1. Hypothesis: We hypothesized that genes/signatures in the ANG/TIE signaling axis specifically predict response to angiogenesis (ANG1/2) inhibition, and that hypoxic tumors with a fragile blood supply are especially vulnerable to drugs in this class.

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

- Phase 3, adaptively-randomized neoadjuvant trial
- Standard control arm
- Simultaneous experimental arms
- Up to 5 years
- Primary endpoint: pathologic complete response (pCR)

- Biomarkers tested: 11 genes: TIE2, ANGPT1/2, AGT/MMP2, VEGFA, ICAM1, PLAG1, and MMP2, and 2 signatures: hypoxia (PRC134320) and angiogenesis (G0/031612).

3. DATA: Gene expression microarrays

4. METHODS: Qualifying Biomarker Evaluation (QBE)

5. RESULTS: Association between ANG/TIE pathway genes and hypoxia/angiogenesis signatures, and response to the ANG1/2 inhibitor trebananib (AMG86)

A. Unsupervised clustering heatmap

B. Association with response, by arm and receptor subset

C. Exploratory analysis: Immune signaling, not ANG1/2 pathway or hypoxia, predicts response in the TN subset

6. CONCLUSION

Following our pre-specified analysis, ANGPT1 associates with differential response to trebananib in I-SPY 2. In addition, ICAM1 and PLAG1 associate with pCR in the Hh/HhER2 subset; and, in exploratory analysis, immune signaling predicts response in the TN subset. These biomarkers may merit further evaluation in future trials.