

Abstract #25

Title: *GRB7*-dependent pathways are potential therapeutic targets in triple-negative breast cancer.

Sparano JA, Gray R, Goldstein LJ, Childs BH, Bugarini R, Rowley S, Baker J, Shak S, Badve S, Baehner FL, Perez EA, Shulman LN, Martino S, Sledge Jr. GW, Davidson NE Eastern Cooperative Oncology Group, Brookline, MA; Genomic Health, Inc., Redwood City, CA; Sanofi-aventis, Bridgewater, NJ; North Central Cancer Treatment Group, Rochester, MN; Cancer and Leukemia Group B, Chicago, IL; Southwest Oncology Group, Ann Arbor, MI

Background: Breast cancer lacking expression of the estrogen and progesterone receptor and overexpression of *HER2/neu* (ie, "triple-negative" disease) accounts for about 10-15% of all breast cancer and is characterized by a higher risk of recurrence, early recurrence, resistance to cytotoxic therapy, and lack of any specific targeted therapy.

Methods: We extracted RNA from primary tumor samples of 246 patients with stage I-III triple-negative breast cancer (confirmed in a central lab) treated with 4 cycles of adjuvant doxorubicin (60 mg/m²) plus cyclophosphamide (600 mg/m²) or docetaxel (60 mg/m²) who were enrolled on trial E2197, and correlated RNA expression (by quantitative RT-PCR using a panel of 371 rationally selected genes) with recurrence. There was no difference in recurrence between the two treatment arms in the entire study population, nor in the 246 patients in this analysis (of whom 59 recurred) after a median followup of 76 months.

Results: Higher expression of *GRB7* was the only gene significantly associated with an increased risk of recurrence (nominal p value 0.0000853, Korn's adjusted p value controlling false discovery at 10% (KP10) p=0.0359), but did not correlate with any clinicopathologic features except age (low expression associated with age > 65 years, p=0.03). In a Cox proportional hazards model adjusted for age, nodal status, tumor size, and grade, higher *GRB7* expression was associated with an increased risk of recurrence when evaluated as a continuous variable (hazard ratio 3.41; p = 0.001) or as a dichotomous variable (hazard ratio 2.24 above vs. below median; p=0.006). The 5-year recurrence rates were 10.5% (95% C.I.7.8%, 14.1%) in the low and 20.4% (95% C.I. 16.5%, 25.0%) in the high *GRB7* groups. There were only six genes whose expression correlated with *GRB7* (r > 0.4), including *ERBB2* (r=0.70), *DDR1* (discoidin domain receptor tyrosine kinase 1; r=0.53), *KRT19* (keratin 19; r=0.49), *ERBB3* (r=0.48), *GPR56* (G protein-coupled receptor 56; r=0.48) and *PHB* (prohibitin; r=0.42).

Conclusions: *GRB7* is a calmodulin-binding protein which has an SH2 (Src homology 2) domain that binds to phosphorylated tyrosine residues and other specific protein targets, and which plays a critical role in signaling (EGFR, *HER2*), motility (ephrins), migration (focal adhesion kinase), and cell-matrix/cell-cell interactions (integrins). Higher *GRB7* RNA expression is associated with a significantly higher risk of recurrence in triple-negative breast cancer, indicating that *GRB7* or *GRB7*-dependent pathways are potential therapeutic targets in triple-negative disease.