Genotypic characterization of phenotypically defined triple-negative breast cancer.

Author(s): J. A. Sparano, L. J. Goldstein, B. H. Childs, S. Shak, S. Badve, F. L. Baehner, N. E. Davidson, G. W. Sledge, R. Gray, North American Breast Cancer Intergroup; Albert Einstein Cancer Center, Bronx, NY; Fox Chase Cancer Center, Philadelphia, PA; sanofi-aventis, Bridgewater, NJ; Genomic Health, Inc., Redwood City, CA; Indiana University School of Medicine, Indianapolis, IN; University of Pittsburgh Cancer Institute, Pittsburgh, PA; Eastern Cooperative Oncology Group, Boston, MA

Background: Triple negative breast cancer (TNBC) is associated with a higher risk of recurrence and earlier recurrences than other breast cancer phenotypes. We evaluated the genotypic features of TNBC compared with hormone receptor (HR)-positive disease, and also evaluated genotypic features associated with recurrence.

Methods: RNA extracted from tumor samples obtained from 764 patients with stage I-III breast cancer was analyzed by RT-PCR for 371 genes. All patients received adjuvant chemotherapy (plus hormonal therapy in HR-positive disease) in trial E2197; HR and HER2 expression were evaluated by immunohistochemistry (IHC) in a central lab [J Clin Oncol 26:2473-2481]. An unsupervised clustering analysis was performed in all samples (N=764). Cox proportional hazard models were used to identify differences in gene expression in TNBC versus HR-positive disease, and with recurrence in phenotypically defined (by IHC) TNBC (N=246) and HR-positive (N=465) disease.

Results: Unsupervised analysis revealed two major clusters that differed with regard to HR expression by IHC. Supervised analysis comparing the TNBC vs. HR-positive phenotypes revealed 269 genes (73%) with significantly different expression (p<0.0001). The top 10% of genes exhibiting higher expression the TN group included genes associated with nucleosome assembly (CENPA), kinase activity (TTK), cell division (KIFC2), proliferation (BUB1), intracellular signaling (DEPDC1), DNA repair (CHK1), anti-apoptosis (GSTP1), and transcriptional regulation (MYBL2). There was increased expression of genes for which inhibitors are currently being evaluated, including AURKB and CHK1 in TNBC, and IGF1R and RhoC in HR-positive disease. Although GRB7 expression was significantly lower in the TN group, increased expression of GRB7 was the only gene in the TNBC group (but not the HR-positive group) associated with increased recurrence (p=0.04), and did not correlate with nodal status, tumor size, or grade.

Conclusions: We genotypically characterized breast cancers that have also undergone rigorous phenotypic characterization. There were significant differences in gene expression between the TN and HR-positive groups, including genes for which targeted agents are currently being evaluated in the clinic.