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

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

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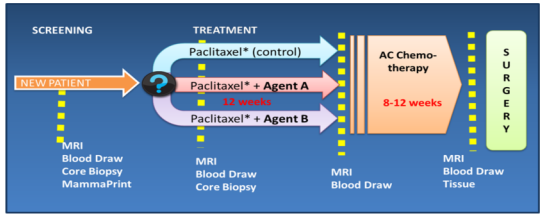
Background and Rationale

- The type I insulin-like growth factor receptor (IGF1R) has been implicated in breast cancer growth, survival, and motility
- IGF1R inhibitors disrupt growth hormone endocrine feedback. Elevation in GH results in increased free fatty acid hepatic output with subsequent insulin resistance and subsequent hyperinsulinemia and hyperglycemia (Haluska, et al. Clin Cancer Res 13:5834 2007 PMID: 17908976).
- The biguanide metformin reduces insulin resistance by decreasing hepatic glucose output and increasing insulin sensitivity at target organs.
- Metformin has been associated with improved pathological complete responses in patients with type 2 diabetes mellitus receiving neoadjuvant chemotherapy for breast cancer (Jiralerspong, et al. J Clin Oncol 27:3297 2009 PMID: 19487376).
- Ganitumab, a human monoclonal antibody directed against IGF1R disrupts signaling through this receptor.
- Ganitumab in combination with metformin may reduce the insulin resistance seen in previous trials.

Methods

- **Eligibility:** Women with invasive breast cancer ≥2.5 cm on exam or ≥2 cm on imaging
- **Trial**: adaptive randomization to 12 weekly paclitaxel +/- exp agent → AC x 4 (FIG. 1)
- **Stratification:** 3 subsets (Table 1) based on hormone-receptor and HER2 status. HER2-positive patients were not eligible to receive ganitumab/metformin.
- **Primary endpoint:** pCR (no residual invasive disease in breast or nodes)
- **Evaluable patients**: those who received any taxane +/- investigational therapy. Patients who progressed, changed to non-protocol therapy or left the treating institution were evaluable and counted as not having pCR.
- **Non-Evaluable patients:** Patients who withdrew consent prior to surgery;
- **Dosing:**
  - ganitumab (12mg/kg iv q 2 weeks)
  - metformin (850mg po BID)
  - weekly paclitaxel (80mg/m2 weekly x 12)
- **Graduation by signature** is based on Bayesian predictive probability >85% for success in a 2-arm, N=300 Phase 3 randomized 1:1 trial with pCR endpoint. Futility stopping is based on <10% probability of success

Figure 1: I-SPY2 Study Schema



Results

Figure 2: Patient Enrollment

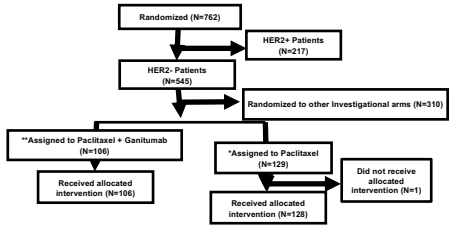


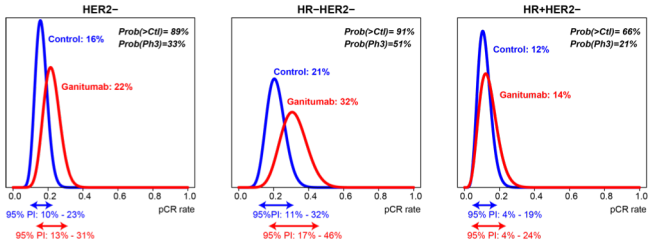
Table 1: Biomarker Distribution During Enrollment

Enrollment through Feb 2015	MP high-1 (MP1)		MP high-2 (MP2)	
	HR+	HR-	HR+	HR-
HER2+	15%	5%	3%	5%
HER2-	27%	7%	9%	29%

Table 2: Efficacy Results

Arm	Estimated pCR Rate (95% PI)	Prob(>Ctrl)	Prob(Ph3)
HER2-			
Control (n=128)	0.16 (0.10 – 0.23)		
Ganitumab/Metformin (n=106)	0.22 (0.13 – 0.31)	**0.89**	**0.33**
HR-HER2-			
Control	0.21 (0.11 – 0.32)		
Ganitumab/Metformin	0.32 (0.17 – 0.46)	**0.91**	**0.51**
HR+HER2-			
Control	0.12 (0.04 – 0.19)		
Ganitumab/Metformin	0.14 (0.04 – 0.24)	**0.66**	**0.21**

Figure 3: Bayesian pCR Probability Distributions



Conclusions

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

For more information visit: ispy2trial.org