Characterizing the HER2-Immune/DNA repair (DRD-) response predictive breast cancer subtype: the hunt for new protein targets in a high-needs population with low response to all I-SPY2 agents

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1. Background
- Previously we leveraged the I-SPY1 trial to create treatment response predictive subtypes (RPS) incorporating tumor biology beyond clinical HER2 status, to better predict drug responses in an expanded treatment landscape that includes platinum agents, dual HER2-targeting regimens and immunotherapy [1].
- Best performing schemas incorporate immune, DRD and HER2/Luminal phenotypes, and treatment allocation based on these schemas increase the overall pCR rate up to 56% from 51% using HER2-targeted treatment selection alone.
- An RPS schema has been selected for prospective evaluation in I-SPY2.

2. THE PATIENTS: I-SPY 2 TRIAL: Standing Platform

3. DATA/METHODS: patients and comparisons
- SET: I-SPY 2 patients from 15 arms of the trial were considered for this analysis.
- All have gene expression, pCR and RPS class assignments; patients have baseline free serum (OPSS) data.
- 756 have reverse phase protein array (RPPA) data from laser micro-dissected breast tumor epithelium.
- These data - known collectively as the I-SPY1-2 RPPA/RPPA Data Resource - were recently made public on NCBI Gene Expression Omnibus (GEO: GSE59185).

4. RESULTS: Characterization of HER2-Immune/DRD- breast cancers

4.1 HER2-Immune-/DRD- subset: prevalence, response and survival
- Of these, 8.3% (17/205) CR achieved pCR across arms.
- Non-responding HER2-clients had worse outcomes than responders (>75% vs <45% DRP at 5 years).

4.2 Proteins characterizing HER+Her2-DRD+ tumors
- 60/139 proteins and phosphoproteins differed significantly between HER+Hr2-DRD+ and HER+Hr2-DRD- tumors (Fig. 2, top row).

4.3 Proteins characterizing TH+Her2-DRD- tumors
- Only 31/139 proteins and phosphoproteins differed significantly between TH+Hr2-DRD- and other TN (Fig. 2, bottom row). These were all immune, with lower expression in TH+Immune-DRD.

5. CONCLUSION
- HH+HER2 and TH+HER2 patients who are Immune-Low and DRD-Low have very low pCR rates to all I-SPY2 agents including standard chemotherapy, platinum, and immunotherapy.
- Senolytics (possibly targeting Cxcl5 D1, anti-HER2/207 agents, or AR modulators may overcome resistance in HH+HER2-Immune-DRD- patients. Irrelevant activation beyond pCDP/CDT is suggested for TH+Immune-DRD patients with low response to all I-SPY2 agents. Characterizing HER2/Immune/DRD repair (DRD) tumors, provides a golden opportunity to hunt for new protein targets that may benefit patients.