

# Triple Negative Breast Cancer (TNBC): A Challenge for Current Cancer Therapy

## Abstract

Breast cancer is one of the most common causes of worldwide human deaths. Triple Negative Breast Cancer (TNBC) is advanced cancer does not show immune histochemical expression of estrogens receptors, progesterone receptors or HER2 and it not respond to their respective therapy. It was found that approx 20% of breast cancer is a triple negative. The description of well-defined molecular subtypes of breast cancer, together with the identification of the driving genetic alterations and signalling pathways, has led to chance of the clinical development of a number of successful molecular targeting and therapeutic agents. At present, no suitable treatment option is available for patients with TNBC. This short review presents recent information associated with an improved understanding of the biology of TNBC that has led to development of new chemotherapy drugs, such as platinum compounds, antibodies, siRNA and several targeting agents, including poly (ADP-ribose) polymerase inhibitors, epidermal growth factor receptor (EGFR) inhibitors, angiogenesis inhibitors, vascular endothelial growth factor (VEGFR). Ongoing clinical trials will further define the optimal chemotherapy regimen and most effective targeted therapeutic strategy for TNBC.

**Keywords:** TNBC; Estrogens; Progesterone; HER2; EGFR inhibitor

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**Abbreviations:** TNBC: Triple Negative Breast Cancer; VEGFR: Vascular Endothelial Growth Factor; EGFR: Epidermal Growth Factor Receptor; MDR: Multi-Drug Resistance; LAR: Luminal Androgen Receptor; PR: Progesterone Receptor; MSL: Mesenchymal Stem-Like

## Introduction

Breast cancer is a big challenge for universal public health and has made as nuisance for every people who suffered from this disease. It is the second most common cause of cancer-related deaths in women worldwide. Triple-negative breast cancer (TNBC) is an advanced multi-drug resistance (MDR) breast cancer which affect majority of women worldwide Bakrania et al.<sup>1</sup> TNBC is distinct by the lack of estrogens receptor (ER), progesterone receptor (PR) expression, and normal human epidermal growth factor receptor 2 (HER2). Breast cancer is a leading cause of cancer deaths in women, it was estimated that worldwide over 508 000 women died in 2011 due to breast cancer Global Health Estimates, WHO 2013 in that about 12% to 20% (more than 1 out of 10) of cases being classified as triple-negative breast cancer. It is well known fact that ER, PR and HER2 receptor protein are absent in triple negative breast cancer cells Fleisher et al.<sup>2</sup> Consequently, it does not respond to hormonal therapy such as tamoxifen or aromatase inhibitors and other or therapies that target and inhibit HER2 receptors, such as trastuzumab or other related drugs. In a previous study it was found that a higher rate of basal-like breast cancer in premenopausal women compared with postmenopausal women. The prognosis of TNBCs generally found in more likely to be younger than 40 years Criscitiello et al.<sup>3</sup>; Anders et al.<sup>4</sup>

Given the lack of validated molecular targets and the poor outcome in patients with TNBC, there is a clear need for a greater understanding of TNBC at all levels and for the development of better therapies Chavez et al. 2012. TNBC share common clinical features such as poor long term prognosis or a specific pattern of relapse, mainly during the first five years after diagnosis. TNBC has a higher mortality and risk of metastasis compared with other subtypes

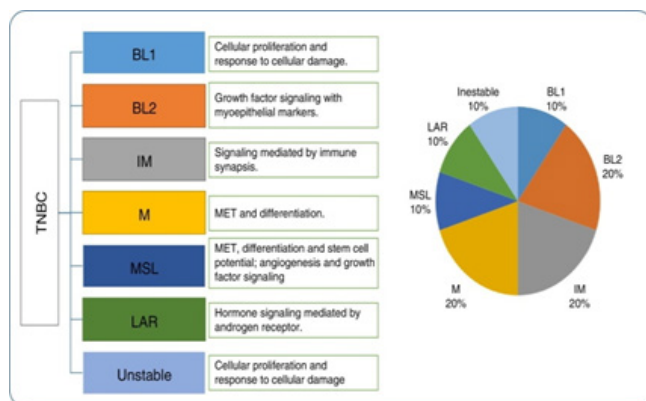
of breast cancer. In addition; it is highly invasive and is associated with a high local reappearance risk, and poor cancer-specific and disease-free survival Ocana & Pandiella.<sup>5</sup> Breast cancers exhibit very different clinico-pathologic characteristics and increasingly defined patterns. TNBC often includes high grade, high production rate and necrosis Badve et al.<sup>6</sup> TNBC can increase in women with germline BRCA1 mutations and about 70% of the breast cancers that TNBCs express programmed death-ligand (PD-L1), cancer cells and tumour-infiltrating inflammatory and immune cells both are expressed by a transmembrane protein.

PD-L1 binding to programmed death 1 (PD-1) on T cells is one potential mechanism of tumour immune evasion Tung et al.<sup>7</sup> Triple negative tumours share specific morphologic characteristics which include markedly elevated mitotic count, tumour necrosis, pushing margin of invasion, and stromal lymphocytic response and high nuclear-cytoplasmic ratio. Histological, they are generally ductal invasive carcinomas, but other histologies can also be found, such as metaplastic and medullary. TNBC is characterised by the marked expression of certain biomarkers. The presence of these molecules though is not restricted to TNBC but somehow show increased prevalence in this subgroup Yadav et al.<sup>8</sup>

## Molecular subtypes of TNBC

Several molecular sub classifications of TNBC have been proposed based on gene expression profiling Lehmann et al.<sup>9</sup> One of the most frequently used sub-classifications was proposed by Lehmann et al and included six subtypes: two basal-like (BL1 and BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and a luminal androgen receptor (LAR) subtype (Figure 1). More recently, the same investigation revised the classification system into four subtypes only, including BL1, BL2, M, and LAR Szekely et al.<sup>10</sup> TNBC is usually associated with basal-like intrinsic subtype. A basal-like subtype is termed after the basal epithelial layer cells due to their similarities in gene expression pattern. Basal-like breast cancers typically express basal cytokeratins such as CK5/6, CK17

as well as cadherin, and epidermal growth factor receptor (EGFR) Nielsen et al.<sup>11</sup> Claudin-low is another less common subtype of TNBC that shows low expression of luminal differentiation markers, low expression of genes involved in tight cell junctions such as E-cadherin, intense immune infiltrate, high enrichment for epithelial-to-mesenchymal transition (EMT) markers and stem cell-like features that may be enriched in BRCA pathway alterations Goldhirsch et al.<sup>12</sup> The clinical relevance of these subtypes is yet to be defined in possible studies. However, several potentially therapeutically important TNBC Szekely et al.<sup>10</sup>



**Figure 1** Type of Triple Negative Breast Cancer (TNBC).

### Some potential targeted treatments in TNBC

The goal of improving survival in TNBC, the study is focusing on identifying potential molecular targets and markers to guide treatment options for this heterogeneous group of breast cancers Costa et al.<sup>13</sup> growth factor receptors such as EGFR are expressed in a large portion of basal-like TNBC; EGFR is one of the members of four closely related receptors each perform a significant role in tumour cell survival. The four receptors being EGFR (or ErbB-1), HER-2/neu (ErbB-2), HER-3 (ErbB-3), and HER-4 (ErbB-4). The inactive monomer receptor dimerizes after ligand activation followed by TK, intracellular domain of the receptor is activated by autophosphorylation, leading to cascade of intracellular events. EGFR signal cascade is important for cell proliferation, angiogenesis, metastatic spread, and the inhibition of apoptosis Siziopikou et al. 2007. Other potential targets in TNBC include the vascular endothelial growth factor receptor (VEGFR).

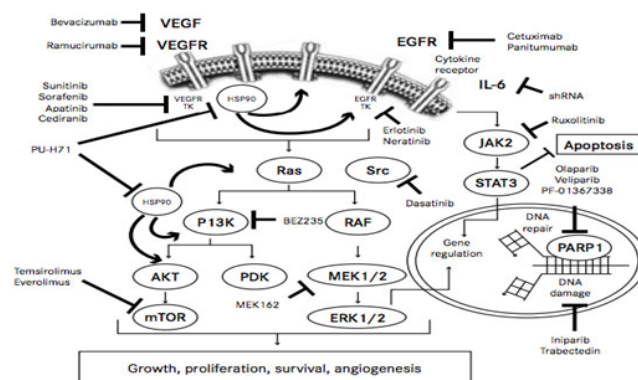
### Vascular endothelial growth factor

Angiogenesis is important for tumour growth and spread especially beyond a diameter of 2 mm as oxygen and nutrients cannot spread beyond this space. Angiogenic signals are mediated by vascular endothelial growth factor (VEGF) to aid neovascularisation. VEGF A, B, C, D, E (viral factor) and placental growth factor is a family of six proteins VEGF shows multiple interactions with receptor TKs, such as VEGFR-1, VEGFR-2, and VEGFR-3. The angiogenesis is initiated by VEGF binding to VEGFR-2 which triggers the specific activation of TKs followed by multiple signalling cascades resulting in the endothelial cells survival, proliferation, migration, adhesion, actin remodelling and vessels permeability Iosifidou et al. 2008 and broblast growth factor receptor (FGFR).

Amplification of FGFR1 is found in approximately 9% of TNBC and FGFR2 in 2% to 4% of TNBC. And other is PARP: PARPs are a family of cell signalling enzymes present in eukaryotes, which catalyses the poly (ADP ribosylation) of DNA binding proteins. Till now eighteen enzymes of PARPs has been detected, but PARP1 the most common isoform. PARP1 is responsible for majority

of its functions. Main function of PARP1 is as DNA damage nick sensor. It forms polymers of AD ribose and Nicotinamide with use of NAD<sup>+</sup>. Activation of PARP1 is important in tumours because of three interesting biological reasons: First, it plays a vital role in DNA repair through base excision repair pathway; second, it is capable of depleting cellular energetic pools, which results in cell dysfunction and necrosis; and third, its ability to promote the transcription of proinflammatory genes. Studies have indicated that TNBC can be divided into distinct subtypes that have unique responses to treatment Farmer et al.<sup>14</sup> Finally, there is an immunomodulatory and luminal androgen receptor subtype that involves androgen signaling.

Each subtype has distinct pharmacologic targets and can help guide treatment Costa et al.<sup>13</sup>, (Figure 2) Current treatment strategies include many chemotherapy agents, such as the anthracyclines, taxanes, ixabepilone, and platinum agents, as well as selected biologic agents and possibly anti-EGFR drugs The anti-EGFR monoclonal antibody cetuximab has been shown to have limited activity as single agent in TNBC Rugo et al.<sup>15</sup> but does increase the antitumor activity of platinum salts. In one randomized Phase II study about, cetuximab given in mix with cisplatin resulted in a doubling of the response rate and improvement in time to disease progression and survival when compared with cisplatin alone Baselga et al.<sup>16</sup> However, the performance of cisplatin as a single agent was disappointing, and it is not clear that the combination of cisplatin and cetuximab would to positively with conventional therapy in this disease setting. Nevertheless, these results cannot be ignored; as they point out that a subpopulation of TNBC may be sensitive to EGFR inhibition. The anti-VEGF-A monoclonal antibody bevacizumab was the first anti-angiogenic strategy to be rigorously evaluated in breast Sunitinib (Sutent; Pfizer) is a small-molecule multi-TKI that targets KIT, FLT3, RET, VEGFR2, and PDGFRB Deprimo et al.<sup>17</sup> In breast cancer, a single-agent Phase II study demonstrated clinical benefit in 16% of 64 heavily pretreated patients Miller et al.<sup>18</sup>



**Figure 2** Mechanism of cytotoxic action of different therapeutic agent.

In any case, two studies with sunitinib, either alone versus capecitabine or in mix with paclitaxel versus bevacizumab plus paclitaxel have been recently closed due to futility Sorafenib is another multikinase inhibitor targeting VEGFR1, VEGFR2, VEGFR3, PDGFRB, RAF, KIT, and FLT-3 Michaela et al.<sup>19</sup> The failure of bevacizumab to prolong OS has tempered expectations for the success of anti-angiogenic TKIs, but these compounds certainly have activity, and translational work to identify the subgroup of responsive patients will be critical. The lack of success of anti-angiogenic therapies to date in breast cancer may in part be explained by activation of additional pro-angiogenic switches upon blockade with bevacizumab, as has been shown in experimental systems Páez-Ribes et al.<sup>20</sup>

## Conclusion

The development of resistance to all of these therapies is an ongoing challenge and opportunity for learning. In concert with robust clinical trials of these agents, biomarkers of response or prediction of benefit to these interventions must be developed and validated. Just as cancer is a dynamic, adaptive process, so too must our clinical trial designs become innovative, flexible, and informative<sup>21</sup>. In this way we will select the right patient, for the best drug or combinations of drugs, at the most effective time few targeted therapies are being effectively developed like Poly (ADP-ribose) polymerase-1 (PARP-1), which is a nuclear DNA-binding enzyme activated by DNA strand breaks and has a key role in the signaling of DNA single-strand breaks as part of the repair process. Initial exciting data suggesting that iniparib improved outcome in patients with TNBC in combination with chemotherapy have not been confirmed in phase III studies, although there are clearly patients who benefit from this agent. Several other targeted agents are being developed in the setting of managing TNBC including epidermal growth factor receptor (EGFR), FGFR2, VEGF.

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## Conflicts of Interest

None.

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