The Evaluation of Trebananib plus Standard Neoadjuvant Therapy in High-Risk Breast Cancer: Results from the I-SPY 2 TRIAL

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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 so far 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.

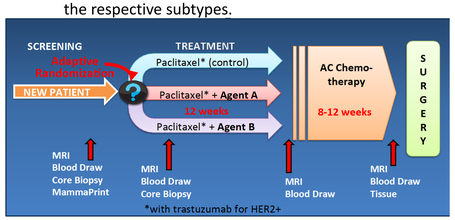
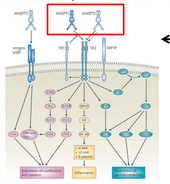


Fig 1. I-SPY 2 Study Schema

- The primary endpoint is pathologic complete response (pCR) at surgery.
- 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) or safety issues or following accrual of maximum sample size (10%< probability of success <85%).
- I-SPY 2 has evaluated or is presently evaluating 10 experimental arms from 6 pharmaceutical companies. To date 3 of the 10 have graduated to phase 3.
- We report the results for experimental arm trebananib, an angiopoietin-1/2-neutralizing peptibody that inhibits interaction with the Tie2 receptor

Investigational Agent Evaluation: Trebananib

- Trebananib is an angiopoietin-1-2-neutralizing peptibody that prevents angiopoietin-1 (ANGPT1) and angiopoietin-2 (ANGPT2) from binding with its tie2 receptor thereby inhibiting angiogenesis and tumor cell proliferation (**FIG 2**)
- Based on safety data on the combination of trebananib plus taxanes and trastuzumab, trebananib was tested in the I-SPY 2 TRIAL.



Trebananib binds to ANGPTI & ANGPT2 preventing interaction with TIE2

Adapted from Nature Reviews: Targeting the ANGPT-TIE2 Pathway in Malignancy

Figure 2

Eligibility and Methods

- Women with invasive breast cancer ≥2.5 cm on exam or ≥2 cm on imaging were adaptively randomized to 12 weekly paclitaxel (and trastuzumab if HER2+) cycles (control) or in combination with one of several experimental agents 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.
- MP1 and MP2 are determined by the predefined median cut-point of I-SPY 1 participants with high MP scores who fit eligibility criteria for I-SPY 2

Table 1: Biomarker Subtypes with Overall Prevalence in I-SPY 2 to Date

Enrollment through August 2015	MP high-1 (MP1)		MP high-2 (MP2)		Totals
	HR+	HR-	HR+	HR-	
HER2+	133 (15%)	42 (5%)	25 (3%)	50 (6%)	250 (28%)
HER2-	233 (26%)	55 (6%)	86 (10%)	262 (30%)	636 (72%)
TOTAL	366 (41%)	97 (11%)	111 (13%)	312 (35%)	886 (100%)

- pCR was the primary endpoint (no residual invasive disease in breast or nodes).
- 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.
- 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.
- Trebananib was initially assigned only to HER2- patients; once additional safety data with trastuzumab was confirmed, the agent was also assigned to HER2+ patients
- We report results of trebananib 15 mg IV weekly evaluated in all 8 subsets.
- Adaptive assignment to the experimental arms was based on current Bayesian probabilities of superiority over control.

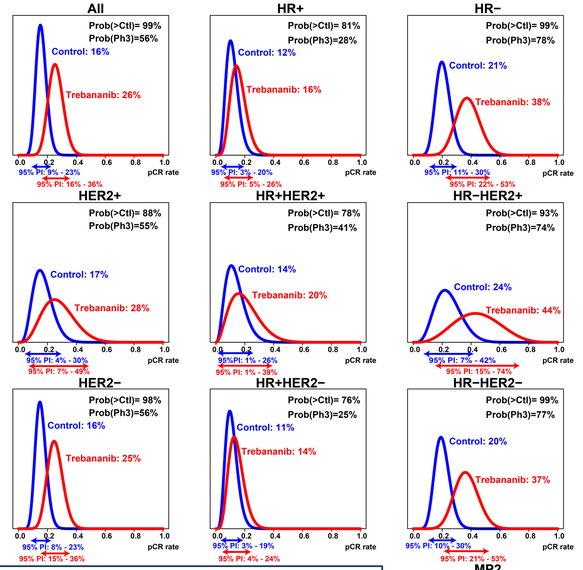
Dose Delays

- Dose delay/reduction occurred in 14% of patients in the experimental arm, compared to 20% in the control arm and the time to surgery between these arms are comparable
- 19% of patients discontinued early in the experimental arm (similar to 17% of controls)

Enrollment/Disposition for Trebananib and Control Arms

- Randomized to trebananib = 134 (19 with trastuzumab)
- Control arm = 133 (31 with trastuzumab)
- Intent-to-treat analysis - all patients (8 trebananib and 17 control) who initiated treatment but withdrew consent for follow-up, progressed, switched to non-protocol therapy or left the study institution were considered evaluable and designated as non–pCR

Figure 3: Bayesian pCR Probability Distributions: Results



Legend:

- Estimated (mean) pCR rates are included on curve labels
- 95% PI: 95% Bayesian Probability Interval
- Prob(>Ctrl): Probability of trebananib showing superiority to control
- Prob(Ph3): Probability of success in a 1:1 randomized 2-arm 300-patient phase 3 trial within the respective subtype population
- MammaPrint High-1 (MP1) or High-2 (MP2) – (see Methods)

Table 2: Adverse Events

	Trebananib (n=134)	Control (n=133)
Available for Evaluation, n	130	132
Missing Data, n	4	1
Grade ≥ 3		
Neutrophil count decreased	20 (15%)	14 (11%)
White blood cells decreased	13 (10%)	9 (7%)
Anemia	11 (8%)	7 (5%)
Febrile Neutropenia	8 (6%)	12 (9%)

Signature Arm	Estimated pCR (95% PI)	Prob(>Ctl)	Prob(Ph3)
ALL		0.986	0.564
Control	0.158 (0.09-0.23)		
Trebananib	0.259 (0.16 -0.36)		
HR+		0.805	0.281
Control	0.115 (0.03- 0.20)		
Trebananib	0.157 (0.05-0.26)		
HR-		0.991	0.784
Control	0.207 (0.11- 0.31)		
Trebananib	0.378 (0.22-0.53)		
HER2+		0.879	0.553
Control	0.17 (0.04-0.30)		
Trebananib	0.279 (0.07-0.49)		
HER2-		0.981	0.555
Control	0.155 (0.08-0.23)		
Trebananib	0.254 (0.15-0.36)		
MP2		0.991	0.786
Control	0.177 (0.07-0.28)		
Trebananib	0.342 (0.19-0.49)		
HR-HER2-		0.988	0.771
Control	0.201 (0.10-0.30)		
Trebananib	0.368 (0.21-0.53)		
HR-HER2+		0.926	0.739
Control	0.244 (0.07-0.42)		
Trebananib	0.444 (0.15-0.74)		
HR+HER2+		0.775	0.41
Control	0.135 (0.01-0.26)		
Trebananib	0.201 (0.01-0.39)		
HR+HER2-		0.758	0.248
Control	0.11 (0.03-0.19)		
Trebananib	0.143 (0.04-0.24)		

indicates signature that may be of interest in future studies

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 trebananib in the setting of neoadjuvant breast cancer.
- Trebananib was well-tolerated with only minor toxicity observed.
- **Although no subtype reached the efficacy threshold, the data suggested there may be a benefit in HR-, MP2 (highly correlated with HR-), HR-/HER2-, and HR-/HER2+ tumors, which may be explored in future studies.**
- The I-SPY 2 standing trial mechanism is effective in defining agents/combinations most likely to succeed in phase 3 biomarker-defined patient subsets.

I-SPY…The Right Drug, The Right Patient, The Right Time…NOW!

For more information visit: ispy2trial.org