# Profiling Triple-Negative Breast Cancers After Neoadjuvant Chemotherapy Identifies Targetable Genetic Alterations

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Neoadjuvant chemotherapy (NACT) is now widely used in the management of locally advanced breast cancer and in patients with relatively large tumors who are interested in breast conservation. Critical studies have highlighted differences in pathologic complete response (pCR) rates between breast cancer subtypes, with triple-negative breast cancer (TNBC) having a higher pCR rate compared with the other subtypes [Carey LA et al. *Clin Cancer Res* 2007]. Patients who do not have a complete pCR typically have poorer outcomes compared with patients with a pCR [Rastogi P et al. *J Clin Oncol* 2008].

Justin M. Balko, PharmD, PhD, Vanderbilt-Ingram Cancer Center, Nashville, Tennessee, USA, presented molecular profiling data on residual TNBCs after NACT.

Dr. Balko and colleagues hypothesized that profiling residual TNBCs would identify targetable lesions in the component of the tumor that was resistant to chemotherapy, and these findings may reflect the phenotype of potential micrometastases. The study included tumor samples from 102 patients (median age 48 years) who had clinically defined TNBC with residual disease following NACT. Of the 89 evaluable post-NACT-treated tumors, 64% were basal-like, 19% were human epidermal growth factor 2 (HER2)-enriched, 6% were luminal A, 6% were luminal B, and 5% were normal-like. The most common tumor stage was IIIb (69%), and 33% of the patients were node negative. Half of the patients were premenopausal and 48% were postmenopausal. Immunohistochemistry for Ki67, estrogen receptor, progesterone receptor, HER2, and androgen receptor was conducted on 112 of the samples. Nanostring digital expression analysis of 450 genes was performed in 89 of the samples, and next-generation sequencing (NGS) of 182 oncogenes and tumor suppressors was completed on 81 of the samples.

A diverse range of genetic aberrations were found in the majority of residual tumors following NACT, including alterations in the PI3K/mTOR pathway (38%), DNA repair genes (12%), cell cycle genes (38%), Ras/MAPK pathway (12%), and growth factor receptors (15%). The most common findings were mutations in TP53 (89%) and amplifications of MCL1 and MYC. The antiapoptosis gene MCL1 was amplified in 56% of the tumors, and MYC was amplified in 33%. An interaction between a high MEK activation score and MYC amplification predicted poor recurrence-free survival (RFS).

JAK2 amplifications were identified in 11% (8/72) of the patients. Both RFS (p=0.005) and overall survival (OS; p=0.002) were significantly decreased in these patients. High IL6 mRNA levels correlated with JAK2 amplification (p=0.008). In contrast, high Ki67 scores after NACT in TNBC residual disease did not predict RFS (p=0.42) or OS (p=0.84). Growth factor receptor amplifications were identified in EGFR, PDGFRA, PDGFRB, KIT, MET, IGF1R, FGFR1, and FGFR2 genes. ERBB2 amplifications were found in 7 patients, and these were confirmed by fluorescence in situ hybridization in both the pre- and post-treatment tissue, suggesting that NGS could assist in the identification of ERBB2-overexpressing tumors misclassified at diagnosis [Balko JM et al. *Cancer Res* 2012].

According to Dr. Balko, "Efforts to determine whether lesions present in the residual disease mirror those in the recurrence and whether they are selected during neoadjuvant treatment are underway." The diversity of lesions in residual TNBC after NACT highlights the need for broad molecular approaches to better inform personalized therapy in these patients [Balko JM et al. *Cancer Res* 2012].

Peer-Reviewed Highlights from

**35th Annual San Antonio Breast Cancer Symposium**

**December 4-8, 2012**
**San Antonio, Texas, USA**