the neoadjuvant setting when combined with trastuzumab (H) and docetaxel(D) for early breast cancer.

- In this intent-to-treat analysis, patients were considered evaluable if they received any protocol therapy. A non-pCR was assigned if patients received any therapy but withdrew consent, progressed, changed to non-protocol therapy or left the treating institution.

Eligibility and Methods

- Women with invasive breast cancer ≥2.5 cm were adaptively randomized to 12 weekly cycles of paclitaxel and trastuzumab, (TH, qwk x 12) (control) or in combination with pertuzumab (THP (P, q3wk x 4) followed by doxorubicin/cyclophosphamide (AC) x 4 with serial biomarkers (biopsies, blood draw and MRI scans). **(FIG. 1)**
- MP low/HR+/HER2- tumors were ineligible for randomization
- Patients were stratified to 8 subsets (Table 1) based on hormone-receptor, HER2, and MammaPrint gene profiling score (high-1 [MP1] vs high-2 [MP2]), with combinations of subsets defining 10 agent signatures.

Table 1: Biomarker Subtypes with Overall Prevalence in I-SPY 2 to Date (as of 3/15/16)

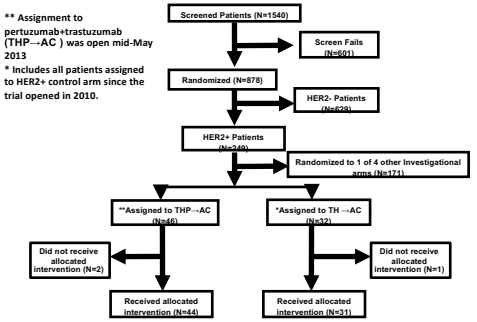
Enrollment through Feb 2016	MP high-1 (MP1)		MP high-2 (MP2)		Totals
	HR+	HR-	HR+	HR-	
HER2+	15%	5%	3%	5%	28%
HER2-	26%	6%	10%	30%	72%
TOTAL	41%	11%	13%	35%	**100%**

- Within-patient longitudinal modeling of MRI volume was used during the trial to predict whether the patient would experience a pCR and improve the efficiency of adaptive treatment assignments.
- Adaptive assignment to the experimental arms was based on current Bayesian probabilities of superiority over control.
- Pertuzumab+ trastuzumab+ paclitaxel (TCP) was assigned to only HER2+ patients.
- We report results of TCP evaluated in the 3 HER2+ subsets (HER2+, HER2+/HR+, HER2+/HR-).

Enrollment/Disposition for THP vs. Control (TH)

Figure 2: CONSORT

- ** Assignment to pertuzumab+trastuzumab (THP→AC) was open mid-May 2013
- * Includes all patients assigned to HER2+ control arm since the trial opened in 2010.

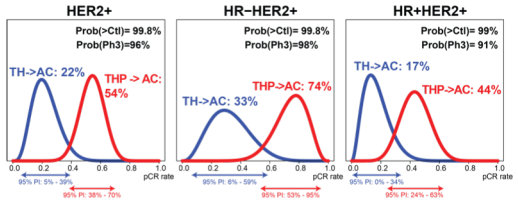


Results: Efficacy

Table 2: Posterior and Predictive Probabilities by Signature

Arm	Estimated pCR Rate (95% PI)	Prob(>Ctrl)	Prob(Ph3)
HER2+			
TH->AC	0.22 (0.05 – 0.39)		
THP->AC	0.54 (0.38 – 0.70)	**0.998**	**0.96**
HR-HER2+			
TH->AC	0.33 (0.06 – 0.59)		
THP->AC	0.74 (0.53 – 0.95)	**0.998**	**0.98**
HR+HER2+			
TH->AC	0.17 (0.00 – 0.34)		
THP->AC	0.44 (0.24 – 0.63)	**0.99**	**0.91**

Figure 4: pCR Probability Distributions by Signature



Legend:

- Estimated (mean) pCR rates are included on curve labels
- 95% PI: 95% Bayesian Probability Interval
- Prob(>Ctrl): Probability of THP->AC showing superiority to control (TH->AC)
- Prob(Ph3): Probability of success in a 1:1 randomized 2-arm 300 patient phase 3 trial within the respective subtype population

Results: Safety and Tolerability

Table 3 : Adverse Events (Preliminary)

Summary of on-treatment adverse events experienced by >5% of THP->AC Treated Patients

	THP->AC (n=44)	TH->AC (n=31)
Available for Evaluation, n	**35**	**31**
Grade ≥ 3, n (% of non-missing)		
Neutrophil count decreased	5 (14%)	2 (6%)
Febrile neutropenia	5 (14%)	3 (10%)
Anemia	3 (9%)	1 (3%)
Hypertension	3 (9%)	4 (13%)
Alanine aminotransferase increased	2 (6%)	1 (3%)

- AE data from 9 patients in the experimental arm is still pending

Dose Delays as Reflected by Time to Surgery

- Three patients (THP->AC: 2 ; TH->AC: 1) did not proceed to surgery
- Among patients who procced to surgery, time to surgery is similar between the experimental and control arms , with a median of 175.5 and 170.5 days for THP->AC and TH-> AC respectively

Conclusions

- I-SPY 2 is a phase 2 screening process that attempts to match experimental therapies with responding patient subtypes.
- I-SPY 2's adaptive randomization was successful in efficiently evaluating Pertuzumab + Trastuzumab + Paclitaxel (THP) in the setting of HER2+ neoadjuvant breast cancer.
- **THP -> AC substantially improves pCR rates over standard TH -> AC in all 3 HER2+ signatures, including HR+ and HR- subsets.**
- The I-SPY 2 standing trial mechanism is effective in defining agents/combinations most likely to succeed in phase 3 biomarker-defined patient subsets.

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