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

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Efficacy of Hsp90 inhibitor Ganetespib plus Standard Neoadjuvant Therapy in High-Risk Breast Cancer: Results from the I-SPY 2 TRIAL

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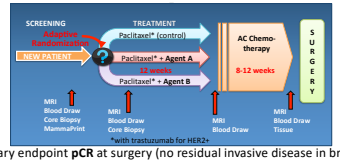
Background and Rationale: I-SPY 2

- 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 pathological complete remission (**pCR**) rate than the control rate in the respective subtypes.

Fig 1. I-SPY 2 Study Schema



- The primary endpoint **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 in all subtypes)
  - Following accrual of maximum sample size, n = 75, (120 if drug is evaluated across all signatures. (10% ≤ probability of success <85%)
  - Safety Issues
- I-SPY 2 has evaluated or is presently evaluating 12 experimental arms from 9 pharmaceutical companies. To date 5 of the 12 have graduated.
- We report here the results for experimental arm:
  Hsp90 inhibitor Ganetespib plus standard neoadjuvant therapy

Investigational Agent Evaluation: Hsp90 inhibitor Ganetespib

- Ganetespib, a selective inhibitor of Hsp90, induces the degradation/deactivation of key drivers of tumor initiation, progression, angiogenesis, and metastasis including HER2, p95-HER2, EGFR, ER, PI3K, AKT, MET and VEGFR. The combination of Hsp90 inhibitors and taxanes has shown promise in preclinical evaluations.
- Ganetespib in combination with taxanes previously have resulted in a superior therapeutic response compared to monotherapy in multiple solid tumor models including Breast Cancer (NCT01677455).
- 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 (T) (qwk x 12) (control) or in combination with Ganetespib (G) (weeks 1-3, 5-7, 9-11) followed by doxorubicin/cyclophosphamide (AC) x 4 with serial biomarkers (biopsies, blood draw and MRI scans). **(FIG. 1)**
- MP low/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.

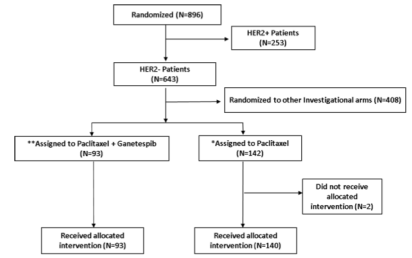
Table 1: Biomarker Subtypes with Overall Prevalence in I-SPY 2 from the beginning of trial till Ganetespib exited the trial (Oct 2015)

Enrollment through Oct 2015	MP high-1 (MP1)		MP high-2 (MP2)		Totals
	HR+	HR-	HR+	HR-	
HER2+	15.1%	4.7%	2.9%	5.6%	28.3
HER2-	26.4%	6.1%	9.6%	29.6%	71.7
Totals	41.5%	10.8%	12.5%	35.2%	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.
- Paclitaxel + Ganetespib (TG) assigned to HER2- patients
- We report results of TG evaluated in the 3 HER2- subsets (HER2-, HER2-/HR+, HER2-/HR-).

Enrollment/Disposition for TG vs. Control (T)

Figure 2: CONSORT



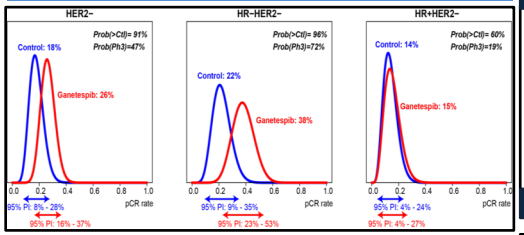
* Includes all patients assigned to HER2- control arm since the beginning of the I-SPY 2 standing trial until Ganetespib exited the trial (Oct 2015)
** Assignment to Ganetespib was open (Oct 2014)

Results: Efficacy

Figure 3: Bayesian pCR Probability Distributions

Arm	Estimated pCR Rate (95% PI)	Prob (>Ctrl)	Prob (Ph3)
HER2-			
Control (n=140)	0.18 (0.08 – 0.28)		
Ganetespib (n=93)	0.26 (0.16 – 0.37)	**0.91**	**0.47**
HR-HER2-			
Control	0.22 (0.09 – 0.35)		
Ganetespib	0.38 (0.23 – 0.53)	**0.96**	**0.72**
HR+HER2-			
Control	0.14 (0.04 – 0.24)		
Ganetespib	0.15 (0.04 – 0.27)	**0.60**	**0.19**

Figure 4: pCR Probability Distribution



Legend:
- Estimated (mean) pCR rates are included on curve labels
- 95% PI: 95% Bayesian Probability Interval
- Probability (>Ctrl): Probability of TG->AC showing superiority to control (T->AC)
- Probability (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 2 : Adverse Events

Non-baseline AE G3-5 experienced by ≥5% of patients in the ganetespib arm

	Ganetespib	Control
Number of patients with available AE data	91	127
Neutrophil count decreased	19 (21%)	10 (8%)
White blood cell decreased	9 (10%)	5 (4%)
Diarrhea	6 (7%)	1 (1%)
Peripheral sensory neuropathy	6 (7%)	2 (2%)
ALT increased	4 (4%)	1 (1%)

Non-baseline AE of interest (any grade)

	Ganetespib	Control
Diarrhea	71 (78%)	51 (40%)
ALT increased	10 (11%)	11 (9%)
AST increased	10 (11%)	9 (7%)
EKG QT corrected interval prolonged	2 (2%)	0 (0%)

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 Paclitaxel + Ganetespib (TG) in the setting of HER2- neoadjuvant breast cancer.
- **TG combination was well tolerated.**
- **TG -> AC did not meet the graduation threshold in any of the 3 HER2- signatures (HER2-, HR-/HER2- or HR+/HER2-).**
- **TG did demonstrate activity in the HR-/HER2- signature. Qualifying biomarker analyses are underway to determine if there are clues for how to improve the targeting or combinatorial impact of this agent.**

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