1. Background
The explosion in new treatment options targeting immune checkpoints, HER signaling, DNA repair deficiency, AKT, and other pathways calls for updated breast cancer subtypes beyond HR and HER2 status to predict which patients will respond to which treatments.

Here we leverage the I-SPY 2 TRIAL biomarker program over the past 8 years across 10 treatment arms to evaluate a minimal set of biomarkers that may improve response prediction in a modern treatment context, and to investigate which new patient phenotypes are identified by these response-predictive biomarkers.

2. THE PATIENTS: I-SPY 2 TRIAL Standing Platform
- Phase II, adaptively-randomized neoadjuvant trial
- Shared control arm
- Standardized chemotherapy
- Simultaneous experimental arms
- Up to 1
- Primary endpoint: pathologic complete response (pCR)
- No residual invasive cancer in breast or axilla
- Match therapies with most responsive breast cancer subtypes
- Deemed: HR+, HER2- and HR-/HER2+ subtypes
- Agnostic/combination "radar" for efficacy - matching with predictive probability of success in a subsequent trial phylogenetic/carcinogenetic
- Biomarker component: evaluate biomarkers associated with mechanism of action of each agent, along with the pre-defined subtypes

3. DATA/METHODS: Predictive expression biomarkers across 10 arms

Data from 440 patients were considered in this analysis. Treatments included pertuzumab or venetoclax as a single agent or in combination with investigational agents, neoadjuvant HER2+ patient (NCI) randomization (MP1, ganitumab, pertuzumab, AMG/Theranostics 5/1) randomization (I-SPY 2 trial).

- Predictive mechanism of action biomarkers
- Immune therapy
- PARPi (venetoclax), AKT
- Multiple HER2-targeted agents
- Other

4. RESULTS: Patient subgroups with predicted differential response to I-SPY 2 agents

A. Unsupervised clustering of 24 continuous biomarkers

- Our initial set of 24 predictive biomarkers reflects DNA repair deficiency (p53, immune activation (p1), ER signaling (p2), HER2 signaling (p3), proliferation (p4), phospho-activation of AKT/mTOR (p5), and ANG/TIE2 (p6) pathway, among others.
- Biomarkers reflecting similar biology are combined and cluster together

B. Reduced to 5 predictive biological signals

- We make use of this correlation structure to reduce the dimensionality of the biomarker set to five predictive signals: proliferation, DNA repair deficiency (ORC), immune-activated (immune, luminal ER-b), and HER2-activated.
- These biomarkers, when dichotomized, identify patient groups with differential predicted sensitivities to I-SPY 2 agents and are present at different proportions within receptor subtypes.

5. CONCLUSION
Molecular phenotypes reflecting proliferation, immune engagement, HER2 activation, luminal ER signaling, and DNA repair deficiency may provide a roadmap to guide treatment selection for patients in clinical trials. In all, these biomarkers predict sensitivity to one or more I-SPY 2 Investigational agents for 75% of the ~1000 patients.

Advocate perspective: Providing the right drug for the right patient is not only a hallmark of the I-SPY 2 TRIAL, but also an advocate’s perspective, which is about side effects and varied from drug to drug and from patient to patient. Understanding the drug biomarker data makes it easier for advocates to put the right patients on the right drugs, which can have major implications for all patients. Understanding the implications of predictive biomarkers can give patients an important tool for treatment decision making.

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