

Abstract: 500

Genotypic characterization of phenotypically defined triple-negative breast cancer.

Author(s): J. A. Sparano, L. J. Goldestin, 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 in 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.