Molecular subtypes of invasive lobular breast cancer in the I-SPY2 Trial

Zelos Zhu BS, Christina Yau PhD, Laura Van’t Veer PhD, Laura J Esserman MD MBA, Rita A Mukhtar MD on behalf of the I-2 SPY 2 TRIAL Consortium

BACKGROUND

- Invasive lobular carcinoma (ILC) of the breast has distinct histological and molecular features compared to invasive ductal carcinoma (IDC), including absence of the adhesion protein E-cadherin.
- A recent analysis from The Cancer Genome Atlas (Ciriello et al) identified three distinct molecular subtypes within ILC based on gene expression:
  - REACTIVE-LIKE
  - IMMUNE-RELATED
  - PROLIFERATIVE
- In this study, we applied this 60-gene classifier to a locally advanced cohort of ILC and mixed ILC/IDC cases screened for the I-SPY 2 trial and evaluated associations with response to treatment.
- We evaluated concordance with signatures derived from I-SPY 2 APTIVE DESIGN

METHODS

- Clinical Eligibility Criteria: Stage II or III, or T4, any N, M0, including clinical or pathologic inflammatory cancer or Regional Stage IV, where supracapsular lymph nodes are the only metastasis
- Molecular Eligibility Criteria: Triple Negative, or HER2+, or MammaPrint High risk HR-HR2+.
- HR+HER2+ MammaPrint: Low risk patients ineligible for I-SPY 2 randomized is invited to join a low risk registry.
- In an exploratory analysis, we used consensus clustering based on the 1000 most varying genes within the HR+HER2+ ILC cases to generate new unsupervised groupings, and assessed the concordance with the TCGA reactive-like, immune-related and proliferative subtype assignments.
- Upon applying the TCGA 60-gene classifier, the distribution of ILC subtypes was as follows: 33 (25%) were classified as reactive-like, 50 (38%) were immune-related, and 48 (37%) were proliferative.
- Among the 80 I-SPY 2 cases, the overall pathologic complete response rate was low (16.3%) but equivalent to the overall HR+HER2+ I-SPY2 population (16.5%). This did not differ across groups defined by the TCGA ILC subtypes (p=0.79).

RESULTS

- 132 ILC and mixed ILC/IDC tumors from I-SPY 2 and Low Risk Registry with pre-treatment Agilent microarrays were available for analysis.
- We used the Classification to Nearest Centroid technique to assign TCGA subtypes to our cohort.
- We assessed association between TCGA subtype, clinical covariates and response to therapy using a chi-squared test.
- BACKGROUND

- The right drug, the right patient, the right time

CONCLUSIONS

- We found associations between TCGA molecular subtypes and HR/HER2 status in ILC patients from the ISPY2 Trial.
- There was no association between TCGA subtype and pCR.
- The TCGA subtypes were not the best classifiers for ILC cases in ISPY, possibly reflecting underlying differences within a locally advanced high-risk cohort compared to the overall lower stage TCGA ILC cases.

- These findings suggest that considerable molecular heterogeneity exists in lobular cancers, which merits further investigation.

- Future work will include pathway analysis of CC subtypes and comparison to signatures derived other groups (Michael et al).

ACKNOWLEDGEMENTS:

- I-SPY 2 is supported as a cooperative clinical trial, with study sponsorships from Daiichi Sankyo (2011-2013) and Genentech (2014-present).
- I-SPY 2 has received the gracious support of: the San Antonio Breast Cancer Symposium (SABCS), the Susan G. Komen Foundation, the Breast Cancer Research Foundation, and the Kay Hulsman Foundation.
- I-SPY 2 has received the gracious support of: the San Antonio Breast Cancer Symposium (SABCS), the Susan G. Komen Foundation, the Breast Cancer Research Foundation, and the Kay Hulsman Foundation.
- I-SPY 2 has received the gracious support of: the San Antonio Breast Cancer Symposium (SABCS), the Susan G. Komen Foundation, the Breast Cancer Research Foundation, and the Kay Hulsman Foundation.
- I-SPY 2 has received the gracious support of: the San Antonio Breast Cancer Symposium (SABCS), the Susan G. Komen Foundation, the Breast Cancer Research Foundation, and the Kay Hulsman Foundation.

- Appendices and additional information are available at ispy2trial.org.

The right drug, the right patient, the right time... now.