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TRIPLE-NEGATIVE BREAST CANCER: AN OVERVIEW.

SARVANTI R. BHAIRI* AND DEEPALI M. JAGDALE

Department of Pharmaceutical Chemistry, Bharati Vidyapeeth's College of Pharmacy,Sector-8, C.B.D. Belapur, Navi Mumbai, Maharashtra, India – 4006r

ABSTRACT

The term "triple-negative breast cancer (TNBC)" refers to the subtype of breast cancer and is defined by the lack of expression of genes for hormone receptors (estrogen and progesterone receptors) and human endothelial growth factor 2 (HER2) protein. Absence of these receptors makes the treatment difficult because the drugs tamoxifen and transtuzumab, which act on hormone receptors and HER2 respectively and inhibit cell division, can no longer be prescribed. Hence, conventional cytotoxic therapies remain the main treatment approach. Despite of sensitivity of tumor cells to cytotoxic agents, relapse and metastatis is commonly seen and also survival rate is poor. Considering all these problems, in the present review, we have discussed various types of TNBCs and its treatment approaches which includes surgery, chemotherapy and some targeted therapies such as poly(adenosine diphosphate [ADP]-ribose) polymerase inhibitors, tyrosine kinase inhibitors, mammalian target of rapamycin inhibitors, fibroblast growth factor receptor inhibitors, androgen receptor inhibitors, inhibition of trop-2, inhibition of JAK2/STAT3 pathway and gamma secretase inhibitors.

KEYWORDS:Breast cancer, triple-negative, basal-like, epidemiology, targeted therapy

SARVANTI R. BHAIRI
Department of Pharmaceutical Chemistry, Bharati Vidyapeeth's College of Pharmacy, Sector-8, C.B.D. Belapur, Navi Mumbai, Maharashtra, India – 4006r

INTRODUCTION

Breast cancer is the most common disease among women in the United States. Every year about 2 million cases of breast cancer are diagnosed worldwide, of that nearly15% to 20% are of triple negative (TN) phenotype. This subtype of breast cancer is diagnosed based upon the presence or absence of three "receptors" viz., estrogen receptor (ER), progesterone receptor (PR) and human endothelial growth factor 2 receptor (HER2) (Fig. 1). The most effective treatments for breast cancers target these receptors. Unluckily, none of these receptors are found in women with triple negative breast cancer (TNBC). Therefore, the drugs like transtuzumab (which act on HER2) and tamoxifen (which act on Estrogen and progesterone receptors), can no longer be effective. Triple negative breast cancer often overlaps with the term 'basal-like breast cancer' (BLBC) which is the molecular subtype of TNBC. Gene expression analysis depicts that the molecular characteristics of TNBC generally overlaps with BLBC.[1] Studies revealed that approximately 75% of TNBCs are basal like tumors.[2] More than 90% of TNBCs and BLBCs are present as invasive ductal carcinomas of no special type. They are usually of high grade, demonstrate a high mitotic index and contain central necrotic index, pushing borders of invasion and obvious lymphatic infiltration. However, not all the TNBC can be defined by BLBCs, as a small percent of BLBC patients do have some ER and HER2 expression.[1] Similarly a small percent of TNBC patients also have shown other molecular subtype of breast cancer, which is 'claudin-low' subtype. Till date, many efforts were made to distinguish between basal and non-basal subtypes within TNBC; but there is yet no clinical value in understanding whether a TNBC is of basal-like or other intrinsic subtype of breast cancer. Therefore TNBC and BLBC should never be synonymous and they should always be considered two separate categories for clinical as well as research purpose.[3] TNBC also encompasses other molecular subtypes of breast cancer which are discussed later in this article.

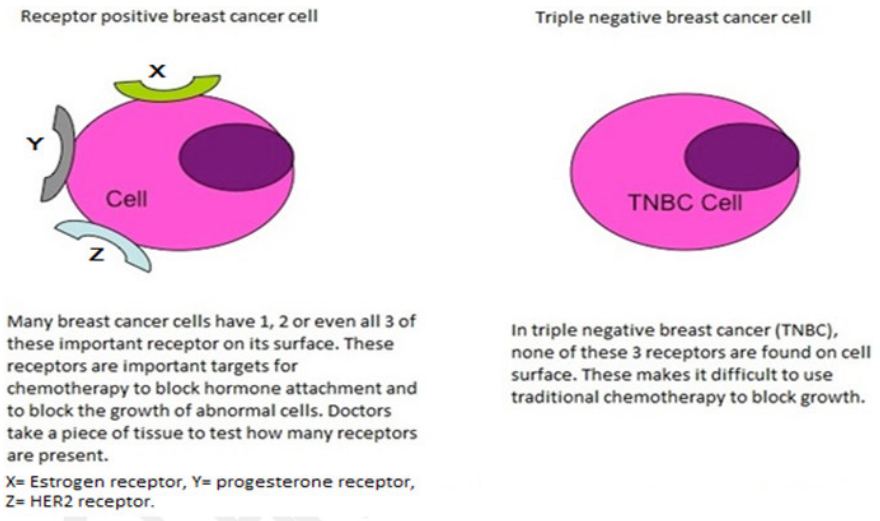

Figure 1

Diagrammatic representation of difference between normal breast cancer cell and triple negative breast cancer cell.

EPIDEMIOLOGY

Breast cancer accounts for 22.9% of all new cancer cases among women worldwide and 13.7% of cancer deaths.[4] In 2014, 235,030 new cases of breast cancer were estimated in both sexes in US; out of these, 232,670 were in women and 2360 were in men.40430 deaths were reported in both sexes; out of which 40000 were women and 430 were men. Lifetime risk of dying because of breast cancer is 3.4%.[2]Nearly 15-20% cases of breast cancer (BC) are of TN phenotype.[1] TNBC is more aggressive subtype of breast cancer which is characterized by high recurrence rates and greater chances of deaths compared to other breast cancers. Recurrence usually occurs within 5 years after diagnosis. If a woman is successfully treated for TNBC and is disease free for 5 years or more then there is almost no risk of cancer coming back. Metastasis often occurs in the lung and the brain. The risk for disease relapse is dependent upon the tumor size and number of lymph nodes found at the time of diagnosis. However, it is important to know that TNBCs at early stage is highly treatable and often curable disease.[5] Breast cancer prevalence is highest among non-hispanic white women, followed by African American women and is lowest in Asian or Pacific Islander women whereas mortality rates are highest for African American women, followed by non-hispanic white women are lowest among Asian or Pacific Islander women.[6] In US, around 15% of all Breast cancers in white women are TNBC compared with 30% in black women.[7]TNBC tends to occur in younger, premenopausal African American women, in women with an elevated hip-to-waist ratio and in women who have had fewer children, have not breast fed or have breast fed for short period of time.[7] It is also associated with BRCA1 and BRCA2 mutation. BRCA2 mutation is rare in TNBC women. BRCA1 mutation is more common in Ashkenazic Jewish women, so these

groups of population are at higher risk of TNBC.[5] Data on TNBC in Indian population is limited because of the financial constraints in performing immunohistochemistry evaluation. In a study conducted at tertiary care hospital in central India, 85 breast cancer patients were enrolled and 37 (43.7%) were of TN phenotype.[8] In another study, conducted at Dr. B. R. A. Institute of rotary cancer hospital, from 706 breast cancer patients, 21.9% patients had TNBC.[9] In a retrospective study, 11.8% breast cancer patients had TN phenotype.[10]

SUBTYPES OF TRIPLE NEGATIVE BREAST CANCER

As described by B D Lehmann, six distinct TNBC subtypes have been identified using gene expression analysis, each having unique biologies.[11] These subtypes have been characterized on the basis of their affected cellular mechanisms (Table 1).

Table 1
TNBC subtypes based upon affected cellular mechanisms

TNBC subtype	Affected cellular mechanism
Basal-like 1 (BL1)	Cell cycle DNA Replication Reactome G_2 Pathway RNA Polymerase ATR/BRCA Pathway G_1 to S Cell cycle
Basal-like 2 (BL2)	Endothelial Growth Factor (EGF) Pathway Nerve Growth Factor(NGF) Pathway MET Pathway WNT β-catenin Pathway Insulin Growth Factor-1 Receptor (IGF1R) Pathway Glycolysis/Gluconeogenesis
Immunomodulatory (IM)	Cytotoxic T-Lymphocyte Associated protein-4 (CTLA4) Pathway Interleukin-12 (IL12) Pathway Natural Killer (NK) Cell Pathway T-helper 1 (Th1)/T-helper 2 (Th2) Pathway Interleukin7 (IL7) Pathway Antigen Processing/Presentation Nuclear Factor KappaB (NFKB) Pathway Tumor Necrosis Factor (TNF) Pathway T cell Signal Transduction DC Pathway B- cell receptor (BCR) Signaling Pathway NK Cell Mediated Cytotoxicity Janus Kinase (JAK)/ signal transducer and activation of transcription (STAT) Signaling Pathway ATR/BRCA Pathway
Mesenchymal-like (M)	Insulin Growth Factor (IGF)/mammalian target of raamycin (mTOR) Pathway Extracellular matrix (ECM) Pathway Regulation of Actin by RHO WNT Pathway Anaplastic Lymphoma Kinase (ALK) Pathway Transforming Growth Factor β (TGFβ) Pathway
Mesenchymal stem-like (MSL)	ECM Receptor interaction T Cell Receptor (TCR) Pathway WNT β-catenin Focal Adhesion Inositol Phosphate Metabolism NFKB Pathway EGF Pathway ALK Pathway GH Pathway Natural Killer (NK) Cell Mediated Toxicity RAC1 Pathway G-Protein Coupled Receptor (GPCR) Pathway Extracellular signal-regulated kinase1/2 (ERK1/2) Pathway Integrin Mediated Adhesion ATP-Binding Cassette (ABC) Transporters General RHO Pathway Smooth Muscle Contraction Calcium Signaling Pathway Adipocytokine Signaling Pathway Platelet derived Growth Factor (PDGF) Pathway TGFβ Pathway
Luminal androgen receptor (LAR)	Pentose/ Glucuronateinterconversion Glutathione Metabolism Tyrosine Metabolism Steroid Biosynthesis Porphyrin Metabolism Androgen and Estrogen Metabolism Flagellar Assembly Citrate Cycle Tricarboxylic acid (TCA) Phenylalanine Metabolism

	ATP synthesis
	Starch and Sucrose Metabolism
	Arginine and proline Metabolism
	Metabolism of Cytochrome P450
	Fructose and Mannose Metabolism
	Fatty acid Metabolism
	Alanine and Aspartate Metabolism
	Elcosanoid Synthesis
	CHREB Pathway
	Tryptophan Metabolism

When compared with the intrinsic subtypes, it was found that BL1, BL2, IM and M are largely composed of basal-like subtype, MSL has large fraction of normal-like and LAR mostly composed of Luminal and HER2 subtypes. Apart from intrinsic subtypes, a claudin-low subtype has recently been described and is enriched for EMT markers, immune response and cancer stem cell-like genes.[12] This claudin-low type is mainly composed of M and MSL TNBC subtypes.[13] Cell lines representative of the six TNBC subtypes demonstrated differential sensitivity to chemotherapy and targeted agents.BL1 cell lines are sensitive to genotoxic agents, LAR cell lines have differential sensitivity to the LAR antagonist bicalutamide and PI3K Inhibitors, M cell lines are more sensitive to the TK inhibitors dasatinib and some sensitivity to PI3K/mTOR inhibitors.[14] A similar genomic analysis was recently performed and the investigators identified four stable TNBC subgroups associated with distinct clinical outcomes. These subgroups are defined as “luminal/androgen receptor (LAR)”, “Mesenchymal (MES)”, “Basal-like/Immune-activated (BLIA)” and “Basal-like/Immune-suppresed (BLIS)”. According to a study, TNBC patients with tumors expressing immune component features had the best outcome. Between the two studies, there has been clearly evident overlap between MSL and MES, IM and BL1 with BLIA, M with BLIS and two LAR subtypes.[14]These findings suggest that the reproducible and distinct transcriptional subtypes can be unmasked in the absence of ER and HER2 expressing tumors and as the sample size is increased there will likely be additional unique subtypes revealed.

DIAGNOSIS

Diagnosis helps the physicians to predict the suitable treatment option. The tests of TNBCs are same as that of other type of breast cancer. The most important test is removing a small piece of tissue from breast and its examination under microscope for cancer cells. Other methods of diagnosis are magnetic resonance imaging (MRI) and ultrasound. MRI is useful technique for screening individuals with known BRCA2 mutation. Patients are subjected to BRCA testing if they have family history of breast or ovarian cancer or they are diagnosed with breast cancer younger than 60 years of age.[15,16] Mammograms could assist in both pretreatment planning and prognosis, as well as add to our understanding of the biologic behavior of this disease. It is recommended to perform mammography each year.[17] Ultrasound technique is useful in finding more information about lumps detected by touch.[7]

TREATMENT

Treatment depends upon the cancer stage and aggressiveness of the disease. Standard treatment is surgery with adjuvant chemotherapy and radiotherapy.

Surgery

Mastectomy is an option to prevent recurrence of cancer in breast tissue. But generally mastectomy is not preferred instead neoadjuvant treatment is given before performing surgery as it reduces the size of tumors, allowing the breast conservation and decreasing the need for mastectomy. A marker is usually inserted into the location of the cancer in case the tumor becomes so small during treatment that an X-ray is needed to locate it later for surgery.

Chemotherapy

Several reports suggests that TNBC or BLBC respond to the chemotherapy better than other types of breast cancer, but still the prognosis is poor because of two factors: shortened disease free interval in the adjuvant and neoadjuvant setting and a more aggressive clinical course in the metastatic setting.[1]TN tumors have good response to anthracycline (doxorubicin, cyclophosphamide) and taxane (docetaxel and paclitaxel) (Fig. 2) based therapy, along with platinum based agents (Cisplatin and carboplatin) (Fig. 3). Combination therapies have shown better results but it is not known exactly that response is due to which drug.[3,18,19] Several studies have shown that TN tumors have good initial response to chemotherapy. However, it is contrary in patients with advanced disease. Also these tumors eventually develop resistance to chemotherapy. However, several studies are going on to treat the patients with advanced disease and metastasis. In a single arm phase II trial conducted by X. U. Binghe et al, capecitabine along with cisplatin has shown overall response rate of 63.6% in metastatic TNBC patients.[20] Several other drugs like brostallicin and eribulin mesylate are under clinical trials for metastatic and advanced disease.[21,22]

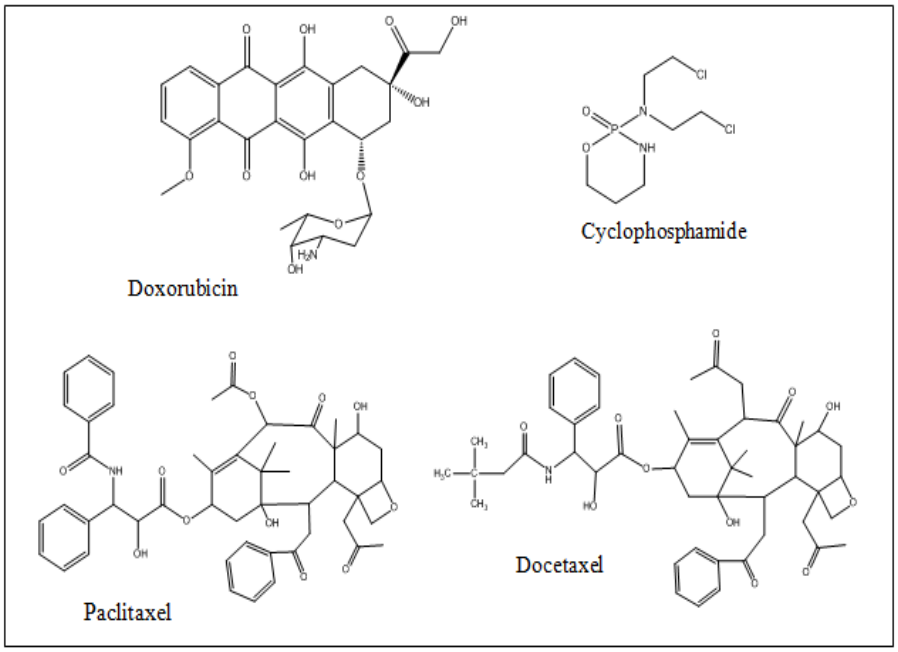

Figure 2
Chemotherapeutic agents.[23]

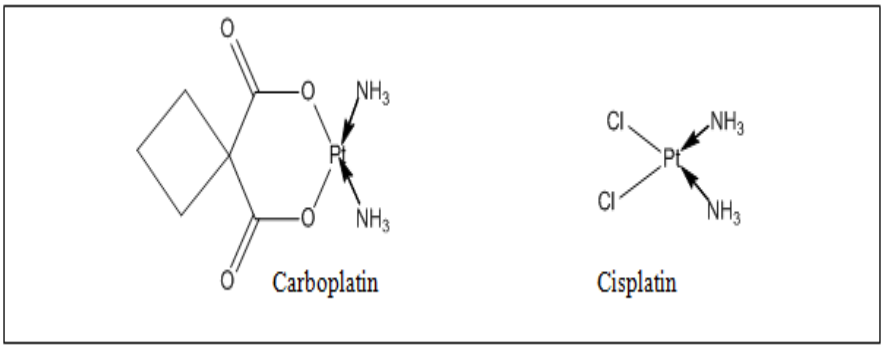

Figure 3
Platinum based agents.[23]

TARGETED THERAPIES

Because the likelihood of metastasis and relapse is high in TNBC, targeted therapies are being investigated. Several enzymes and growth factor receptors are expressed in TNBC, including Poly (ADP-Ribose) Polymerase (PARP), Vascular endothelial growth factor (VEGF), Epidermal growth factor receptor (EGFR), Mammalian target of rapamycin (mTOR), Tyrosine kinase, Fibroblast growth factor receptor (FGFR) and Androgen receptor (AR). Phase II and III clinical trials with drugs that interrupt the EGFR and VEGFR signaling pathways have been conducted in breast cancer, but these approaches are no longer being pursued because it has limited activity in an unselected TNBC population.[24-28]

Poly (ADP-Ribose) Polymerase inhibitors

Cell survival and genomic integrity are dependent on coordinated pathways of DNA repair. Poly (ADP-Ribose) Polymerase (PARP) enzyme play a key role in these pathways by mediating the repair of single stranded DNA breaks via base excision repair. Loss of PARP activity results in accumulation of single stranded breaks, which are normally repaired by tumor suppressor protein BRCA1 and BRCA2. But 10 to 19.8% of TNBC is associated with BRCA1 and BRCA2 mutations. Therefore, cells which are deficient in BRCA genes are sensitive to PARP inhibitor, resulting in cell death and apoptosis.[3] Olaparib (Fig. 4) is an oral PARP inhibitor. Studies have shown that Olaparib have a favorable therapeutic index for a novel targeted treatment strategy in patients with tumors that have BRCA1 or BRCA2 mutation.[17,24,29] In a phase-II, multicenter trial, conducted by K. A. Gelmon et al., 15 non BRCA TNBC patients had no response to olaparib, indicating that olaparib as a single-agent PARP inhibitor is not likely to be a treatment approach for sporadic TNBC.[30] Iniparib (Fig. 4)was originally believed to act as an irreversible inhibitor of PARP1 but its effects against PARP was later disproven.[2,17] Veliparib (Fig. 4) is an oral PARP1 and PARP2 inhibitor. In a study conducted by Isakoff et al., it has demonstrated preliminary activity in phase II study when combined with temozolomide in patients with BRCA mutated TNBC.[31] To date the data suggests that PARP inhibitors as monotherapy is not active in sporadic

TNBC, but preferentially active in BRCA-mutated Breast cancer. Several other drugs like Rucaparib, MK-4827 and PF-01367338 are currently the subjects of early development in TNBC or BRCA-mutated breast cancers.[32,33.]

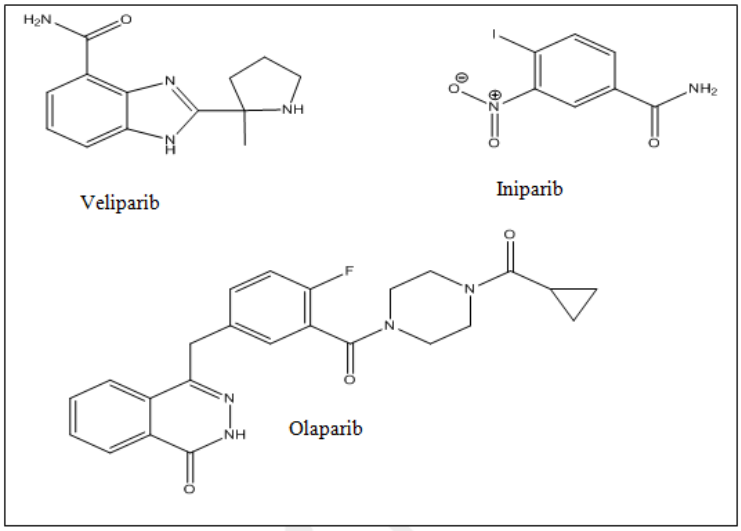

Figure 4
***Poly (ADP-Ribose) Polymerase inhibitors.*[23]**

Tyrosine kinase inhibitors

Src tyrosine kinase is overexpressed in TNBC and is associated with metastatic disease progression. Dasatinib (Fig. 5) when combined with cisplatin have synergistic activity in dasatinib sensitive cell lines. Recently published phase I/II study of dasatinib with weekly paclitaxel showed preliminary activity with a manageable toxicity profile.[3]Recently studied drug SU011248 has shown good response in previously treated advanced TNBC and metastatic breast cancer patients.[34]

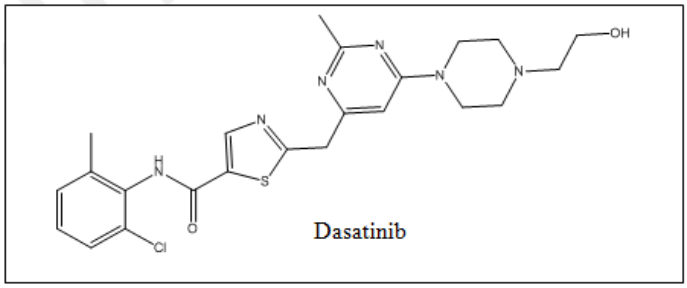

Figure 5
***Tyrosine kinase inhibitors.*[23]**

mTOR inhibitors

mTOR (mammalian target of rapamycin) is an effector of the phosphoinositide3-kinase (PI3K) signaling pathway are frequently affected by mutations in breast cancers and loss of phosphatase and tensin homolog gene (PTEN) is common finding to mTOR activation in the disease.[17] In a phase II trial conducted by Singh J et al., everolimus (Fig. 6), a novel mTOR inhibitor, in combination with carboplatin has shown effective response in metastatic TNBC.[35] Currently, temsirolimus is under clinical trials in combination with bevacizumab and doxorubicin for TNBC patients who are insensitive to standard neoadjuvant chemotherapy.[36]

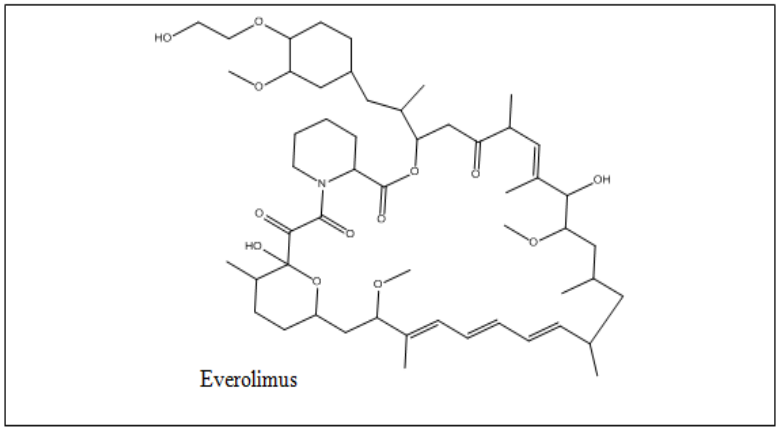

Figure 6
mTOR inhibitors.[23]

Fibroblast growth factor receptor (FGFR) inhibitors
FGFR signaling stimulates cell growth, survival, migration, and differentiation. Nearly 9% of TNBC has FGFR1amplification and approximately 4% of TNBC has amplification of the FGFR2 gene. FGFR mutations are less common in TNBC (< 1%). Cell lines with FGFR1 amplification or FGFR2or FGFR4mutations were sensitive to FGFR inhibitors in cell line models. Additionally, inhibition of FGFR in basal-like TNBC cell lines with FGFR2 amplification led to decreased growth. These data support the clinical investigation of FGFR inhibitors in TNBC, which may only benefit a very small subgroup. Although no current study specifically targets the TNBC population, a phase II trial (NCT02202746) is ongoing in metastatic breast cancer (MBC) evaluating oral lucitanib (Fig. 7)in tumors that have an FGFR1-amplification, and patients with TNBC are eligible.[14] A phase I trial is evaluating JNJ-42756493 in patients with solid tumors, and one cohort includes patients with breast cancer of any subtype as long as the tumors harbor an FGFR translocation or FGFR activating mutation (NCT01703481).[37] These trials with inclusion criteria more selective to specific FGFR alterations may prove more effective than previous trials treating unselected patients with breast cancer.

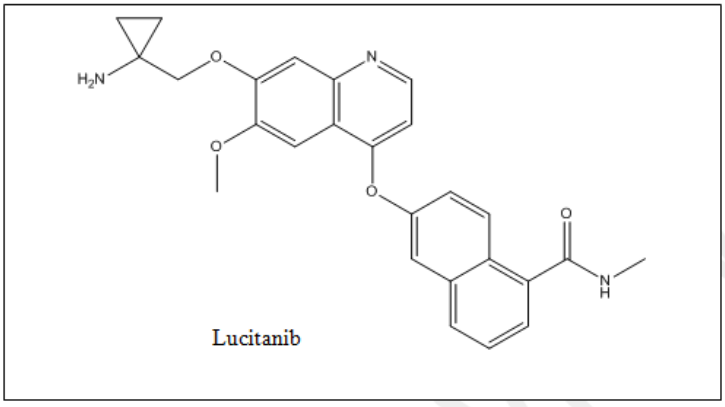

Figure 7
FGFR inhibitors.[23]

Gamma secretase inhibitors
Research is beginning to show that the potential of targeting the notch signal pathway as a possible treatment approach for patients with TNBC. The notch signaling pathway affects many cellular processes including proliferation, apoptosis, angiogenesis, and stem cell self-renewal. Notch receptor is activated by the binding of membrane-bound ligand on a neighboring cell. This results in sequential cleavage by the ADAM17/TACE metalloprotease and gamma-secretase, leading to release of the intracellular domain of notch (NICD). The NICD then translocates to the nucleus, activating downstream target genes, including HES and HEY.[38] A preclinical study showed that TNBC xenograft models with NOTCH1 rearrangements, retaining the gamma secretase cleavage site, were associated with elevated levels of activated NOTCH1 and has sensitivity to gamma-secretase inhibitors.[39] However, there were several rearrangements in NOTCH2 that displayed constitutive signaling and were insensitive to gamma-secretase inhibition. Several drugs like R04929097, PF-03084014 and NCT02338531 are currently being investigated for TNBC.[40-42]

Blockade of Androgen Receptor
Nearly 10% to 15% of TNBC express the Androgen receptor (AR).[43] The LAR subclass of TNBC is characterized by luminal gene expression and enriched for AR and AR gene targets.[44] This is the basis for

targeting this subset of TNBC with anti-androgen therapy. Two anti-androgen drugs bicalutamide and enzalutamide (Fig. 8) have been tested in phase II trials and it has shown clinical benefit rate of 18% and 42% respectively.[45,46] Another anti-androgen therapy under evaluation in AR-positive TNBC is orteronel, which is a nonsteroidal, androgen synthesis inhibitor that has been shown in preclinical studies to selectively inhibit the 17,20-lyase enzymes, critical to the production of androgens.[47] These studies have shown that AR is a promising and suitable therapeutic target in a small subset of TNBC, particularly the LAR subtype.Another drug GTx-024 is under phase II clinical trial for patients with androgen positive TNBC patients.[48]

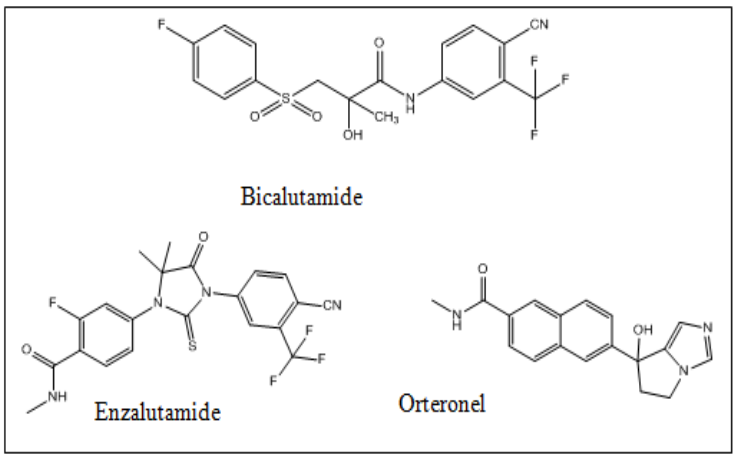

Figure 8
***Anti-androgen agents.*[23]**

Inhibition of JAK2/STAT3 pathway

Janus kinases (JAKs) are tyrosine kinases, and signal transducer and activation of transcription 3 (STAT3) proteins are major components of several cytokine receptor systems which regulate cell growth and survival.[49] Binding of the cytokine to the receptor induces dimerization which activates the associated JAKs. The JAKs also phosphorylate STATs which leads to their dimerization, nuclear translocation, and transcriptional regulation of genes that regulate cell differentiation, proliferation, and apoptosis. There is emerging preclinical evidence that disruption of the JAK2/STAT3 signaling could be an effective clinical strategy to treat TNBC. Ruxolitinib (Fig. 9), a potent JAK1 and JAK2 inhibitor, is being evaluated for patients with metastatic breast cancer.[50] Once the recommended dose is determined, the study will treat patients with triple negative inflammatory breast cancer.

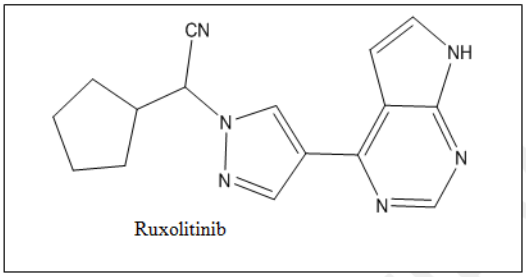

Figure 9
***Janus kinase inhibitor.*[23]**

Inhibition of Trop-2

Trop-2 is a cell surface protein overexpressed in several epithelial cancers, but not in corresponding normal tissues.[51] Trop-2 is a transmembrane calcium signal transducer and is involved in the regulation of cell-cell adhesion.[52]Membrane-associated Trop-2 was found to be associated with poor prognosis in breast cancer.[53] There is a growing interest in targeting Trop-2 in TNBC. IMMU-132 (isactuzumab-govitecan) is an antibody-drug conjugate containing the humanized mono-clonal antibody, hRS7, which is linked to the active metabolite of irinotecan, 7-ethyl-10-hydroxycamptothecin (SN-38).The antibody moiety of IMMU-132 selectively binds to Trop-2; after internalization and proteolytic cleavage,SN-38 is delivered preferentially to the tumor cells. Preclinical data shows that IMMU-132 resulted in decreased tumor growth in MDA-MD-468 TNBC xenograft models, compared to irinotecan or to the antibody-drug conjugate control.[54] IMMU-132 received approval in January 2015 from the FDA for treatment of patients with TNBC who have progressed on prior therapies for metastatic disease. A phase I trial of IMMU-132 was conducted in advanced epithelial cancers, including TNBC. There was no prescreening for Trop-2 expression. The recommended phase II dose of IMMU-

132 was 10 mg/kg intravenously on days 1 and 8 of a 21-day cycle. A phase II trial will treat 80 patients with metastatic TNBC who have received two or more prior regimens with IMMU-132 alone or in combination with carboplatin.[54] Further research is necessary to evaluate the strategy of using antitrop-2 therapy for breast cancer and the relationship of Trop-2 expression to response.

CONCLUSION

The term TNBC covers a heterogeneous group of tumors that show distinctive, but rather heterogeneous, pathological and the clinical features. Although, patients with TNBC respond to neoadjuvant chemotherapy, but chemotherapy has many side effects. Various targeted therapies such as PARP inhibition, FGFR inhibition, mTOR inhibition etc are used to treat TNBC. In spite of this survival of patients is still poor and their management may require a more aggressive alternative intervention, therefore, the development of newer targeted therapies for triple negative cancers is of paramount importance. This can be achieved only by understanding the complexity of this heterogeneous group of tumors. Although, it is challenging at first glance but thoughtful planning and coordinated efforts between collaborating preclinical, translational and clinical investigators will continue to move the development of newer compounds and hold the potential to improve the lives of hundreds and thousands of women diagnosed with breast cancer worldwide each year.

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