# Heterogeneity, Genome Complexity of TNBC Complicate Therapy

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Triple-negative breast cancer (TNBC) lacks estrogen receptors (ER), progesterone receptors, and amplification of human epidermal growth factor receptor 2 (HER2) [Sikov WM. Breast Cancer Symposium. 2014]. TNBC accounts for 15% to 20% of breast cancer cases diagnosed in the United States alone.

Nicholas Turner, PhD, Institute of Cancer Research, London, United Kingdom, discussed the heterogeneity in TNBC and the challenges it presents for effective treatment.

From a global level, BC can be divided into 2 specific subtypes called BRCA luminal and BRCA basal-like. Basal-like BCs comprise the majority of TNBC subtypes (approximately 80%), while luminal-androgen receptor (AR) BC is clearly distinct [Weigelt B et al. *J Pathol.* 2010]. Luminal-AR TNBC, although ER- and progesterone-receptor-negative, has high expression of hormonal driven pathways [Lehmann BD et al. *J Clin Invest.* 2011]. They express the AR, and in vitro, they are sensitive to the AR antagonist bicalutamide. In a phase 2 trial of 28 patients with AR-positive, ER-negative metastatic BC, 19% had stable disease > 6 months when treated with bicalutamide [Gucalp A et al. *Clin Cancer Res.* 2013], showing proof of principle that AR is a potential target in this group of cancers, said Prof Turner.

The other key feature of luminal-AR TNBC is enrichment for mutations in phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) [Lehmann BD et al. *Breast Cancer Res.* 2014]. PIK3CA mutation correlates in TNBC cell lines with activation of the pathway, and these cell lines are sensitive to PIK3 inhibitors. Luminal-AR TNBC has several similarities to HER2-amplified BC (eg, ER-negative, PIK3CA mutation, histologic grade 2/3, and apocrine features), and both cell lines were found to be sensitive to cyclin D kinase 4/6 inhibition [Finn RS et al. *Breast Cancer Res.* 2009].

A mesenchymal subtype of TNBC is characterized by expression of genes associated with epithelial-to-mesenchymal transition [Burstein MD et al. *Clin Can Res.* 2014]. Another subtype, mesenchymal stem-like TNBC, is enriched for stem cell-like phenotypes [Hennessy BT et al. *Cancer Res.* 2009], frequently has an immune infiltrate, has a lower proliferative rate than basal-like cancers, and has intermediate levels of PIK3CA mutation [Lehmann BD et al. *J Clin Invest.* 2011]. High lymphocytic infiltration is a subset of basal-like and mesenchymal stem-like TNBC; it represents a subtype of TNBC that has an excellent prognosis [Loi S et al. *J Clin Oncol.* 2013].

Approximately 60% of patients with TNBC express epidermal growth factor receptor; they demonstrated some evidence of sensitivity to cetuximab but only at a low level that is insufficient to drive future clinical development [Baselga J et al. *J Clin Oncol.* 2013].

TNBC is complicated by intratumoral heterogeneity. TNBCs have been shown to vary widely in their clonal frequencies and display a complete spectrum of mutational and clonal evolution, leading to intrinsic resistance to targeted therapy [Shah SP et al. *Nature.* 2012].

Andrew Tutt, PhD, Kings College, London, United Kingdom, discussed the genome complexity of TNBC. BRCA1/2 are involved in the repair of DNA damage; each plays an important role in homologous recombination (HR). Sporadic TNBC and BRCA1-associated breast cancer share features suggesting a common pathogenesis. TNBC also has significant subpopulations with defective DNA repair; BRCA1/2 is mutated in about 15% of patients with TNBC [Sharma P et al. *Breast Cancer Res Treat.* 2014], and HR deficiency has been implicated in sporadic TNBC. When HR fails, other DNA repair processes take over, driving a mutator phenotype. Defects in HR repair can engender sensitivity to platinum therapy and poly (ADP-ribose) polymerase (PARP).

BRCA1-deficient cells are especially vulnerable to the interstrand cross-linking agents cisplatin and mitomycin [Silver DP et al. *J Clin Oncol.* 2010]. High rates of pathologic response were achieved with neoadjuvant platinum therapy in BRCA1 mutation carriers.

A genomic scar—a genomic aberration with a known origin—are reporters of HR deficiency and drug response [Watkins JA et al. *Breast Cancer Res.* 2014]. Tracing scars in a patient's tumor

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genome to particular drivers of the mutator phenotype that caused them may enable treatments that target these origins. A tumor with an allelic balance phenotype extending to the telomere had higher sensitivity to drugs that induce DNA crosslinks (eg, platinums) [Birkbak NJ et al. *Cancer Discov.* 2012].

An HR deficiency (HRD) score is a measure of the genomic HRD footprint in a tumor caused by defects in the HR pathway; it is derived by counting the number of regions with loss of heterozygosity of intermediate size in the tumor genome [Telli ML et al. SABCS 2012; (abstr PD09-04)]. The HRD score was found to be significantly correlated with pathologic response to platinum-based chemotherapy in early-stage TNBC ($P = .0003$) and BRCA1/2 mutation-associated BC ($P = .0006$).

PARP inhibitors appear promising as treatment for BRCA-associated cancers and sporadic TNBC. Most studies of PARP inhibition thus far have focused on germline BRCA-mutated cancer. Combining HR-targeting chemotherapy with PARP inhibition attempts to inhibit the DNA damage caused by platinum therapy, increasing cytotoxicity. However, in one trial, adding low-dose rucaparib, a PARP inhibitor, did not improve 1-year disease-free survival (DFS) or impact the toxicity of cisplatin [Dwadasi S et al. ASCO 2014 (abstr 1019)].

Eric P. Winer, MD, Dana-Farber Cancer Institute, Boston, Massachusetts, USA, discussed current and new approaches to adjuvant and neoadjuvant therapy. Combination chemotherapy remains effective adjuvant therapy for TNBC. For stage II/III TNBC, standard adjuvant chemotherapy is considered to be an anthracycline/taxane regimen, either adriamycin, cyclophosphamide, and paclitaxel (dose-dense weekly); docetaxel, adriamycin, and cyclophosphamide; or 5-fluorouracil, epirubicin, and cyclophosphamide therapy plus docetaxel.

Neoadjuvant therapy for TNBC can successfully downstage disease to facilitate less radical surgery while improving prognosis, although overall prognosis remains inferior to that of other breast cancer subtypes, said Dr Winer. As neoadjuvant therapy, a pathologic complete response (pCR) was achieved in 45% of patients with TNBC treated with 5-fluorouracil, doxorubicin, and cyclophosphamide [Rouzier R et al. *Clin Cancer Res.* 2005] and 36% with adriamycin, cyclophosphamide, and paclitaxel [Carey LA et al. *Clin Cancer Res.* 2007], and 5-year distant DFS was >90% in those who achieved pCR. Failure to achieve pCR is associated with poorer event-free and overall survival (OS) in TNBC.

In 2 trials, carboplatin improved the rate of pCR [von Minckwitz G et al. *Lancet Oncology.* 2014; Sikov WM et al. *J Clin Oncol.* 2014]; however, a definitive study is needed showing improvement in DFS or OS before carboplatin can be considered a new standard.