

## Tackling intra- and inter-tumor heterogeneity to combat triple negative breast cancer

Nikita Wright<sup>1</sup>, Padmashree C. G. Rida<sup>1,2</sup>, Ritu Aneja<sup>1</sup>

<sup>1</sup>Department of Biology, Georgia State University, Atlanta, GA 30303, USA, <sup>2</sup>Novazoi Theranostics, 26 Aspen Way, Rolling Hills Estates, CA 90274, USA

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## 1. ABSTRACT

Rampant inter-patient and intra-tumor heterogeneity present formidable challenges in the clinical management of triple-negative breast cancer (TNBC) and mandate a “divide-and-conquer” approach wherein deep biomarker profiling drives patient segmentation and development of customized treatments. Genomic and proteomic studies have uncovered several TNBC subtypes each of which represents a distinct disease pathobiology and harbors unique actionable targets that may illuminate sensitivities to specific classes of therapeutics. This review details the mind-boggling complexity of TNBC, its ramifications for prognosis and therapeutic response, and discusses what treatments might befit each TNBC subtype. Additionally, focused efforts geared toward translating these findings into the clinic are urged. This review also supports an evidence-based paradigm shift towards inclusion of agents that target the mechanisms that drive intra-tumor heterogeneity, in order to improve long-term outcomes for TNBC patients.

## 2. INTRODUCTION

The clinical management of triple-negative breast cancer (TNBC) continues to confound clinicians. Accounting for a small subset (10-20%) of all breast cancer cases, TNBC patients experience notably lower survival rates than non-TNBC patients (1-3). The defining feature of this subtype is its lack of estrogen receptor (ER), progesterone receptor (PR) expression, and human epidermal growth factor receptor 2 (HER2) overexpression (4); therefore, the only treatment options for TNBC are conventional chemotherapy, surgery and radiation therapy. TNBC is a breast cancer subtype defined by the *absence* of three biomarkers; these breast cancer patients by no means comprise a homogeneous group amenable to common treatment approaches. Instead, TNBC is notorious for inter-patient heterogeneity (IPH) as well as intra-tumor heterogeneity (ITH) that collude to produce poor clinical outcomes (5). In fact, TNBC is renowned for its aggressive clinical disease course and its higher prevalence among women of younger age and African descent (2,6-8). Higher visceral and cerebral metastasis and local relapse rates typify their clinical course (9,10). Furthermore, TNBC tumors display more unfavorable clinico-pathological features upon presentation such as larger tumor size, higher nuclear grade, higher stage, higher mitotic index, higher Ki67 proliferation index, and lymph node involvement compared to other breast cancer subtypes (6,12-13). These tumors also possess a higher likelihood of exhibiting distant recurrence within the first five years of diagnosis (6). These statistics have highlighted the need for finding new treatment modalities to improve TNBC outcomes. However, these efforts have

been met with a stalemate in the clinic owing to the heterogeneous nature of the disease. Approximately 70% of patients diagnosed with metastatic TNBC will not survive within the first 5 years of diagnosis despite undergoing neoadjuvant or adjuvant chemotherapy, the conventional form of treatment administered to this subset of patients (7). This review aims to dissect the complexity of TNBC, which underlies these unsettling rates, spotlight the challenges that clinicians face in managing this disease, and summarize efforts to stratify patients according to their unique tumor biomarker profile for targeted therapy.

## 3. CHEMORESISTANCE: THE SCOURGE OF TNBC MANAGEMENT

Presently, neoadjuvant chemotherapy is the first-line treatment choice for TNBCs due to their relatively higher chemosensitivity and pathological complete response (pCR) rates compared to non-TNBC patients (7). Clinical trials observed twice as high pCR rates to neoadjuvant chemotherapy in TNBC patients compared to hormone receptor-positive patients. In fact, a notably improved response is often observed in TNBC patients after only two cycles of chemotherapy (14). These positive results correlate with improved disease-free survival (DFS) in responding patients (14). Furthermore, neoadjuvant therapy can reduce the size of aggressive TNBC tumors rendering them more resectable during surgery as well as making breast conservation surgeries more feasible (15). Despite reportedly higher pCR rates, TNBC patients tend to experience significantly reduced progression-free survival (PFS) and lower overall survival (OS) within 3 years post-treatment compared to non-TNBC patients (16). This contradiction, often termed by clinicians and researchers as “the triple-negative paradox”, may in part be explained by the small percentage of TNBC patients that actually fall into the pCR group (6,16). Only 30% of TNBC patients that undergo anthracycline and taxane-based cytotoxic chemotherapy prior to surgery achieve pCR and experience improved DFS rates (17-18). In addition, among patients with residual disease, TNBC patients experience higher relapse and death rates than non-TNBC patients within the first three years of follow-up (19-21). This outcome may partially be reflected by the high administration of adjuvant endocrine therapy for patients with luminal tumors. Thus, an ultimatum is often presented to TNBC patients in the clinic: they must achieve pCR following neoadjuvant chemotherapy or risk the inevitable onset of relapse and subsequent death. Chemoresistance is thus the scourge of TNBC treatment.

Several mechanisms have been implicated in the development of chemoresistance in TNBC patients. Upregulation of ATP-binding cassette (ATP) transporters such as multidrug-resistant protein-1 (MRP1), breast cancer resistance protein

(BRCP), and P-glycoprotein (MDR1) that expel drugs such as anthracyclines and taxanes out of cancer cells have been suggested to contribute to the chemotherapy-resistant phenotype of TNBCs(22). Overexpression of  $\beta$ -tubulin III has been associated with paclitaxel resistance in advanced breast cancer (23-24). Mutations in DNA repair enzymes such as topoisomerase II, tumor suppressors such as p53, and key regulators of apoptosis such as Bcl-2 have also been discovered to promote chemoresistance in cancer cells (25-31). Overexpression of proteins that inactivate chemotherapeutics such as ALDH1A1 and ALDH3A1 have also been associated with acquired chemoresistance of cancer cells (32). Furthermore, aberrant NF- $\kappa$ B signaling has also been linked to chemoresistant behavior in TNBC (33). Perhaps the most significant culprits implicated in conferring TNBCs with chemoresistance are cancer stem cells (22,34). This aggressive subpopulation of cancer cells possess the ability to regenerate new cancer cells after chemotherapy treatment thus, promoting tumor repopulation and disease recurrence (34). Accumulating evidence also suggests that upregulation of hypoxia in TNBCs may also contribute to their chemoresistant phenotype by increasing cellular senescence which maintains cellular viability (35-38). Hypoxia also drives autophagy, which has been suggested to promote cancer cell survival during chemotherapy and radiation treatment by engendering cells with an anaerobic metabolism, which confers them the ability to survive during oxidative stress and nutrient deprivation (22,39). Autophagy markers have been observed to be more upregulated in TNBCs compared to non-TNBCs (40-41). Thus, inhibition of autophagy has emerged as a potential effective therapeutic strategy in circumventing chemoresistance in TNBC patients (41).

Many strategies are currently being pursued in the clinic to circumvent chemoresistance. High dose chemotherapy is one such strategy that has shown some promise. Von Minckwitz *et al* discovered significantly higher pCR rates in TNBC patients after they received higher successive doses of taxanes and anthracyclines compared to lower successive doses (18). Another strategy of strong interest in the clinical community is targeting TNBC patients with BRCA1 mutation. Mutations within the BRCA1 gene trigger deficiencies in DNA repair mechanisms in cells rendering them more sensitive to platinum-based agents, such as carboplatin and cisplatin (42-43). With 90% of breast tumors harboring BRCA1 mutations displaying a triple-negative hormonal receptor status, administering platinum-based therapies to TNBC patients has become a popular approach, especially for genomically unstable tumors (44-45). Clinical studies have reported marginal improvements in pCR rates following single agent platinum-based chemotherapy in metastatic TNBC patients (45).

Enhanced response was observed when platinum agents were administered to early stage TNBC patients in combination with taxane and anthracycline-based neoadjuvant regimens (14,46). Thus, the addition of platinum agents in the neoadjuvant setting shows therapeutic promise for TNBC patients. Nonetheless, these platinum/taxane- based treatments conceivably benefit primarily TNBC patients harboring BRCA1 gene mutations, limiting their therapeutic scope. Furthermore, despite considerably improved clinical efficacy of incorporating platinum agents in neoadjuvant regimens for TNBC patients, enhanced toxicity is a major concern. In addition, there remains a discordance between improved pCR and improved event-free survival rates (45-46).

The direct route of developing more efficacious chemotherapeutics to circumvent anthracycline and taxane failure is also currently being pursued. For example, the microtubule-targeting drug, ixabepilone, has recently been approved by the US Food and Drug Administration (FDA) after two phase III clinical trials observed that the addition of ixabepilone to capecitabine, a DNA synthesis inhibitor, generated a twofold increase in PFS than single-agent capecitabine therapy (47). Moreover, response levels to ixabepilone were similar between TNBC and non-TNBC patients (48). Eribuline, another microtubule-antagonizing drug, was also recently approved by the FDA to be administered post anthracycline and taxane failure (49). In the phase III clinical investigation (EMBRACE), Eribulin was administered as a single agent against a chemotherapeutic(s) of a physician's choosing (50). Eribulin performed significantly better as reflected by much higher OS rates compared to the drug(s) of physicians choice. From this patient cohort, 19% of the TNBC patients displayed a 29% reduction in death risk.

However, current tactics to evade the “triple-negative paradox” still appear to come up short. Successful treatment of TNBC will indubitably require implementation of targeted therapies and thus, research is underway to identify novel biomarkers in TNBCs that can serve as targets for therapeutic intervention.

#### 4. THE ELEPHANT IN THE ROOM: DISSECTING THE HETEROGENEOUS MOLECULAR LANDSCAPE OF TNBC

The aggressive clinical behavior displayed by TNBC tumors can be ascribed to the diverse molecular landscape within and between individual patients with this breast cancer subtype. This prohibitive heterogeneity has presented a grave challenge to clinicians for decades. Thus, TNBC research has primarily centered around utilizing multiple “omics’

platforms to acquire a deeper understanding of the complex and diverse molecular landscape of TNBC tumors, identifying novel molecular therapeutic targets, and stratifying TNBC patients into readily identifiable, stable, differentiable and actionable subgroups based on their biomarker profiles for optimal therapy selection.

Seminal gene expression-based studies have identified five major intrinsic molecular subtypes of breast cancer (Luminal A, Luminal B, HER2-enriched, basal-like, and normal-like) (4). Basal-like breast cancers are characterized by a basal-cell morphology, expression of cytokeratins 5/6, epidermal growth factor receptor (EGFR) amplification, TP53 mutations, high proliferation rates, upregulation of angiogenesis markers, central necrosis, and a pushing invasion border (46,51-52). C-myc is amplified in roughly 30% of basal-like breast cancers as well as in TNBCs (53-55). The majority (71%) of basal-like breast cancers are classified as TNBC (56). Inversely, a basal-like phenotype represents the vast majority (77%) of TNBCs (56). Basal-like TNBCs exhibit one of the highest pCR rates compared to the other TNBC intrinsic subtypes post chemotherapy (57). Although the terms basal-like breast cancers and TNBCs are often used interchangeably, these disease types are not synonymous. All basal-like breast cancers do not fit the profile of TNBCs and not all TNBCs fit the basal-like profile (58). For example, not all basal-like breast cancers lack immunohistochemical expression of ER, PR, and HER2 receptors. Thus, strictly defining and distinguishing basal-like breast cancer from TNBC is critical for the proper management of these two molecular disease entities. To elucidate the clinical heterogeneity of TNBC, Prat *et al*, exploited previously known 11-protein proliferation and luminal A gene signatures to evaluate response of TNBC patients to multi-agent chemotherapy (59). The prognostic biomarkers in the protein signatures were able to successfully stratify TNBC patients with a basal-like profile into more favorable and poorer response (pCR) but not for all TNBC patients. The highly proliferative nature of basal-like breast cancers may underlie these results as highly proliferative tumors are known to display higher chemosensitivity than more quiescent tumors (60-61). Thus, TNBC patients concurrently identified as basal-like breast cancer may exhibit preferential response to taxane/anthracycline-based chemotherapy (59).

Loss of function of breast cancer 1 (BRCA1) has been proposed to underlie the pathogenesis of a subset of TNBCs with approximately 10% of TNBCs harboring a BRCA1/2 germline mutation (62-63). This prevalent mutation among TNBCs has earned this subgroup to be considered a subtype of its own, often referred to as “BRCAness” (64-65). Breast tumorigenesis driven by BRCA1 mutations share

molecular features with basal-like breast cancers including high tumor grade, ER/PR negativity, HER2 negativity, high Ki-67 expression, and a high rate of p53 mutations (62,66). Deregulated growth factor signaling such as overexpression of EGFR also characterize BRCA-deficient TNBCs (62,64). High grade breast tumors typically display increased aberrant expression of other genes involved in DNA repair pathways such as ataxia telangiectasia mutated (ATM) and TP53 (62,66). As previously mentioned, BRCA1-mutated TNBCs show improved response to platinum agents in combination with taxane/anthracycline-based neoadjuvant chemotherapy. Thus, this subset of TNBCs characterized by BRCA1 gene deficiency warrant clinical trials that further therapeutically explore the role of platinum-based chemotherapy and alternative molecular agents that target anomalies in DNA damage repair pathways.

Perhaps the most groundbreaking attempt to subcategorize TNBCs according to common molecular features was undertaken by Lehmann *et al*. (57). Lehmann and his colleagues analyzed gene expression profiles of human TNBC tumor samples and conducted consensus clustering on the most differentially expressed genes to segment the subtype into seven unique clusters sharing common gene expression profiles. Six stable clusters and one unstable cluster was classified by Lehmann *et al* as seven distinct TNBC subtypes characterized by shared gene ontologies and unique enriched canonical pathways. These seven molecular TNBC subtypes were labeled basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), luminal androgen receptor (LAR), and unstable (UNS).

### 4.1. Basal-like 1(BL1) and Basal-like 2(BL2)

The BL1 and BL2 subtypes stratify the intrinsic basal-like breast cancer molecular subtype. These subgroups of basal-like breast cancers were found to be enriched in components of the cell cycle, DNA replication pathways, DNA damage response, and exhibit upregulation of genes associated with proliferation such as Ki67. The BL2 subtype is particularly enriched in growth factor receptor expression such as EGFR, Insulin-like growth factor (IGFR), and hepatocyte growth factor (MET). Increased expression of Ki67 and cell cycle proteins may explain increased sensitivity of BL1 and BL2 to antimetabolic agents such as taxanes (paclitaxel and docetaxel) in clinical studies (67-68). BL1 and BL2 patients exhibited significantly higher pCR rates after receiving taxane-based neoadjuvant chemotherapy compared to MSL or LAR TNBC patients (57). Alternatively, as BL1 and BL2 molecular subtypes display enrichment in DNA replication machinery, these subtypes may be more responsive to cell cycle agents



such as anthracyclines (doxorubicin), which inhibit DNA synthesis. Furthermore, observed elevation of DNA damage response genes may permit this subgroup of TNBC to respond well to platinum agents (cisplatin and carboplatin) that impede DNA repair.

#### 4.2. Immunomodulatory (IM)

As reflected in its name, this subgroup of TNBC is enriched for gene ontologies involved in fundamental signaling immune pathways such as T cell and B cell receptor signaling, natural killer cell pathway, and cytokine signaling. Additionally, this group has been observed to display increased antigen processing and presentation (57). Thus, this TNBC subtype may be a good candidate for receiving anthracycline-based therapy as studies have revealed that anthracyclines can elicit tumor-specific immunogenic death (69). The IM subtype has also been histologically linked to medullary breast cancer.

A highly active immune tumor microenvironment such as a high presence of tumor infiltrating lymphocytes has been linked with a better prognosis in early stage TNBC patients including lower risk of residual disease and relapse following systemic chemotherapy (70-72). Hence, it has been proposed, that immune markers can stratify TNBC patients according to risk of relapse post neoadjuvant or adjuvant chemotherapy and may be incorporated in clinics in the future for standard risk prognostication for TNBC patients (70-72).

#### 4.3. Mesenchymal (M) and Mesenchymal stem-like (MSL)

The M and MSL subtypes are both enriched in genes that regulate cell motility, extracellular matrix receptor interaction, and cell differentiation including enhanced Wnt/ $\beta$ -catenin and TGF- $\beta$  signaling. However, the MSL subtype differentiates itself from the M subtype with increased expression of genes in pathways that promote growth factor (i.e. EGFR, platelet-derived growth factor (PDGF)), calcium, and extracellular signal-regulated kinase signaling. In addition, MSL exhibits high activity of genes involved in angiogenesis and epithelial-mesenchymal transition. Perhaps the most distinguishing feature of the MSL subtype from the M subtype is a reduced expression levels of markers associated with cell proliferation along with elevated expression of stem cell and mesenchymal stem cell genes. Studies have suggested that EMT promotes chemoresistance in cancer cells (73). In fact, the M and MSL subgroups gene profiles overlap with a histological form of TNBC, metaplastic breast cancer, which is known to be chemoresistant (57). Thus, alternative molecular therapeutic targets are urgently needed to effectively manage these subgroups of TNBC. The MSL subtype

also overlaps with the claudin-low subtype profile by exhibiting low expression levels of claudins 3,4, and 7 and subsequent upregulation of EMT-associated genes such as matrix metalloproteinase 2 (MMP2) (57).

#### 4.4. Luminal Androgen Receptor (LAR)

Although ER negative, LAR subtype gene expression analysis revealed enhanced androgen and estrogen metabolic pathways. Particularly, increased expression of androgen receptor (AR) and its downstream targets was observed and further supported by enhanced nuclear AR immunohistochemical staining. Additionally, hierarchical clustering revealed that the LAR subtype exhibit a luminal-like gene signature making them resemble luminal ER positive breast cancer. Lehmann *et al*, also discovered an overlap in gene expression profiles between the histological subtype of TNBC, apocrine carcinoma, as the LAR subtype and the molecular apocrine subtype is also enriched for AR. Phosphoinositide 3-kinase (*PI3KCA*) mutations also strongly characterize the LAR tumor profile.

Lehmann *et al*, further dissected the TNBC subtype by correlating TNBC gene expression profiles with the gene set characterizing the five intrinsic molecular breast cancer subtypes (luminal A, luminal B, HER2-enriched, normal-like, and basal-like) by using the PAM50 gene panel. The TNBC tumor profiles overwhelmingly overlapped with the basal-like profile (80.6%). The remaining molecular subtypes correlated with the minority of TNBCs with the HER2-enriched subtype accounting for 10.2% and only 3.5% and 1.1% classified as luminal B and luminal A, respectively. Furthermore, a comparative analysis performed by the group between the TNBC subtypes and the PAM50 intrinsic subtype classifier noted that the basal-like phenotype predominantly comprised each subtype (BL1 (99%), BL2 (95%), IM (84%), and M (97%)) with the exclusion of the LAR and MSL subtypes. The MSL subtype overlapped with gene profiles of basal-like by 50%, normal-like by 28%, and luminal B by 14%. The LAR subtype was characterized as 74% HER2-enriched and 14% luminal B.

Masuda *et al*. discovered that pCR rates differed across the subtypes and that TNBC subtype can independently predict patient response to neoadjuvant chemotherapy (74). The group performed a retrospective analysis of TNBC patients that were administered a neoadjuvant chemotherapy regimen of taxane and anthracycline and observed subtype-specific responses. BL1 tumors exhibited the best response among the TNBC subtypes with a 52% pCR rate. Interestingly, BL2 displayed the poorest response among the subtypes, with a pCR rate of 0%. The LAR and MSL subtypes also displayed dismal responses in comparison to the other subtypes with pCR rates

of 10%, and 23%, respectively. The groups also uncovered that the TNBC subtypes and pCR status are significantly associated ( $p=0.0.4$ ) and validated TNBC subtype as an independent prognosticator for neoadjuvant chemotherapy response ( $p=0.0.2$ ).

Lehmann and colleagues also uncovered subtype-specific sensitivities among the TNBCs to conventional therapeutic agents. They identified TNBC cell lines that share homogenous gene ontologies with each of the major TNBC subtypes through conducting gene expression profiling and clustering analysis. Their work yielded a comprehensive panel of TNBC cell lines representative of the six identified molecular TNBC subtypes. They utilized the panel to analyze differential drug response between the subtypes to traditional therapeutic agents administered in clinics. Cell viability assays revealed that the cell lines characterized as basal-like displayed significantly higher sensitivity to cisplatin compared to mesenchymal- and LAR-like lines likely due to their enrichment in DNA damage response markers. As one may suspect, the AR-dependent LAR-like cell lines displayed significantly higher sensitivity to the AR antagonist, bicalutamide, than the basal-like lines. These results suggest that the increased AR signaling present in LAR tumors permit this subgroup of TNBC patients to be selectively susceptible to anti-androgen targeted therapy. This clinically translatable information is valuable and warrants further investigation to discriminate TNBC subtypes according to their favorable therapeutic response to guide clinical decision-making.

Clinical outcomes also significantly varied between the subtypes irrespective of treatment regimen and duration (57). Patients diagnosed with the LAR subtype displayed the lowest relapse-free survival (RFS) among the TNBC subtypes. The M subgroup of patients exhibited lower RFS compared to the BL1, IM, and MSL patients. Interestingly, distant-metastasis-free survival (DMFS) did not differ significantly between the subtypes with the exception of the M subtype patients who exhibited significantly higher DMFS than the BL1 subtype patients. Age at diagnosis was greatest in the LAR subtype, which may partly rationalize their lower rates of RFS compared to other subtypes. Other clinico-pathological features such as, tumor size and grade, was found not to significantly differ between the TNBC subtypes.

### 4.5. Reclassification of TNBC molecular subtypes

Recently, Lehmann *et al.*, refined the 6 classified TNBC subtypes into 4 subtypes based on their discovery that infiltrating lymphocytes and tumor-associated stromal cells influenced the identification of the original subtypes, particularly the IM and MSL subtypes (75). The newly refined 4-subtype panel consist of BL1, BL2, M and LAR and were discovered

to exhibit differences in diagnosis, age, grade, local and distant disease progression, and histopathology. Furthermore, they were found to display significant differences in response to neoadjuvant chemotherapy. In their study utilizing 300 TNBC biopsied patient specimens, 41% of BL1 patients achieved pCR, while only 18% of BL2 and 29% of LAR patients achieved pCR.

Current clinical practices engage IHC methods to detect ER, PR, and HER2 protein expression to identify TNBC patients. Only 5 out of the 6 TNBC subtypes, classified by Lehmann *et al.*, were detected in tumor samples IHC-screened for all three receptors(57). Thus, Burnstein *et al.* sought to further fine-tune the Lehmann TNBC subtype classification system. Through exploiting mRNA and DNA expression profiling, the group identified four molecularly distinct TNBC subtypes that sharply define Lehmann's classified subtypes(76). They include another LAR subtype (LAR 2), mesenchymal (MES), basal-like immune suppressed (BLIS), and basal-like immune activated (BLIA). The LAR 2 subgroup closely resembles Lehmann's characterization of the LAR subtype. The MES subtype shares characteristics with Lehmann's BL1, BL2, and MSL molecular subtypes with enrichment in components of cell cycle, DNA damage repair, and inherent breast cancer signaling pathways. In addition, the MES group is highly enriched in gene expression for osteocytes, adipocytes, and growth factors such as IGF. BLIS TNBCs display upregulation of SOX family transcription factors but downregulation of key immune-signaling such as B cell, T cell, natural killer cell, and cytokine pathways. Furthermore, this subtype is characterized by suppression of antigen presentation, immune cell differentiation, and innate and adaptive immune systems. Interestingly, this subtype displays the poorest DFS and disease-specific survival (DSS). In contrast, the BLIA subtype displays upregulation of these immune-regulatory pathways including STAT-mediated pathways and exhibits the most favorable prognosis. The group observed subtype-specific molecular expression among the four subgroups. Particularly, DNA copy number analysis revealed overexpression of AR and mucin 1 (MUC1), IGF-1 and placental transforming growth factor (PTGF), v-set domain-containing T-cell activation inhibitor 1 (VTCNI), and cytotoxic T-lymphocyte associated protein 4 (CTLA4) in LAR 2, MES, BLIS, and BLIA tumors, respectively.

Roughly 6-8% of TNBCs minimally express HER2 indicated through gene expression analysis and thus, has been suggested to stand on its own as a separate clinical entity within the TNBC subtype (77). HER2 "enriched" TNBCs predominantly share gene ontologies with Lehmann's molecular classification of LAR and BL2 subtypes(57,78). In particular, HER2-enriched TNBCs closely resemble the LAR subtype by

harboring *PIK3CA* mutations and elevated levels of AR expression (79-80). Remarkably, p53 mutations have been detected in 100% of HER2-enriched TNBCs (63). In addition, this subset of TNBCs expresses angiogenesis factors such as VEGF (81). However, the biological role of this subset of TNBCs marginally expressing HER2 remains a mystery and elucidation of this phenomenon is critical to therapeutically targeting this unique disease. Preliminary results from the NSABP-B31 trial revealed that HER2 minimally-expressing breast cancer patients exhibited some clinical benefit to the FDA approved HER2 antagonist, trastuzumab however, these results are not considered concrete (82). The NSABP-B47 trial will exclusively address the clinical efficacy of HER2-targeted endocrine therapy in TNBC patients exhibiting low HER2 expression (63).

### 4.6. Claudin-low TNBCs: a class of their own

Recently, a new distinctive TNBC molecular subtype was identified and labeled as claudin-low (83). This novel breast cancer subtype is primarily characterized by low gene expression of the tight junction proteins claudin 3, 4, 7, E-cadherin, and occludin (84). Clustering analysis revealed that the claudin-low subtype resembles the basal-like subgroup of breast cancer by exhibiting variable expression of basal cytokeratins and downregulation of HER2 and luminal protein markers (84). However, low expression of proliferation markers such as Ki67, distinguishes claudin-low from basal-like tumors (84). Tumors with a claudin-low profile were also uncovered to be enriched for epithelial-to-mesenchymal transition markers (84). Furthermore, claudin-low tumors exhibit upregulation of genes involved in immune system response, cell communication, extracellular matrix, cell differentiation, cell migration, and angiogenesis (84). Perhaps the most definitive characteristic of this TNBC subtype is enrichment of breast tumor initiating cells and stem cells markers. The claudin-low subtype was found to differ from the other intrinsic breast cancer subtypes by their clinico-pathological features (84). Patients harboring a claudin-low tumor phenotype display worse prognosis (RFS and OS) than luminal A patients but exhibit a similar prognosis to luminal B, HER2-enriched, and basal-like patients. Moreover, claudin-low patients display higher pCR rates than luminal A and luminal B patients but lower pCR rates than basal-like patients to anthracycline/taxane-based neoadjuvant chemotherapy. Thus, with apparent minimal success, these outcomes suggest a chemotherapeutic regimen cannot adequately manage the claudin-low subtype and alternative treatment strategies are compulsory for successfully eradicating these tumors. Prat *et al.* took the initiative to design a panel of claudin-low breast cancer cell lines through performing hierarchical cluster analysis (84). Studies analyzing drug responses of these cell lines in *in vitro*

or *in vivo* models may be highly useful in augmenting the clinical management of claudin-low breast cancer.

### 4.7. Copier overdrive: TNBC sub-classification based on copy number aberrations

Curtis and his colleagues performed integrative clustering of copy number aberrations (CNAs) and gene expression profiles of the intrinsic breast cancer subtypes to further delineate the complex molecular landscape of the disease (85). Their analysis yielded 10 integrative clusters (IntClust) differentiated by their genomic copy number profiles and clinical outcomes. Basal-like breast cancers predominantly corresponded with IntClust 4 and 10 by 80%. IntClust 4 tumors are characterized by lymphocytic infiltration and harboring robust immune and inflammatory signature. This subgroup is often referred to as the “CNA-devoid” group owing to its low number of CNAs. Thus, this group often exhibits favorable clinical outcomes. IntClust 10 tumors are typified by extensive genomic instability and chromosomal aberrations. This subgroup of patients experience satisfactory long-term clinical outcomes. This method of deeper molecular segmentation of the disease may provide an additional layer of risk-predictive information as well as illuminate potential therapeutic targets for TNBC/basal-like cancers. Patients with IntClust 4 tumors may benefit from immunotherapy and patients harboring IntClust10 tumors may respond sufficiently to platinum-based chemotherapy. Further integration clustering of genomic data selectively extrapolated from TNBC tumors may further enhance these therapeutic predictions.

### 4.8. TNBC subtyping based on histology

Perhaps one of the longest established systems of subclassifying TNBCs is not according to their molecular profile but according to their unique histological profile. The vast majority (95%) of the TNBC subtype is classified as invasive mammary or ductal carcinomas and lack defined histological features (5). Medullary carcinoma is a rare (0.4-1%) form of TNBC characterized by high lymphoplasmacytic infiltration and favorable outcomes compared to the other histological subtypes (86). The other subgroups of TNBC, adenoid cystic carcinoma, adenosquamous carcinoma, and fibromatosis-like spindle-cell metaplastic carcinomas are also rare (<1%) forms of TNBC and are typically less aggressive and only exhibit local recurrences (87). Furthermore, adenoid cystic carcinoma is distinguished from the other TNBC subgroups genomically by harboring a low number of CNAs and a unique chromosomal translocation observed in approximately 90% of cases characterized by this subtype (87). However, differential responses between the subgroups to conventional therapeutic agents and regimens remain unclear and warrant

further investigation to selectively manage these histologically-distinct subgroups of TNBC(5).

### 4.9. Proteomic approaches to TNBC subtyping

Although current clinical practices recommend that lymph node negative TNBC patients undergo adjuvant chemotherapy to avert the onset of distant metastasis, only 30% of these patients actually experience this outcome (6,88). Thus, the vast majority of these patients are unnecessarily receiving cytotoxic chemotherapy (89). The highly heterogeneous nature of lymph node negative TNBC patients and the shortage of highly sensitive and specific biomarkers that can accurately predict prognosis, primarily underlie this major clinical hurdle (89). Through exploiting nanoscale liquid chromatography and tandem mass spectrometry (nLC-MS/MS) to quantitatively profile the proteome of lymph node negative TNBC specimens, Liu *et al.* designed and validated a prognostic 11-protein signature that correlates with a poorer prognosis to prevent overtreatment of these patients with systemic adjuvant chemotherapy (89). The identified signature proteins are involved in molecular mechanisms implicated in tumor progression such as immune response, cell death, and cell metabolism as well as clinical prognosis. Thus, the group's protein signature has also uncovered novel potential therapeutic targets for aggressive TNBC (89).

### 4.10. Mutational analysis of TNBCs

Many genomic studies have begun to unravel the mutational landscape of TNBC to identify novel molecular pathway anomalies underpinning onset of the disease. Given the IPH seen in TNBCs, significant differences were anticipated between different TNBC subtypes, including in the driver mutations. *TP53* was found to be the most frequent (60-70%) mutated gene in TNBC with *PIK3CA* following behind (10%) (80,90-91). However, within the LAR subtype, *PIK3CA* is more frequently mutated (46.2%) than in the other subtypes (91). Gene deletions (i.e. *PTEN*) and amplifications (i.e. *KRAS*, *BRAF*, *EGFR*, *IGFR*, or *MET*) have been identified in TNBC as potentially actionable targets although clinical studies are needed to substantiate these claims (80,85,91). The remaining somatic mutations in TNBC arise at a very low rate presenting an obstacle in developing targeted therapeutics (5).

Hence, the race to discover more TNBC tumor-specific molecular alterations that can serve as viable targets is currently underway. The previously mentioned preliminary studies have served as fuel to execute this pursuit by exposing the numerous layers of TNBC and identifying molecular anomalies to differentiate these complex layers. This demystification has begun to provide a platform for novel TNBC drug development and it is anticipated that these

contemporary therapeutics may elude intrinsic chemoresistance to effectively manage the large pool (60-70%) of TNBC patients who do not achieve pCR post chemotherapy.

## 5. HITTING THE NAIL ON THE HEAD: STRATIFYING TNBC PATIENTS ACCORDING TO THEIR UNIQUE MOLECULAR TUMOR PROFILE FOR TARGET THERAPY

Amid the recent influx of studies that have dissected the molecular landscape of TNBC to identify discriminative biomarkers, numerous translational and clinical studies have utilized this information to initiate the development of novel agents that target these molecular aberrations. Selectively targeting biomarkers that correspond to each TNBC patient's unique tumor profile may reap significantly improved pCR and survival rates for TNBC patients in the clinic. The identified homogeneous TNBC subgroups along with agents under clinical investigation that have been designed to target their specific molecular alterations are outlined below.

### 5.1. Basal-like TNBCs

Enrichment of c-myc in both TNBCs and basal-like breast cancers has suggested these diseases may be susceptible to MEK inhibitors as MEK stabilizes c-myc (92). In addition, MEK activates mitogen-activated protein kinase (MAPK) and basal-like breast cancers harbor gene copy number alterations in key Ras/MAPK pathway components such as *BRAF* and *KRAS*(80). *In vitro* studies have reported increased sensitivity of cell lines derived from both TNBC and basal-like breast cancers to MEK inhibitors (93). Preliminary data from clinical investigations have shown that among patients with solid tumors that received gemcitabine and trametinib (MEK1/2 inhibitor), only the patients with metastatic TNBC achieved complete response (94). Clinical trials exploring the efficacy of the combination of chemotherapy and MEK inhibitors for specifically TNBC and basal-like breast cancer patients are currently in progress(5). However, c-myc degradation through MEK inhibition can in turn activate receptor-tyrosine kinases that can interfere with the inhibition (95). Hence, it may be sensible to combine the administration of MEK inhibitors with small molecules and/or monoclonal antibodies that hinder receptor-tyrosine kinase activity (tyrosine-kinase inhibitors) (5).

As mentioned earlier, somatic *TP53* mutations strongly underlie the onset of basal-like TNBCs (85%)(78). Conveniently, researchers are actively exploring mechanisms to reactivate p53 tumor suppressor function in mutant breast tumors. A preclinical study has investigated the use of non-toxic small molecules referred to as p53 re-activation and



induction of massive apoptosis (PRIMA-1) to induce apoptosis by restoring functionality of mutant p53 in *in vitro* and *in vivo* breast cancer models and observed notable tumor regression (96). Another novel approach researchers are currently investigating to counteract the lethality of p53 mutations is WEE1 kinase or CHK1 inhibition to override S-phase arrest in mutant p53 cells promoting subsequent mitotic catastrophe and apoptosis (57,97-99). The addition of WEE1 inhibitors to chemotherapy is currently under clinical evaluation in phase I trials (100). Perhaps the most recent novel approach suggested to override the detrimental effects of p53 inactivation is using small molecules to target mutant p53 proteins to restore its translational activity (101). These molecules referred to as mutant-specific inhibitors are currently being developed (101-102). Because p53 promotes the onset of apoptosis, agents targeting the apoptotic signaling pathway, which are currently under clinical investigation, may also serve as a novel therapeutic approach for p53-deficient TNBC patients.

EGFR inhibitors are perhaps one of the most clinically approved agents on the market for breast cancer patients. With EGFR overexpression rampant among basal-like breast cancers, this subgroup of TNBCs may experience improved response with EGFR inhibitors. Preclinical data have shown that EGFR monoclonal antibodies added to chemotherapy results in favorable objective response rates (ORR) in TNBC patients (103). However, the clinical efficacy of EGFR inhibitors for specifically TNBC patients have been disappointing with two phase II trials reporting statistically insignificant improved response in patients treated with cetuximab combined with platinum-based chemotherapy (104-105). The small-molecule EGFR tyrosine kinase inhibitors, gefitinib and erlotinib, have generated marginal anti-cancer activity in metastatic breast cancer patients and remain under clinical evaluation in phase I/II trials (106). However, these TNBC patients were not screened prior for EGFR amplification (106-107). Thus, selection of TNBC patients harboring EGFR mutations will be essential in future clinical trials to accurately assess the efficacy of EGFR inhibitors for EGFR amplified TNBC patients (107). Researchers from the I-SPY2 clinical trials recently reported that the tyrosine kinase and PAN-ERBB inhibitor, neratinib, elicited considerably improved pCR in TNBC patients with phosphorylated EGFR arms when combined with paclitaxel. An alternative route that has been suggested to suppress EGFR function is targeting its binding partner MUC1 (108). The MUC1 ligand, often overexpressed in tumors, inhibits degradation of EGFR to stimulate cell transformation and consequently growth of cancer cells. Hence, TNBCs overexpressing EGFR and/or MUC1 may exhibit susceptibility to MUC1-based peptide vaccines, which are currently under clinical evaluation (109-111).

Anti-VEGF agents may serve as a promising therapeutic strategy for basal-like TNBCs, which frequently harbor a VEGF signature (63). Conveniently, VEGF inhibitors are already on the market. The FDA-approved monoclonal anti-VEGF inhibitor, bevacizumab, performed well during phase III clinical trials by decreasing risk of tumor progression in metastatic TNBC by 35% but flopped in the clinic due to dismal performance and adverse side effects in breast cancer patients (63,104,112). When added to adjuvant chemotherapy, bevacizumab, elicited no improvements in DFS in TNBC patients promoting its retraction from the market (112). Subsequent clinical studies evaluating the efficacy of bevacizumab have been conflicting however, clinical trials exploring the addition of this agent with chemotherapy remain ongoing (104). The anti-VEGF tyrosine kinase inhibitor, sunitinib, also performed dismally in HER2-negative advanced breast cancer patients when added to chemotherapy and it is uncertain whether phase II trials and phase III trials exploiting this agent will proceed (103-104). New small molecule anti-VEGF tyrosine kinase inhibitors are currently under clinical evaluation in phase II trials with TNBC patients (104). Nonetheless, the development of more potent, tolerant angiogenesis inhibitors are urgently needed along with robust markers to predict sensitivity of TNBC patients to these agents.

## 5.2. “BRCAness” TNBCs

Perhaps one of the most popular breast cancer agents currently in clinical trials are poly ADP ribose polymerase (PARP) inhibitors. PARP is a nuclear enzyme that activates target proteins in intracellular signaling pathways that regulate DNA repair and cell survival via poly-ADP-ribosylation (5,113). Molecular agents designed to inhibit activity of this enzyme will permit double-strand breaks to persist in replicating cells (5). BRCA1/2 repair double-stranded DNA breaks through homologous recombination (HR) and therefore, BRCA1/2-deficient cells are unable to repair the damage (114). Thus, BRCA1/2 defective cells are highly susceptible to PARP inhibitors, which promote lethally toxic cells or “synthetic lethality” (115). Hence, TNBCs that are BRCA1 mutation carriers may respond favorably to PARP inhibitors (115). PARP inhibitors have performed dismally in clinical trials with TNBC patients. Administered as a single-agent PARP inhibitor in metastatic breast cancer patients harboring defective BRCA, olaparib generated minimal activity with responses ranging from 22% (100mg) to 41% (400mg) (116). In a phase II study, olaparib stimulated reduction in tumor size by more than 30% in 50% of BRCA1/2-defective TNBC patients (117).

Several PARP inhibitors have reached phase III clinical trials such as veliparib, talazoparib, and iniparib (5). Iniparib generated substantial hype

in phase I and phase II clinical trials, earning the reference as a putative PARP inhibitor (118-120). However, these inhibitors were unsuccessful in phase III clinical trials and in subsequent laboratory studies (121-123). Veliparib was one of the novel agents tested in the neoadjuvant I-SPY 2 trial based on biomarker subtypes. When veliparib and carboplatin was added to traditional chemotherapy regimens administered to stage II and III TNBC patients, pCR rates jumped from 26% to a remarkable 51% (124). However, it remains uncertain whether the rise in pCR rates was attributed to veliparib and/or carboplatin (5). Another PARP inhibitor, rucaparib, is currently being tested in a randomized phase II trial of TNBC patients with BRCA mutations and a residual tumor burden after receiving neoadjuvant chemotherapy (46). Cisplatin was combined with rucaparib in one treatment group and absent from the second treatment group. However, preliminary results after one year reveal no significant difference in DFS rates between the treatment groups. Lackluster results from clinical trials have prompted researchers to reroute their strategy by adding in inhibitors of HR along with administration of PARP inhibitors (125). The addition of HR inhibitors is hypothesized to combat HR-proficient TNBCs that can counteract the anti-DNA repair activity of PARP inhibitors (125). A study by Ibrahim *et al.* supports this hypothesis as the HR inhibitor, BKM120, sensitized BRCA-proficient TNBCs to olaparib (126). Recent evidence from a I-SPY2 phase I trial show that HR inhibitors, BKM120 and BYL719, also sensitized HR-proficient TNBCs to olaparib and stimulated anti-tumor activity. In addition, the inclusion of agents that incite DNA breaks such as topoimerase inhibitors has been suggested to potentially improve efficacy of PARP-inhibitor treatment (127). Furthermore, topoimerase II alpha expression levels have been found to be elevated in TNBC (128). The topoimerase inhibitor, etirinotecan pegol, recently performed well in HER2-negative breast cancer patients with a record of brain metastases in which this patient subset experienced twice as high OS compared to patients solely administered single-agent chemotherapy.

With EGFR amplification frequently characterizing BRCA1-deficient TNBCs, EGFR inhibitors may enhance clinical efficacy of PARP inhibition if administered in combination with these agents. Inhibitors are also being developed for the growth factor ligand, fibroblast growth factor receptor (FGFR), which is highly expressed in this subset of TNBC patients (129). Small molecule tyrosine kinase inhibitors that inhibit FGFR and VEGFR are being heavily investigated in clinical trials to modulate FGFR signaling in breast cancer patients (130). The FGFR inhibitor, dovitinib, selectively attenuated tumor activity in both preclinical and clinical FGFR-amplified breast cancer models (131). More potent FGFR inhibitors are currently in ongoing clinical trials (63). Furthermore,

in common with basal-like TNBCs, BRCA-deficient TNBCs may benefit from agents targeting the defective p53 pathway as described above.

### 5.3. BL1 subtype

Deleterious alterations in DNA damage repair pathways largely characterize the BL1 subgroup as well as BL2 TNBC patients. Hence, these subgroups of TNBC patients have been hypothesized to exhibit sensitivity to DNA damage targeting agents such as PARP inhibitors (57,63). However, Lehmann's group performed cell viability assays to assess the sensitivity of their panel of TNBC cell lines to the PARP inhibitors, veliparib and olaparib, and observed variability in their results (57). The BL1, BRCA-null cell line, HCC1937, exhibited sensitivity to veliparib but not to olaparib and the BL1, BRCA-mutant cell line, HCC1599, displayed no sensitivity to either inhibitor. This data suggest that other mutations or inherent properties of these tumors may be at play to influence sensitivity to PARP inhibitors.

Perhaps the most defining feature of the BL1 subtype is enrichment in cell-cycle regulatory proteins and a highly proliferative nature. Inhibitors targeting cyclin-dependent kinase (CDK) may pose a robust front in eradicating BL1 tumors. Small molecular CDK inhibitors such as purvalanol A and dinaciclib have stimulated a reduction in cell growth in *in vitro* TNBC models (132-133). Regression in tumor growth has also been observed with dinaciclib in *in vivo* TNBC models (132-133). However, this data suggest clinical utility of anti-CDK agents only in TNBC tumors that overexpress MYC as MYC is involved in proliferative cell signaling. Hence, screening of MYC status in the clinic through IHC or gene expression profiling methods may be critical to select for patients that will exhibit sensitivity to these small molecular inhibitors (132). Dinaciclib and another CDK inhibitor, seliciclib, are currently in phase II clinical trials but not yet for breast cancer patients.

### 5.4. BL2 subtype

As previously described, the BL2 subtype can be distinguished from the BL1 subgroup of TNBCs by their overexpression of tumor growth promoting factors. With elevated expression levels of EGFR, FGFR, and IGFR, inhibitors directed towards these targets may be selectively beneficial for BL2-subtype patients if future clinical trials with these agents hold well. IGFR inhibitors, in particular, may elicit specificity in basal-like TNBCs as BRCA-deficient TNBCs lack the ability to down-regulate IGFR expression (134). However, BRCA mutation status and IGFR plasma levels serve as poor indicators of IGFR inhibitor sensitivity, as reflected by the lackluster performance of these agents in phase III clinical trials (5,135).

Preclinical *in vitro* and *in vivo* studies have strongly supported the viability of MET inhibitors in abrogating tumor progression in basal-like TNBCs and may be particularly beneficial for BL2 TNBCs characterized by increased MET pathway signaling (136). Kim *et al.* observed reduced cell viability in TNBC cells following *in vitro* treatment with the MET inhibitor, PHA-665752 (136). They discerned increased reduction in cell viability after these cells were treated simultaneously with PHA-665772 and erlotinib, an EGFR inhibitor. This data suggest that dual EGFR and MET inhibition may notably suppress tumor growth activity in basal-like TNBC patients. Sameni *et al.* also observed abrogated tumor growth and metastasis in BL2 TNBCs in *in vivo* assays exploiting the small-molecular c-MET protein inhibitor, cabozantinib (137). Clinical trials evaluating clinical efficacy of MET inhibitors for breast cancer are currently underway in clinical trials. Onartuzumab, a MET inhibitor, performed poorly in an early-stage clinical trial when added to paclitaxel/bevacizumab based regimen administered to metastatic TNBC patients (138). Nonetheless, efficacy testing of MET inhibitors in clinical trials remains ongoing. IGFR inhibitors are also currently in clinical development and investigation and may be useful for BL2 patients in the future (139).

### 5.5. M subtype

Hyperactivity of cell differentiation pathways such as Wnt and TGF- $\beta$ , are unique to this subset of TNBC patients. Fortunately, some FDA approved drugs are already targeting the Wnt pathway to elicit improved patient response (63,140). Furthermore, more novel Wnt inhibitors are currently in clinical development and trials (141). TGF- $\beta$  tyrosine kinase inhibitors are rapidly gaining momentum as a therapeutic alternative for breast cancer patients as preclinical studies have observed a reversal of EMT in CD44+ breast cancer cells (142). The TGF- $\beta$  inhibitor, trabedersen, has exhibited promising preliminary results in patients with solid tumors harboring elevated expression of the TGF- $\beta$ 2 ligand.

The nonreceptor tyrosine kinase, Src, has been suggested as a viable target for mesenchymal-like TNBCs as they exhibit enhanced cell motility signaling. Lehmann's group tested the efficacy of dasatinib on the panel of TNBC cell lines characterizing their identified TNBC subtypes and observed significantly higher sensitivity in M and MSL cell lines compared to LAR cell lines (57). The src inhibitor, dasatinib, has demonstrated growth inhibition in TNBC cell lines and some anti-tumor activity administered as a single-agent or in combination with chemotherapy in TNBC patients (143-145). Phase I/II clinical trials evaluating efficacy of dasatinib remain ongoing.

### 5.6. MSL subtype

Primarily characterizing this subgroup of TNBCs is the increased presence of mesenchymal stem cells (57). The hazards of cancer stem cells such as the ability to repopulate tumors from a single cell, intrinsic chemoresistance, and ability to transform into an EMT-like phenotype, make them an essential target to eliminate (146-148). Furthermore, as previously mentioned, studies have identified the cancer stem cell population as the culprit of residual disease and fostering relapse and/or recurrence post standard chemotherapy. Hence, developing novel agents to target this perilous "cellular entity" has recently aroused high interest among the clinical community as a therapeutic option for eradicating MSL. Recently, a preclinical study revealed that the HDAC inhibitor, entinostat, significantly repressed tumor growth and distant metastasis in TNBC *in vivo* models by inhibiting tumor-initiating cells and facilitating reversal of EMT (149). Thus, HDAC inhibitors, if approved in clinical trials, may be useful for this subgroup of patients in the future. In the meantime, agents selectively targeting signaling pathways that regulate cancer stem cells, may be the best option. As previously mentioned, novel drugs are already targeting the Wnt signaling pathway and inhibitors designed to interfere with the Notch signaling pathway are showing promise in preclinical studies (150-151). Also, recent evidence, indicating that Hedgehog signaling is upregulated in TNBC, is generating buzz as a potential therapeutic target (152). Fortunately, the cancer stem cell population can be readily identified through marker-based methods including assessing aldehyde dehydrogenase activity (ALDEFLUOR assay), evaluation of integrin receptor expression, or measuring ABC transporter activity (153-155).

Upregulation of growth factor signaling suggest that this subtype may potentially be susceptible to EGFR, FGFR, and IGFR inhibitors. Since c-MET signaling is also involved in regulating EMT and cancer stem cell phenotype development, this subgroup of TNBCs may also benefit from molecular interference of the c-MET pathway. The MSL-subtype also exhibits gene mutations in the Ras/MAPK and TGF- $\beta$  pathways (57). The Ras/MAPK pathway induces TGF- $\beta$  signaling to mediate transcriptional control of specific intermediates involved in EMT (156). Thus, MEK and TGF- $\beta$  inhibitors may be advantageous for this subgroup of patients. MMP2 expression, involved in EMT, was particularly found to be enriched in MSL tumors (57). Fortunately, MMP2 inhibitors are currently in clinical trials (157). However, the initial performance of these agents in clinical trials has been disappointing and many strategies are currently being devised to improve their efficacy in cancer patients (157). The upregulation of angiogenesis factors uniquely characterizing this subtype, also suggest that VEGF

inhibitors might hold promise for this subgroup of TNBCs.

### 5.6.1. MES

As previously proposed for the MSL subtype, therapies targeting growth factor signaling may also help eradicate MES tumors. Particularly,  $\beta$  blockers, IGF inhibitors, and PDGFR inhibitors, have been proposed as potential treatment options for this TNBC subtype and merit further evaluation (76).

### 5.7. LAR subtype

A hallmark of LAR TNBC is elevated levels of AR expression. With the lack of IHC expression of ER, PR, and HER2 hormone receptors characterizing TNBCs, the LAR subtype is perhaps the only subgroup of TNBC patients that may benefit from endocrine therapy. As previously mentioned, the LAR subtype exhibit sensitivity to the AR-targeting agent, bicalutamide *in vitro*. Bicalutamide also displayed marginal clinical efficacy in a phase II trial with AR-positive TNBC patients in which 19% of patients exhibited partial or complete response after 6 months and a median PFS of 3 months (158). Hence, the advent of testing more potent AR inhibitors in preclinical and clinical studies is currently underway. Enzalutamide, a contemporary AR-antagonist, suppressed AR-mediated proliferation *in vitro* but demonstrated a dismal response in a phase II trial in which among 75 patients exhibiting >10% AR expression, 2 and 5 patients experienced complete and partial responses, respectively (159). Recent results from the I-SPY2 trial report a clinical benefit (% of patients with complete/partial response, or stable disease) rate of 16 weeks in 42% of advanced TNBC patients (TNBC) (160). Enobosarim, another anti-AR agent, has also shown a 35% clinical benefit in metastatic AR-positive breast cancer (161).

As mentioned earlier, the LAR subtype harbors notably more *PIK3CA* mutations than the other TNBC subtypes. The gene encodes for the PI3K catalytic subunit, which plays a role in cell growth, metabolism, and survival (162). PI3K inhibitors have performed well in *in vitro* and *in vivo* settings exploiting LAR-subtype cell lines and are now currently being tested in clinical trials (163). These trials are implementing the strategy of targeting AR and *PIK3CA* mutations simultaneously in LAR TNBC patients (163). A phase I/II trial is currently evaluating the efficacy of combining enzalutamide and the PI3K inhibitor, taselisib, for AR-positive TNBC patients (159). Downstream proteins of PI3K signaling, AKT and mTOR, may also have value as viable therapeutic targets for TNBCs upregulating this pathway, stimulating interest in development of AKT and mTOR inhibitors Co-inhibition of PI3K and

mTOR with the dual inhibitor, NVP-BEZ235, elicited a potent response in LAR TNBC cells and was further confirmed in a phase I trial (57,63). Recent reports from the I-SPY2 trials claimed that TNBC patients exhibited notably higher pCR following treatment with the AKT inhibitor, MM-2206, combined with a standard chemotherapy regimen compared to TNBC patients with chemotherapy alone. Two mTOR inhibitors, everolimus and temsirolimus, are currently under clinical investigation in phase I/II trials with TNBC patients (48). Disease stabilization or partial response was achieved in TNBC patients treated with class I pan-PI3K inhibitors (164). However, controversy has arisen regarding the loss of the upstream protein of PI3KCA, PTEN, as a robust predictive marker for sensitivity to PI3K inhibition (165). Elimination of this discordance will be vital to adequately preselect for patients that will exhibit susceptibility to PI3K inhibitors. The emerging concept of designing inhibitors that target specific PI3K isoforms that differentiate tumor types is rapidly gaining momentum and will likely become the primary focus in improving patient selectivity for these agents (166).

Histone deacetylase (HDAC) modulates AR gene expression in prostate cancer cells (167). Hence, HDAC inhibitors may be also serve as a practical therapeutic alternative for AR-positive TNBC patients. Preclinical *in vitro* and *in vivo* studies have demonstrated the potential clinical efficacy of HDAC inhibitors in TNBCs. The HDAC inhibitor, panobinostat, upregulated histone acetylation consequently repressing cell proliferation and survival in TNBC cell lines (168). Moreover, panobinostat abrogated cell cycle progression and induced apoptosis in these cell lines. In addition, panobinostat suppressed tumor formation and reversed EMT in *in vivo* TNBC models (169). Furthermore, HDAC inhibitors stimulated TNBCs to express ER and thus increased their sensitivity to ER-targeted endocrine therapy (170). As a result, clinical trials evaluating efficacy of the co-inhibition of HDAC and aromatase are currently in progress (63).

Heat-shock protein 90 (HSP90) chaperone proteins aid in proper post-translational protein folding and stability of the AR gene product (171). Hence, it has been postulated that LAR TNBCs will exhibit sensitivity to Hsp90 inhibition (57). Lehmann *et al* performed cell viability assays to assess their panel of TNBC cells lines for sensitivity to the Hsp90 inhibitor, 17-DMAG (57). The group observed significantly higher sensitivity in LAR cell lines than most of the basal-like and mesenchymal-like cell lines. An *in vivo* study demonstrated the potency of the Hsp90 inhibitor, PU-H71, in TNBC xenografts in which significant tumor regression was observed (172). Hence, these studies support a potential therapeutic role of Hsp90 inhibitors for LAR TNBCs.



### 5.7.1. LAR 2

One of TNBC molecular subtypes defined by Burstein *et al.*, LAR 2, strongly overlaps with Lehmann *et al.* molecular profiling of LAR TNBCs. Hence, this subtype would concurrently benefit from the previously described targeted therapies for LAR TNBCs. MUC1 vaccines may serve as an additional efficacious therapeutic for LAR 2 TNBCs upregulating MUC1 and are currently under clinical investigation (173).

### 5.8. IM subtype

This highly immunogenic subgroup of TNBCs are potentially susceptible to emerging immunotherapies, including immune checkpoint inhibitors, which are currently being investigated in clinical trials. Programmed death ligand 1 (PD-L1) signaling allows immunogenic tumors to escape an immune response attack from the host (63). PD-L1 Inhibitors such as the anti-PD-1 monoclonal antibody, pembrolizumab, suppresses T-cell activity and has displayed promising preliminary results in clinical trials however, the validity of PD-L1 expression as a selective biomarker to predict patient susceptibility to these agents remain controversial (63,174-175). The role of incorporating immune-checkpoint inhibitors with other immunotherapies and/or chemotherapy regimens is also currently under heavy clinical investigation. Results from the I-SPY2 trial reported that the PD-L1 inhibitor, atezolizumab, elicited a 66.7.% ORR in 32 metastatic TNBC patients when added to nab-paclitaxel in a phase Ib study and has entered phase III trials. Furthermore, atezolizumab has received FDA approval for urothelial carcinoma along with its companion diagnostic, Ventana PD-L1 assay (175).

#### 5.8.1. BLIS

This immune-suppressed subtype identified by Burstein *et al.*, may be more susceptible to monoclonal antibody technology that can stimulate an immune response as a therapeutic strategy. Monoclonal antibodies such as PDI and VTCNI, have been proposed to eradicate BLIS tumors (76). These tumors may also exhibit sensitivity to MUC1 vaccines as MUC1 hinders the ability of immune cells to interact with their cancer surface cell receptors to stimulate an anti-tumor immune response (176). Thus, MUC1 vaccines have been postulated to trigger the immune system to recruit T-cells that can destroy cells displaying a MUC1 marker (173). Furthermore, evidence that inhibition of PTEN results in elevated PD-L1 expression, suggests that agents down-modulating PI3K signaling may stimulate an anti-tumor immune response (176).

#### 5.8.2. BLIA

As opposed to the BLIS subtype, this highly immuno-active subtype may exhibit sensitivity to immuno-

suppressive therapies such as janus kinase/signal transducer and activator of transcription (JAK/STAT), PD-L1, and colony-stimulating factor 1-receptor (CSF-1R) inhibitors (76). The advantage of targeting the JAK/STAT signaling pathway in solid malignancies remain unclear and more preclinical and clinical studies are needed to establish clinical utility of JAK/STAT inhibitors (178). Preclinical studies have supported the idea that inhibition of STAT activity in cancer can stimulate anti-tumor activity in both *in vitro* and *in vivo* models (178). However, enhancing understanding of the mechanistic role of JAK/STAT activation in driving breast tumor growth is critical to developing efficacious molecular agents that target this pathway in breast cancer patients. Preclinical studies have demonstrated the utility of inhibiting stimulation of tumor-associated macrophages through blocking activation of CSF-1R to suppress tumor growth and metastasis (179). Preclinical success has streamlined CSF-1R inhibitors into clinical trials (179).

Overexpression of cytotoxic-T-lymphocyte-antigen-4 (CTLA-4) in this subset of TNBC patients suggests potential sensitivity to anti-CTLA-4 monoclonal antibodies, which are currently being explored in clinical trials (76,180). The CTLA-4 inhibitor, ipilimumab, has already been approved by the FDA for metastatic melanoma, and is currently under clinical evaluation in breast cancer along with tremelimumab, another CTLA-4 inhibitor (63,181).

### 5.9. HER2-enriched TNBCs

As previously mentioned, HER2-enriched TNBC gene expression profiles overlap with those of the BL2 and acutely LAR TNBC subtypes. Hence, HER2-enriched TNBCs presumably may respond favorably to the therapeutic options previously discussed for BL2 and LAR TNBCs, particularly anti-AR therapy and PI3K inhibitors. With the presence of p53 mutations robustly underlying the onset of HER2-enriched TNBCs more than any other TNBC subtype, one can infer that p53-restoring agents should strongly be considered as a therapeutic option for this subgroup of TNBCs. A VEGF signature present in HER2-enriched TNBCs, may render this subset of patients susceptible to VEGF inhibitors as well. Neratinib tested in the I-SPY2 clinical trials may benefit HER2-enriched TNBCs as the PAN-ERBB inhibitor also improved pCR in TNBC patients with phosphorylated ERBB2 arms when administered with paclitaxel (182). Vaccines designed to target HER2 are currently under clinical investigation. AE37, a HER2 peptide, recently exhibited promising results in two phase II clinical studies in which TNBC patients expressing low levels of HER2 displayed a 60% reduction in recurrence (183-184). Hence, this vaccine may enter into phase III clinical trials (63).

### 5.10. Claudin-low TNBCs

This newly defined subgroup of TNBCs is also strongly characterized by stem cells and breast tumor

initiating cells. Thus, the unveiling of this previously concealed TNBC subtype may incite more of an incentive for researchers to devise molecular agents to eradicate cancer stem cells and streamline clinical investigations evaluating their efficacy. As previously proposed for MSL TNBCs, HDAC inhibitors and therapeutics targeting regulators of cancer stem cells such as Wnt inhibitors may presently serve as the best option in modulating cancer stem cell activity in this subgroup of TNBCs. With harboring an angiogenesis gene signature, claudin-low TNBCs may also exhibit sensitivity to angiogenesis inhibitors such as VEGF inhibitors. Therapies targeting EMT as previously described may also demonstrate utility in this subset of TNBCs enriched for genes regulating EMT activity.

In sum the targeted therapies discussed hitherto may help better treat subsets of TNBCs defined by their unique profile of biomarkers. These targeted therapies may also be administered to patients in combination with standard chemotherapy regimens to boost pCR rates and OS/PFS. Moreover, companion diagnostic assays that can sensitively identify these biomarkers in a clinical setting to preselect patients for targeted therapy will also be required to augment utility of these drugs in managing TNBC.

## 6. FILL TWO NEEDS WITH ONE DEED: TARGETING ETHNIC DISPARITIES IN TNBC

Intriguingly, racial disparities exist within the inherently aggressive TNBC subtype. As previously mentioned, pre-menopausal African-American (AA) women are overwhelmingly more afflicted with TNBC compared to women of other ethnicities, which is primarily underlying their substantially lower survival rates and poorer clinical outcomes (185-186). Moreover, studies show higher incidence rates and earlier age of onset of TNBC in native African women compared to AA women (187-188). Moreover, accumulating evidence suggests that even among TNBCs, AAs experience poorer clinical outcomes such as lower OS and PFS than EAs owing to more unfavorable clinico-pathological features such as larger tumor size, higher proliferation, more extensive lymph node involvement, and presentation at a younger age (188-190). In addition, ITH was recently found to be greater in AA compared to European-American (EA) TNBC tumors (191). Further evidence has uncovered that AA TNBCs harbor more aggressive TNBC subtypes such as BL1 and MSL while EA TNBCs harbor more favorable TNBC subtypes such as LAR (189,191). These unsettling statistics necessitate further investigation into the potential molecular drivers underpinning disparities in tumor biology between AA and EA TNBCs.

Several studies are addressing inherent biological differences between AA and EA TNBCs. A comparative analysis revealed higher Ki-67 and c-Kit expression and lower CK5, CK8, CK19, CD44 and AR

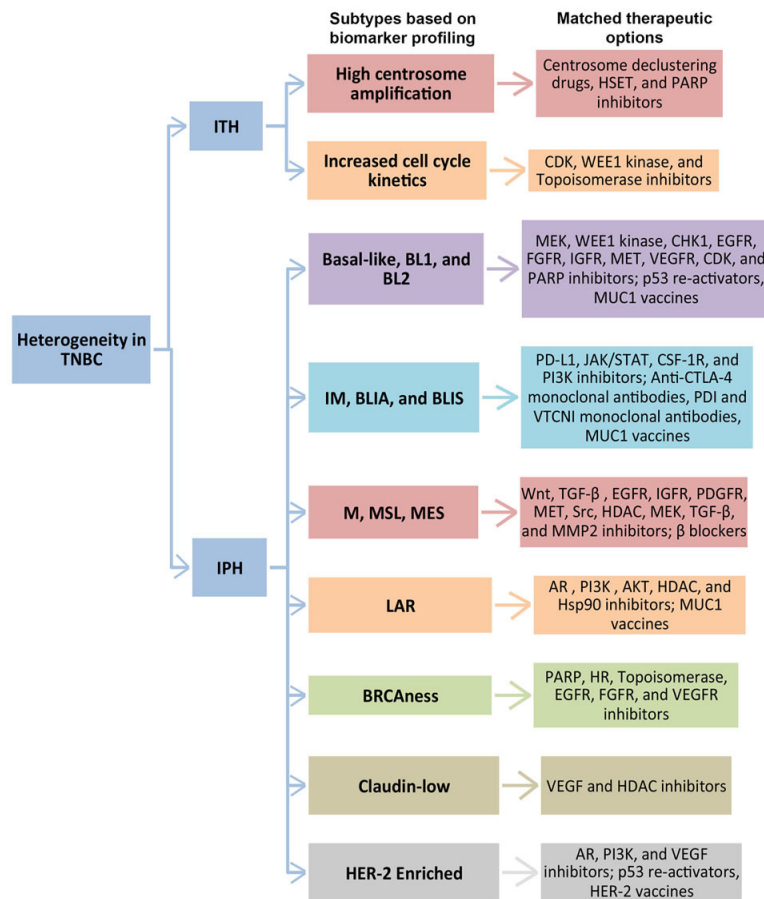
expression in AA than EA TNBC patients (189). Linder *et al.*, transcriptionally profiled AA and EA TNBC samples and observed increased loss of BRCA1 expression and upregulation of IGFR and VEGF in AA compared to EA tumors (192). The group also found higher IGF-1 and VEGF activity and tumor vascularization in AAs compared to EAs among TNBC tumors. Gene-expression studies have uncovered considerably more upregulation of Wnt- $\beta$ -catenin signaling in TNBC patients of African descent compared to TNBC patients of European descent (188). Nalwoga *et al.*, detected notably more enrichment of aldehyde dehydrogenase 1 (ALDH1), a cell surface marker associated with cancer stem cells, in TNBC tumors of African origin compared to TNBC tumors of non-African origin (193). Therapies targeting the previously mentioned inherent molecular differences distinguishing AA from EA TNBCs, such as PARP, IGFR, VEGF, and Wnt inhibitors, may potentially aid in attenuating the ethnic disparity in TNBC.

Disproportions in access to health care and co-morbidity have been hypothesized to contribute to poorer clinical outcomes in AA TNBCs (188). Specifically, disparities in socioeconomic status, diet, physical activity, disease screening, treatment regimens, and more advanced stage and grade upon presentation have been speculated to underlie the racial disparity in TNBC outcomes (188). Co-morbid conditions such as obesity and tissue inflammation have been suspected to drive the more aggressive TNBC tumor biology observed in AA women (188). One study supported this speculation as high body mass index and high waist/hip ratio was demonstrated to elevate the risk of AA women developing basal-like TNBC (194). Obesity often co occurs with the onset of tissue inflammation in which elevated levels of insulin and inflammatory cytokines has been associated with a poorer prognosis in TNBC (195-197). Furthermore, reproductive risk factors such as increased parity and shorter breastfeeding duration, prevalent among the African-American community, has been linked to increased incidence of TNBC (187).

Thus, more comprehensive studies are necessary to elucidate potential molecular drivers underpinning more aggressive tumor biology in AA TNBCs. The uncovering of these molecular distinctions may lay the foundation for parallel co-development of drugs and companion diagnostic assays to provide a more robust, personalized treatment plan for AA patients, which may aid in alleviating the racial disparity in TNBC.

## 7. YET ANOTHER FORMIDABLE CHALLENGE: INTRATUMOR HETEROGENEITY

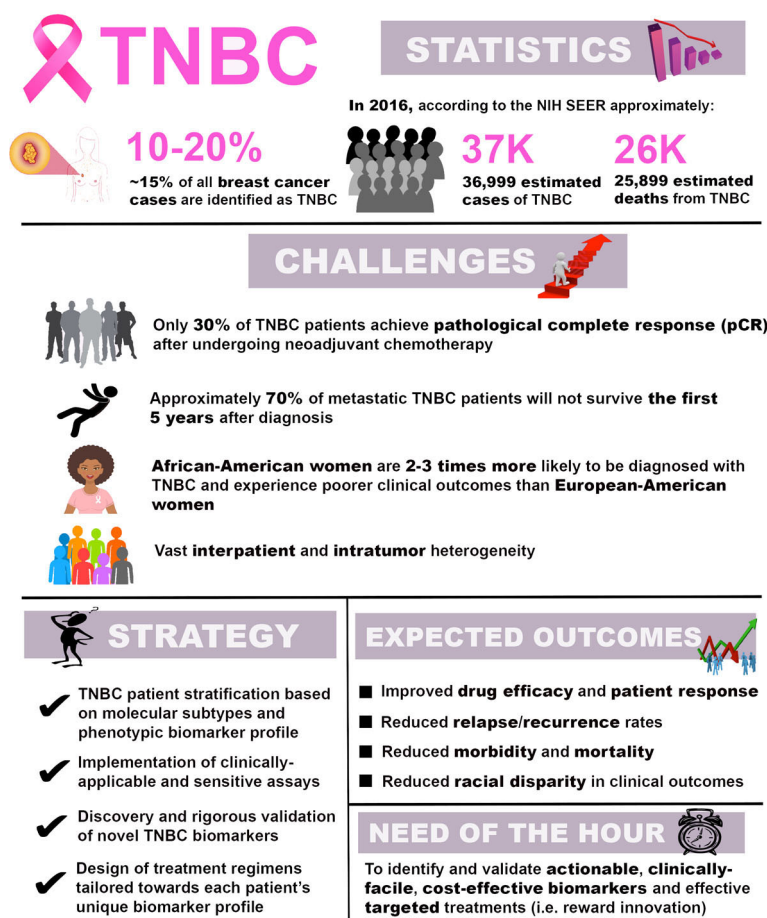
In addition to the stark interpatient heterogeneity (IPH) in clinical behavior among TNBCs,



**Figure 1.** Interpatient- and intratumor- heterogeneity in TNBC. Stratification of TNBCs into distinct subgroups based on precise biomarker profiling along with accompanying therapeutic options.

another feature responsible for the aggressive nature of the disease is intratumoral heterogeneity (ITH). ITH, the diversity of malignant phenotypes within a tumor, engenders tumors with increased invasive/metastatic and chemoresistant capabilities (198). Targeting a highly diversified tumor comprised of a multitude of cell clones equipped with different “weapons” is not only more challenging but also impractical. Thus, it makes sense to investigate more deeply the molecular mechanisms driving ITH in TNBCs to uncover actionable therapeutic targets. Centrosome amplification (CA) and increased mitotic propensity (MP) have been suggested to be critical drivers of ITH (199). CA, frequently observed in cancer cells, often drives chromosomal instability (CIN) through inducing an aberrant, multipolar mitosis that leads to the improper segregation of chromosomes into each daughter cell (200-201). CA has also been proposed to promote tumor cell aggressiveness through CIN-independent mechanisms (202). This increase in cell division errors can foster the accumulation of diverse clones that are more likely to harbor karyotypes that may enable the tumor to overcome therapeutic and other environmental challenges within the host. Thus,

CA serves as a “vehicle” to ITH (203). CA is more rampant in TNBCs compared to non-TNBCs (204). Hence, CA may serve as an efficacious therapeutic target to preclude ITH and poor clinical outcomes in TNBC patients. Fortunately, cancer cells harboring extra centrosomes can be selectively eradicated while normal, healthy cells can be spared (205). These agents include putative centrosome declustering agents such as griseofulvin, commercially available HSET inhibitors, such as CW069, and PARP inhibitors, such as GF-15 (206-208). Successful elimination of cells harboring extra centrosomes may prevent acquisition of ITH and subsequent selection of more aggressive clones in TNBC patients. It will be worth evaluating if differences in the extent of CA drive differences in clinical outcome and response to chemotherapeutic agents among TNBCs, and if quantitation of the extent of CA may serve as a diagnostic test for the prescription of centrosome declustering agents as potentially non-toxic chemotherapeutics. In addition to CA, a faster turnover rate of proliferating cells (or MP) can also lead to the brisk generation of ITH as tumor cell mitoses are inherently more error-prone (203). Importantly, several agents targeting cell cycle machinery are



**Figure 2.** Overview of challenges and strategies for the successful management of TNBC. Summary of current challenges facing the clinical management of TNBC along with proposed strategies for long-term improvement of TNBC prognosis and clinical outcomes.

already in clinical trials. These drugs include CDK inhibitors such as Palbociclib, WEE1 kinase inhibitors, such as AZD1775, and topoisomerase inhibitors, such as doxorubicin (209-211). Successful selection of TNBC patients that will exhibit susceptibility to agents that target these critical drivers of ITH will indubitably require the development of clinically-applicable methods that precisely quantitate both CA and MP within patient tumors and aid in stratification of patients into low- and high-risk groups.

## 8. THE NEED OF THE HOUR: A FOCUSED PUSH TO FIND NEW TREATMENTS FOR TNBC

Given the prohibitively complex molecular landscape of TNBC and the astonishing levels of IPH and intra-ITH that TNBC presents, there is a crucial need to find (a) clinically-translatable and reliable biomarkers for the deeper and more fine-grained segmentation of this patient population, and (b) new targeted treatments to refine and improve

the long-term management of TNBC (Figure 1). The segmentation of the TNBC into numerous subgroups, defined either by their specific tumor molecular alterations, or organellar and cellular phenotypes may lay the foundation for a paradigm shift in TNBC treatment from a heavily chemotherapy-centered “one size fits all” archetype to a subtype-dependent and targeted therapeutic approach. Such an individualized approach to TNBC management may also alleviate the racial disparity in TNBC outcomes among patients with different biogeographic ancestry. This review offers a framework for parsing this complex disease and is meant to serve as a call to action to identify and validate new treatment-relevant biomarkers and targeted therapies so that “niche” therapeutic plans may be developed to better match each patient’s unique disease (Figure 2). In fact, the “therapy bundle” could “evolve” along with the disease course of the patient, offering better optimized solutions for the patient at each stage of their disease. It may indeed be true that, “You can’t be all things to all people”. But careful stratification of TNBCs and personalized treatment helps clinicians give it their best shot.



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**Send correspondence to:** Ritu Aneja, 100 Piedmont Ave., Atlanta, GA 30303, Tel: 404-413-5380, Fax: 404-413-5301, E-mail: raneja@gsu.edu

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