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First International TNBC Conference Meeting Report

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Abstract

Recently, Georgia State University's Centennial Hall was the premier location for the 2017 International Conference on Triple Negative Breast Cancer (TNBC): Illuminating Actionable Biology, which was held from Sept. 18–20, 2017 in Atlanta, USA. The conference featured a stellar line-up of domestic and international speakers and diverse participants including TNBC survivors, luminaries in breast cancer research, medical students and fellows, clinicians, translational researchers, epidemiologists, biostatisticians, bioinformaticians and representatives from the industry. This report distills the burning questions that spiked the event and summarizes key themes, findings, unique opportunities and future directions that emerged from this confluence of thought leaders.

Why Triple Negative Breast Cancer (TNBC)?

“A problem well put is half solved”-John Dewey.

Triple negative breast cancers (TNBCs) test negative for the three commonly assessed and therapeutically targetable breast cancer biomarkers: estrogen receptor (ER), progesterone

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receptor and amplification of Her2/neu. TNBC is characterized by a high propensity to relapse/metastasize within five years of diagnosis and is more common among women of African ancestry, thus contributing to racial/ethnic breast cancer disparities [1]. As TNBC remains defined by what it lacks, there is an unmet need to identify actionable targets for TNBC, which has been left behind in the immense strides in precision medicine for breast cancer in the past decades. This monumental task requires the attention of the best in the field, so Drs. Ritu Aneja (Conference Chair from Georgia State University, Atlanta, USA), Emad Rakha (Co-Chair from University of Nottingham, UK) and Mylin Torres (Co-Chair from Emory University, Atlanta, USA) thought the time was ripe to organize the first-ever international conference focused on burning questions pertinent to TNBC, the key themes, discoveries, and emerging ideas of which are summarized below.

A disease defined by negatives is not a single disease: Manifestations, biology and heterogeneity of TNBC

Classical pathology has always believed that a close look at tumor morphology is the first step towards understanding the biology underpinning the disease. The purely operational term “TNBC” became embedded into clinical practice because of the simplicity of distinguishing this class of BCs based on immunohistochemical determination of just three biomarkers. However, this “negative definition” means that TNBC instead represents a constellation of molecularly, morphologically, and behaviorally diverse entities. TNBC is often viewed as a clinically aggressive subtype, with an earlier age of presentation and requiring adjuvant chemotherapy to improve survival [1]. This view may be appropriate for the most common conventional forms of TNBCs which are high-grade carcinomas with complex genomes, frequent TP53 mutation, high levels of genetic instability, extensive inter- and intratumor heterogeneity, and increased risk of early metastasis and death from breast cancer. However, TNBC is very heterogeneous and also includes low-grade forms driven by distinct sets of genetic alterations [2]. While some inroads have been made in identifying potential precursor lesions of certain types of low-grade TNBCs, the precursor lesions for most conventional high-grade TNBCs are unknown.

Divide and Conquer: Parsing TNBCs to find ways to tailor treatments to each subgroup

TNBCs can be molecularly subtyped by various classification schemes, such as into LAR, basal-like 1 (BL1), basal-like 2, and mesenchymal (M) molecular subtypes, which reflect different gene expression profiles [3]. Firstly, the LAR subtype typified by strong AR signaling and PIK3CA mutations. The BL1, subtype is characterized by high expression of cell cycle and DNA damage markers. The BL2 subtype is enriched in growth factors such as MET and EGFR. The M subtype prominently features trans-differentiation and growth factor signaling (upregulation of NOTCH, PDGFR, FGFR, TGFbeta). Importantly, while TNBCs of BL1, BL2, and LAR subtypes all have some level of lymphocytic infiltration, M TNBCs have very low/no tumor infiltrating lymphocytes at all, indicating a very different tumor microenvironment. These molecular subtypes show distinctive clinical behaviors including treatment responses: for example, BL1 responds best to NAC [3, 4]. By contrast,

M, LAR and BL2 show poorer responses to NAC. However, recent studies have found that LAR cell lines respond to AR antagonists, PI3K inhibitors, and CDK4/6 inhibitors [5, 6]. Regarding which TNBCs are likely to respond well to immunotherapy, those of the M subtype, which are an immune desert and also express very low levels of PD1/PDL1, are unlikely to respond to immunotherapy. Standard chemotherapeutics, platinum salts, and PARP inhibitors might be the most effective options currently available for BL1 patients. AR antagonists, PI3K and CDK4/6 inhibitors might be more effective for LAR TNBCs. FGFR and NOTCH gamma-secretase inhibitors might be promising for M subtype. Nonetheless, there are still no good therapeutic options for BL2 subtype patients, up to half of whom die within three years of diagnosis [4].

TNBCs are the most molecularly diverse breast cancer subtype, and it may be necessary to consider genetic heterogeneity of TNBCs and stromal components when stratifying TNBCs into clinically meaningful phenotypes for tailoring optimal treatments [7]. Basal-like or TNBCs are the most molecularly diverse (in terms of transcriptome, mutations, copy number variations) but have the lowest within-tumor transcriptional variance. By contrast, Luminal A breast cancers show the lowest inter-tumor diversity but highest intra-tumor transcriptional variance. Basal-like tumors that are resistant to multiple-agent chemotherapy exhibit higher transcriptional diversity compared with chemosensitive tumors. Comparison of whole exome sequences between patients with extensive residual disease and those with pCR has uncovered that mutations in AR/FoxA1 pathways are associated with sensitivity to ACT chemotherapy, and patients with mutations in these pathways had a ~90% pCR rate [8]. In non-NAC cohorts, patients with at least one mutation in either pathways have much better survival than those without. Furthermore, TNBCs with few clones but high mutational burden per clone have the highest pCR rate. A high mutational burden means a lot of neoantigens are being produced to elicit an immune response, and tumors with low numbers of clones elicit higher immune metagene expression. Thus, there is a dire need to integrate markers for mutational burden and immune metagene to derive most robust predictions of chemotherapy response.

Aggressive clinical behavior and poor prognosis of TNBCs can be at least partially be linked to the interaction between tumor cells and their microenvironment [9]. Factors playing a pivotal role in this interaction include tumor infiltrating lymphocytes (TILs), tumor associated macrophages, cancer associated fibroblasts and adipocytes as well as expression of genes implicated in the epithelial-mesenchymal transition (EMT). Elevated levels of peripheral and overall TILs in pre-treatment resection specimens are associated with more advanced Nottingham histologic grade but not lymph node status or lymphovascular invasion, and elevated peripheral TILs predict better overall and disease-free survival [10]. Higher TILs also serve as a biomarker for improved NAC response [11]. Interestingly, studies have shown that metastatic TNBCs at first relapse have fewer TILs than their matched primary tumors: in non-TNBCs, the composition of TILs in primary and metastatic lesions is very similar, but in TNBC, FOXP3+, CD3+, CD8+ and CD4+ TILs are diminished in metastatic lesions compared with their primaries [12]. High PDL1 expression is associated with better long-term breast cancer-specific survival, although not independent of lymphovascular invasion and TILs [13]. In metastatic breast cancer, anti-PD-1/PD-L1 monotherapy is associated with modest response rate, with the addition of chemotherapy

improving response rates [14]. Studies have also shown that high densities of FOXP3+ regulatory T cells independently predict better prognosis in TNBC [15]. Tumor associated macrophages, especially those in association with higher levels of cytokines as IL-6, portend poor prognosis [16]. Even though standardized methods for assessment are now available and many studies have shown a significant prognostic value for TILs assessment, St Gallen guideline (2017) still do not require that TILs be included in pathology report.

Novel therapeutic targets and treatments for TNBC

The AR appears to be a promising therapeutic target for TNBC. AR is a member of the steroid-hormone family of receptors, together with the estrogen, progesterone, and glucocorticoid receptors. Recently, it has become well recognized that AR-driven TNBC is an actionable subtype, based on clinical trials testing AR-targeted therapies in AR-driven TNBC such as bicalutamide, enzalutamide, abiraterone and seviteronel. For example, using a cutpoint of 10%, nuclear AR positivity is associated with response of TNBC to enzalutamide [17].

A variety of targeted therapies for metastatic TNBC (mTNBC) have emerged [18, 19]. Significant improvement in outcomes have been observed for mTNBC patients with germline BRCA mutations treated with the PARP inhibitor, olaparib, compared to standard chemotherapy. A Phase II study of the antibody-drug conjugate sacituzumab govitecan (IMMU-132) showed promising results for mTNBC patients who had received at least one prior line of treatment. The antibody moiety targets trans-membrane protein Trop-2, which is expressed in >80% of TNBCs, and is linked to topoisomerase I inhibitor SN-38. Glutaminase (encoded by the GLS gene) is highly overexpressed in TNBC cells that are thus sensitive to the glutaminase inhibitor CB839 [20]. A recent phase I trial, wherein heavily pre-treated TNBC patients (with metastatic or locally-advanced solid tumors) were treated with paclitaxel+CB839 found good response rates with CB839 alone and in combination with paclitaxel [21]. Restriction of methionine has been shown to up-regulate expression of TRAIL death receptors in TNBC cells [22].

Immune checkpoint inhibition has emerged as an effective treatment for a variety of malignancies. Since TNBCs show the most robust immune infiltrate among all breast cancer subtypes, and higher expression of PD-L1 is observed in TNBC compared to non-TNBC, so the rationale for immunotherapy is strongest for TNBC compared to other breast cancer subtypes. Clinical trials of immune checkpoint inhibitors Pembrolizumab (PD-1 inhibitor studied in TNBC and ER+), Atezolizumab (PD-L1 inhibitor studied in TNBC and ER+), and Avelumab (PD-L1 inhibitor studied in all forms of breast cancer) in advanced breast cancer have reported low response rates, although the durability of responses observed is impressive [23, 24]. While immune checkpoint inhibitors are generally safe and tolerable, increased (unexpected) immune-related toxicities have been observed in neoadjuvant setting.

None of the molecular classification/subtyping systems now available for TNBC are able to help decide therapy. However, they are important for defining more precisely patient groups for the next generation of adjuvant clinical trials for TNBC. Modular studies that use pCR as primary endpoint, but are extended into an adjuvant trial with long-term disease-free or

overall survival as endpoints, have so far failed to deliver perhaps because one is asking that a biomarker predict long-term clinical outcomes in addition to predicting effect of treatment (asking too much). Thus, neoadjuvant therapy may be better considered as a model for (a) an accelerated path for drug approval, (b) identifying patient subsets for therapy escalation, and (c) identifying patient subsets expected to have excellent DFS/OS for therapy de-escalation (and reduced toxicity) in the adjuvant setting.

Racial disparities and TNBC: Tumor biology, risk factors, healthcare delivery issues and proposed interventions

Breast cancer death rates have declined 23% in black women and 37% in white women since 1990, leading to a 42% higher mortality in black women compared with white women in the most recent time period [25]. Higher death rates among black women likely reflect a combination of factors, including differences in stage at diagnosis, obesity, comorbidities, tumor characteristics, potentially modifiable risk factors such as smoking, excess body weight, and alcohol intake, which account for ~40% cancer-related deaths [26]. In addition, higher death rates among black women may arise from poorer access and adherence to high-quality cancer treatment. The extent of racial disparities in mortality differ markedly by American state; for example, black women in Boston, MA have a lower risk of death than white women in many of the states, suggesting that it is not biology but perhaps quality of care or other non-biological factors primarily driving disparities in breast cancer mortality [27]. Thus, while in-depth studies looking at racial differences in inherent biology are vital, perhaps the most important question in health disparities research in the US should be, “How can we provide adequate and high-quality care to populations who so often do not receive it?”

Health equity is providing the opportunity for every individual to reach their optimal level of health by giving people what they need, when they need it, in the needed amount [28]. In the context of breast cancer, health equity might mean strategizing and systematizing prevention such that women are only offered the best options (algorithm), improving access to better screening/diagnostics and quality care, good grocery stores in low socioeconomic status neighborhoods, better pharmacy benefits in insurance plan, having a nearby mammography unit, having adequate transportation, or the opportunity to be involved in a clinical trial, or access to timely counseling, having both specialists and primary care physicians and all testing in one facility where the patient is viewed holistically, etc. To address inequities, it is necessary to embrace a systems approach and innovative programs that include research and community efforts. This challenge can only be met through education programs that prepare future health leaders and learners, research, and translation of discoveries into health equity, community engagement and participation, access, and good health policy that builds effective bridges between healthcare and health for all.

Differential access to and utilization of a complex variety of medical or non-medical resources across the cancer care continuum (including differences in access to and receipt of evidence-based cancer screening, diagnosis and treatments, differences in patterns of care, how physicians interact with patients, how healthcare systems support clinicians and

patients) may drive racial disparities in the incidence of and survival after TNBC [29]. If novel, effective and expensive therapies do emerge for TNBC in the future, it is likely that racial disparities in mortality will paradoxically widen if we do not address the issues with access and utilization of cancer care. There is a need to (a) move from describing to actively addressing disparities in healthcare delivery and (b) develop and test interventions aimed at clinician and delivery system factors that contribute to disparities, rather than focusing exclusively on patient factors.

Potentially modifiable risk factors that impact breast cancer-related racial disparities

TNBC is more common among African American women, especially pre-menopausal women [30]. The higher incidence of TNBC in African American women may be explained, in part, by their higher parity, lower prevalence of breastfeeding, and higher prevalence of type 2 diabetes. For example, AA women with type II diabetes have 1.43-fold increased risk of developing ER-breast cancer after accounting for a variety of potential confounders, such as age, body-mass index, and parity [17]. Interestingly, there are nearly double the number of differentially methylated loci between African American and European American patients' ER-breast tumors compared with ER+ breast tumors [31]. One of the top differentially methylated loci that was strongly associated with gene expression is FOXA1, a repressor of the basal phenotype, whose expression is downregulated in ER-tumors from African American patients compared with European American patients [32]. Of note, methylation of FOXA1 is significantly higher in ER-tumors from African American women who had children and did not breastfeed, with concomitantly lower protein expression. These data provide a mechanistic basis for the observation that parity without breastfeeding increases the risk of ER-breast cancer in African American women.

Future directions: Moving the needle by coming together

Throughout the meeting, there was a palpable restlessness about the lack of available therapeutic options available for TNBC patients despite advancements in molecular classification of the disease. The consensus was that mobilizing the movement of precision medicine for TNBC requires constructive coalescence of classical pathology and next generation “omics” technologies and the most burning question for future research to address is: How can we integrate histopathologic assessment of tumor morphology and architecture with molecular profiling at multiple levels (genomic, transcriptomic, proteomic, metabolomic) for more granular classification signatures that can capture tumor-intrinsic and stromal/immune element to “melt” and recast current classification schemes into more clinically actionable forms? Such research is urgently required because the diversity of TNBC classification schemes in existence have thus far failed to transform the clinical landscape, leaving TNBC patients behind in the emerging era of personalized medicine. Clinical trials exploring promising novel targeted treatments in the neoadjuvant and/or adjuvant settings for both early and metastatic TNBC remain more crucial than ever to improve patients' outcomes and alleviate breast cancer-related racial disparities. Equally vital are efforts geared toward increasing access to quality healthcare, improving healthcare

delivery systems, and elucidating and actively addressing potentially modifiable risk factors through education and community engagement, so that we may reduce the burden from TNBC and achieve health equity for all.

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