*Quest Journals*
*Journal of Research in Pharmaceutical Science*
*Volume 9 ~ Issue 12 (2023) pp: 01-11*
*ISSN(Online) : 2347-2995*
www.questjournals.org

**Review Paper**

# Effect of overexpressed protein with different network in breast cancer and advance therapies for triple negative breast cancer: targeted therapy and immunotherapy.

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***Abstract***
*TNBC is an aggressive disease among all the breast cancer subtype. It includes high invasiveness, high metastatic potential, and poor prognosis which are aggregated under this term due to lack of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 expression. In the present status LRRC15, MEX3A, SMYD2 and STAT3 protein along with cytokine receptors interleukin-6 receptor (IL-6R), the interleukin-10 receptor (IL-10R) and its different pathways serves a key role in the pathogenesis of TNBC. Numerous hypotheses based on targeting the pathways explain the ameliorating effect in TNBC. Due to multiple etiological pathways, TNBC cannot be cured with single therapy. Several therapeutic approaches are intended to target the specific pathways, mainly immunotherapy, where immune checkpoint inhibitor and PARP inhibitors displayed an effective role. The immunomarker of immune checkpoint inhibitor PD-1 attached with ligand1 leads to the formation of PD-L1 and it inhibits T cells. Specific biomarkers that can be used as prognostic or predictive indicators for novel therapeutics.*

***Key words:****TNBC, Interleukins, Protein expression, Immune checkpoint inhibitors, PARP inhibitors.*

***R****eceived 18 Nov., 2023;* ***R****evised 01 Dec., 2023;* ***A****ccepted 03 Dec., 2023 © The author(s) 2023.*
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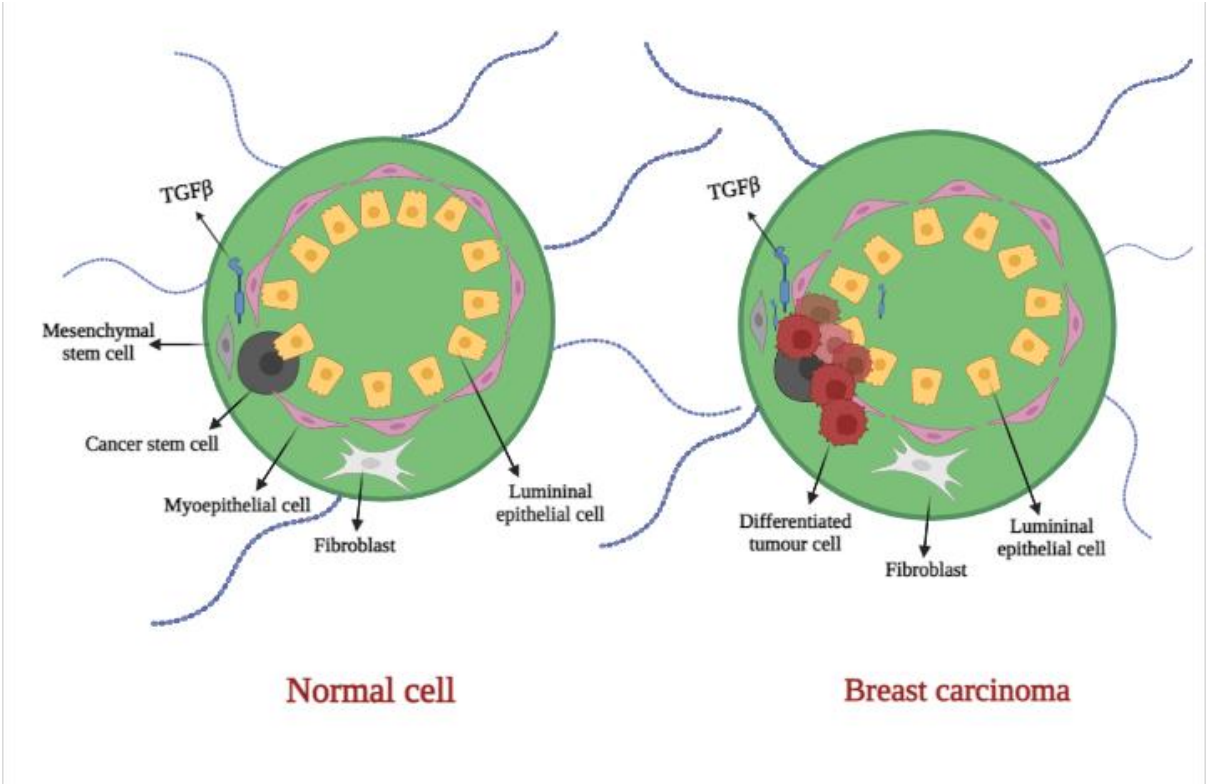
## I. INTRODUCTION

**Breast cancer** (BC) is a complex and heterogeneous disease of carcinoma cells which are malignant neoplasm occurs in epithelial cells [1],[2]. The second leading cause of cancer mortality among women is breast cancer yet early detection and treatment can significantly improve the survival rate[3].BC has various molecular types and subtypes and they show respond in endocrine and targeted therapies, where (TNBC) triple negative breast cancer is the most aggressive molecular subtypes in which Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor 2 (HER2) expressions are absent. TNBCs make up about 10% to 15% of all breast cancers, and there are seven different molecular subtypes:

immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), luminal androgen receptor (LAR), unstable (UNS) subtype, and two basal-like subtypes (BL1 and BL2)[4]. TNBC is compared to other subtypes it accounts for 15–20% of all breast carcinomas and origin in early age ([5]). TNBC is most threatening breast carcinoma lacking in protein expression and receptor including Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor 2 (HER2). There are currently no drugs approved to treat TNBC, leaving cytotoxic chemotherapy and immunotherapy as the current priorities ([6]). TNBC clinical characteristics include high invasiveness, high metastatic potential, relapse proclivity, and poor prognosis[7]. Because of the lack of targetable hormone receptors and HER2 expression, TNBC is often linked with poor medical outcomes and a limited range of therapeutic options[8]. HER2 expression is belongs to EGFR family and have four different receptors they are HER1 or EGFR (ErbB1), HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4) [9]. In 2020 they estimated 2.3million new cases of breast cancer in females and with 685,000 deaths, it was the fifth major cause of cancer death throughout the world [10]. BC mainly gets impact on the pandemic of COVID-19 which delays examination of tumour in breast and its treatment as a result more severe in cases and potentially, increased mortality. ([11]) Based on randomised controlled trials, a strong link has been shown between reduced breast cancer mortality and advanced breast cancer rate ([12], [13]) Mortality occurs from breast cancer can be reduce with the help of Mammography screening for breast cancer has been implemented in several places throughout the world [14]. Mammography screening is a low-dose X-ray examination used to detect breast cancer early. In this mammography screening, two high-resolution X-rays are taken of each breast one from the side view (the "mediolateral" MLO view) and another from the above (the "craniocaudal" or CC view). If any abnormality is found in the images there should be immediate tissue biopsy [15].

TNBC contains elements that may make it more responsive to immunotherapy treatment.[16] Immunotherapy has been shown to enhance survival in other solid tumours, and it may be a treatment option for TNBC. Immune checkpoint inhibitors (ICIs), which target immunosuppressive receptors like CTLA-4 and PD-1 to boost the cytotoxicity and proliferative ability of tumour infiltrating lymphocytes (TILs), are the most successful immunotherapeutic drugs [17]. Programmed cell death 1 (PD-1) is the immunosuppressive receptor which convey at the surfaces of numerous immune cells, including T and B cells, also involved at cell death and apoptosis regulation. [17]. **Fig I ;** shows the difference between normal breast epithelial cell and breast carcinoma in TME.




**FigureI:** Microenvironment of normal breast epithelium and breast cancer cells.

## II. Receptor modulation.

2.1 EGFR Receptor

The human Epidermal Growth Factor Receptor (EGFR) is made in a series of transmembrane glycoproteins. They used the DAKO EnVision method to perform EGFR immunohistochemistry with DAKO Monoclonal Mouse Anti-human Epidermal growth factor Receptor (EGFR), clone H11 as per the manufacturer's protocol, to evaluate EGFR they stain both membrane and cytoplasm. . ErbB-1, HER-2/neu (ErbB-2), HER-3 (ErbB-3), and HER-4 (ErbB-4) are various receptors in EGFR and that is important among all four while playing a role in tumour cell viability [18][20]. The expression of EGFR is related to the disease's aggressiveness and had worse (DFS) disease free survival and proven to be a predictive factor for DFS in both univariate and multivariate analyses ([18],[21]. This EGFR signalling pathway is important for cell proliferation, angiogenesis, metastatic dissemination, and apoptosis suppression. ([18],[22]

Atif Ali Hashmi, Samreen Naz *et al*., in the year 2019 reported that no significant association was found when EGFR expression was examined to several disease pathogenesis of TNBC, zero recurrence state of the cases, but the correlation of TNBC clinicopathological features with EGFR was also investigated applying various H-score cut-offs. In this whole study they used H-score to assess EGFR expression, where both the intensity and percentage of cells must be viewed[18].

2.2 Androgen receptor

The androgen receptor (AR) are a key participant of steroid hormone receptor family, which has oestrogen receptor (ER) and the progesterone receptor (PR). Androgen Receptor is expressed in normal breast epithelial cells as a good prognostic marker, and the connection between AR expression and survival which was independent of ER co-expression. ER-positive tumor tissues, AR expression is a favourable useful biomarker though its prognostic value in TNBC has been debated. AR expression in TNBC patients could be a reason for poor prognosis but for a subset of TNBC, AR was identified as one of the most promising therapeutic goals [23]–[27].

Aye AyeThike, Luke Yong-Zheng Chong *et al*., in the year 2014 reported that AR could be a potential therapy in breast cancer, particularly in ER-negative tumour, with focus on the clinical significance of AR expression in ER or TNBC [24].

## III. Protein Network

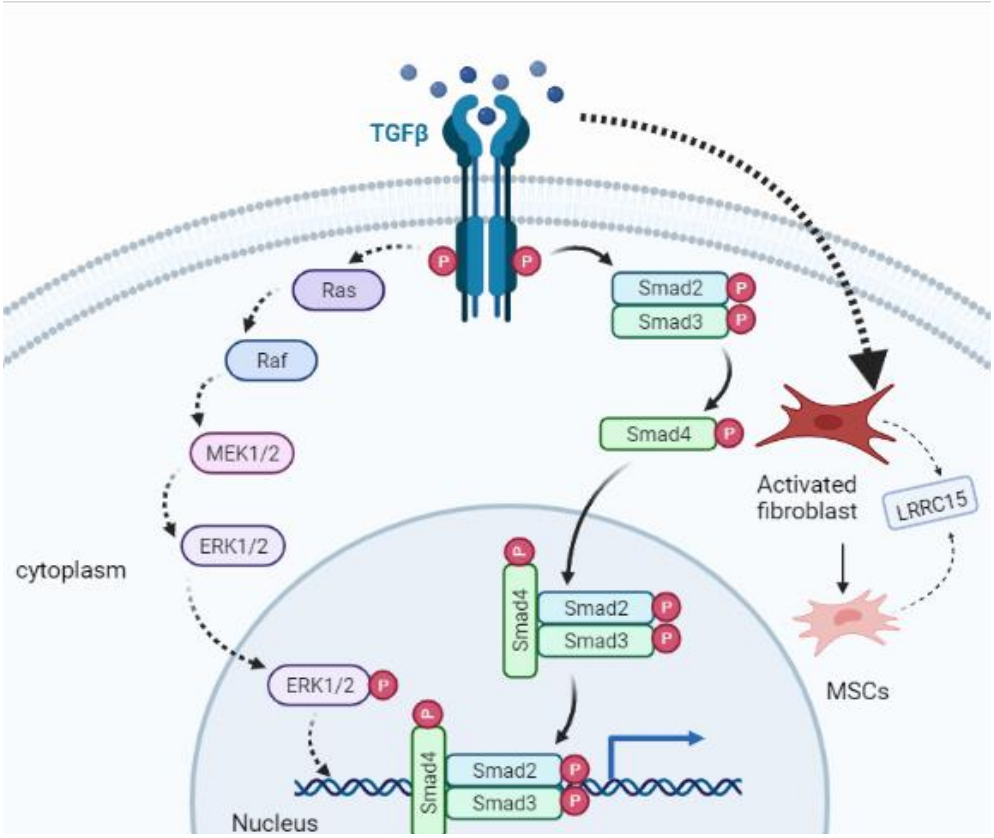
3.1 LRRC15

The LRR superfamily's leucine-rich repeat containing 15 (LRRC15) is a membrane protein which has appeared as cancer-associated fibroblasts related marker. LRR was discovered to be specifically overexpressed in breast carcinoma (BCa). LRRC15 is immensely expressed in a various tumour cells, with only low expression in normal tissue. The levels of LRRC15 mRNA and protein expression are more in malignant group of cell than in normal group of cell. They reported that LRRC15 expression levels were found to be significantly linked with the infiltrating levels of four different categories of immune cells in TNBC, counting CD4+ T cells, macrophages, neutrophils, and dendritic cells. CD274, CTLA4, HAVCR2, PDCD1LG2, and SIGLEC15 all had positive correlations with LRRC15 expression, however LAG3 had a negative correlation. The highest correlation was found between LRRC15 expression and ECM receptor interaction, focal adhesion, actin cytoskeleton management, and the TGF Beta signalling pathway, while the lowest correlation was found between LRRC15 expression and DNA replication, homologous recombination, oxidative phosphorylation, and ribosomes as a result it showed that elevated LRRC15 expression was connected to distant metastasis in breast cancer patients with disease pathogenesis[28], [29]

3.1.1 TGFβ signalling pathway

TGFβ signalling pathway increased LRRC15 expression in activated, fibroblasts and mesenchymal stem cells (MSCs) and also observed in adipose-derived MSCs. TGFβ signalling has potent immunosuppressive effects on critical cell types which coordinate natural and specific immunity, lowering immune cells' inbred antitumor latent within the tumor micro-environment (TME). The pathway suppression thus projected to improve both myeloid and lymphoid cell antitumor responses[30]. TGFβ signalling pathway has been reported to be present in regular tissues that express LRRC15, and MSCs known to reside there. Bone marrow–derived MSCs (BM-MSC) are obtained and flow cytometry and immunoblotting were used to determine whether MSCs express LRRC15. LRRC15 expression was confined mainly among hair follicles, tonsils, stomach, spleen, osteoblasts, and wound healing sites in normal people [31]. **Fig ii.**

Purcell JW, Tanlimco SG *et al*., in the year 2018 demonstrated that LRRC15 is a novel cell-surface marker of the mesenchymal phenotype, which confined upregulation to trigger fibroblasts MSCs, along subgroup of mesenchymal tumor based on expression data[31]. As we have viewed the combine role between LRRC15 protein or TGFβ signalling pathway which shows different cell responses.




**figureii:** TGFβ signalling pathway combines with LRRC15 protein expression

3.1.2 (Wnt/β- catenin signalling pathway)

LRRC15 protein expression increased tumour migration and invasion in TNBC cells, regulating through Wnt/catenin signalling pathway. They recognised the value of the LRRC15 and Wnt/-catenin signalling pathways in the advancement of TNBC. B-catenin levels with the transcriptional activity are upgraded by LRRC15. In CAFs, LRRC15 overexpressed or knockdown had no effect on the p-β-catenin/β-catenin ratio. LRRC15 overexpression in CAFs increased β-TrCP1 levels in MDAMB231 and MDAMB468 cells, but LRRC15 knockdown decreased their levels. The destruction complex protein Axin1 is downregulated by LRRC15, which raises β-catenin levels. LRRC15 overexpressed in CAFs lowered Axin1 expression and enhanced GSK3 and pGSK3 expression levels in MDAMB231 and MDAMB468 cells, but LRRC15 knockdown in CAFs had the reverse effect. In accordance with these results, LRRC15 with high expression level or break down in CAFs either upregulated or downregulated the protein cyclin D1 and c-Myc in cell lines [32], [33]. TNBC tumour development and metastasis are aided by CAFs. Yang Y, Wu H *et al*., in the year 2022 have shown the mechanism of LRRC15 in TNBC development and they use western blotting method to determine the level between MMP-2 or MMP-9, where they reported that increased LRRC15 expression is linked to a poor prognosis in TNBC patients and the impact of the Wnt/-catenin signalling pathway [33].

3.2 MEX3A

MEX3A is one of four members of the RNA-binding protein family (MEX3A-D). MEX3A, like MEX3B, MEX3C, and MEX3D, belongs to the MEX3 superfamily [34]. In research, MEX3A has been associated to cancer pathogenesis [35]. MEX3 is a protein with a KH-domain that was found for the first time in *Caenorhabditis elegans*[36]. The cytoplasm of cells contains four MEX3 proteins that can traverse Chromosomal Maintenance 1 pathway in the middle of the nucleus and the cytoplasm. MEX3A is structurally similar with other four MEX3 chromosome discovered in humans, which shows important role throughout mRNA expression [37]. MEX3A and MEX3B are significant element which is found in cytoplasm in the form of ribonucleoprotein granules (P bodies), according to studies, those two proteins are primarily engaged in messenger-RNA downregulation [38]. Overexpression of MEX3A enhances growth and metastasis in TNBC through modifying PI3K/AKT signalling, and upregulation of MEX3A is linked with mature phase of malignant tumour with serious condition in TNBC [39].

3.2.1 PI3K/AKT Signaling pathway

Phosphoinositide-3 kinases (PI3Ks) is an intracellular kinase regulate cell survival and proliferation. In biological membrane free 3-hydroxyl of phosphoinositides is phosphorylated by PI3Ks. PI3Ks usually classified into several section, where section I PI3K are often changed in carcinoma cells, consisting of two and more dimers that unruffled regulatory (p85) or catalytic (p110) subgroup (13). PI3K/AKT signalling cascade regulates a variety of cellular processes [40]. In class I PI3K inhibitor molecule, which provides initial evidence of anticancer efficacy for the treatment of HR+ HER2[41]. Homology (PH) domain, contains proteins (PDK1 and AKT) that regulates its location as well as activation. When PI3K is activated, AKT is displaced towards the inner membrane and phosphorylated on its T308 loop (activation loop) via PDK1. Following that, the direct phosphorylation and activation of the proline-rich AKT substrate of 40 kDa (PRAS40) and the tuberous sclerosis protein 2 (TSP2) activates the mammalian target of rapamycin complex 1 (mTORC1) [42]. In several human cancers, increase of PI3K/AKT signalling, mutation and also amplification of sequence coding occur at PI3K catalytic subunits p110δ and p110α [43]. The mutations in TNBC at p110α are in majority where 9% of mutation are in primary TNBC cases. The prevalence of PIK3CA mutations is anticipated to be higher in advanced TNBC, representing a subgroup of ER+ breast tumour by disregulating ER and developing secondary TNBC [44].

3.3 STAT 3

Signal transducer and activator of transcription 3 (STAT3) is a member of STAT protein family. The STAT transcription factor family has seven members (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6), each of which is encoded by a different gene but STAT3 serves a distinct role in carcinoma and tumour environment[45]. STAT3 was figured to be an influential checkpoint for antitumor immune responses[46].The epidermal growth factor receptors (EGFR), fibroblast growth factor receptors (FGFR), insulin-like growth factor receptors (IGFR), hepatocyte growth factor receptors (HGFR), platelet-derived growth factor receptors (PDGFR), and vascular endothelial growth factor receptors (VEGFR), are used to activate STAT3 [47].STAT3 activation prevents tumour cell apoptosis at numerous myeloma via increasing the expression of the B-cell lymphoma-2-like 1 protein (BCL-XL) (19). STAT3 is upregulated and activated in TNBC cells, where it regulates downstream target gene expression to maintain survival of cell through proliferating cell, progression of cell cycle, lowering cell death, invasion, resistance to chemotherapy and suppression of immune system [48].

3.3.1 JAK/STAT3 signaling pathway

The Janus kinase (JAK)/STAT3 signalling pathway originate IFN-α (interferon-α), IFN-γ (interferon-γ), and IL-6 (intereukin-6) which regulate downstream signalling pathway [45]. A number of nonreceptor tyrosine kinases can phosphorylate and activate STAT3. Overexpressed cytokine receptors, such as the (IL-6R) interleukin-6 receptor, the (IL-10R) interleukin-10 receptor, as well as growth factor receptor which are hyperactive, such as the EGFR, FGFR and IGFR, activate the tyrosine phosphorylation sequence via ligand binding as a result of STAT3 activation and transcription of target gene [49]. Phosphorylated STAT3 (pSTAT3) forms a homodimer by connecting with the phosphorylated Tyr705 site and SH2 domain, leading STAT3 dimers to detach from cell surface receptors and translocate from the cytoplasm to the nucleus [50]. Several cytokines, peptide hormones, growth factors, and chemokines promote JAK/STAT3 signalling, all of which contribute to cancer progression. JAK/STAT3 signalling is activated by tyrosine receptors and their corresponding ligands, and the neurotropic receptors are TGF receptors, IL-6R/gp130, and EGFR[51].

**Function of IL-6/JAK/STAT3 signalling:** IL-6/JAK/STAT3 cytokine enhance tumour progression. IL-6 involved in tumour invading cells like neutrophils, eosinophils, basophils, cancerous cells and connective tissue cells, and can be found in high concentrations at tumour microenvironment. As a result, IL-6 inflammatory cytokine released by monocytes, granulocytes, and fibroblasts ([50], [52].

**Role of STAT3 signalling:** In TNBC, STAT3 is overexpressed which found to be active all of the time.STAT3 increases cell growth and suppresses cell death in breast cancer through increasing the selected gene expression such as survivin, c-Myc, cyclin D1, B-cell lymphoma-2 (Bcl-2) and B-cell lymphoma extra-large (Bcl-xL) (18). STAT3 easily connect in selected gene which promote TNBC also increase transcription [53], that inhibited by blocking the (XPO1) nuclear export factor exportin 1 where acetylation of STAT3 negotiated by CBP [54]. STAT3 also inhibits apoptosis and increases TNBC cell growth[55].

3.4 SMYD2

SMYD2, the first substrate for a non-histone protein, that able to influence p53 function and genomic transcription. The SMYD2 (1-271 aa) has a heterogeneous form of α-helices (α1-α6), β-strands (β1-β12), or unroll coil, where C-terminal region (272-433 aa) has been warped as 7 α-helical bundle (α8-α14) [56]. The S-series are required in optimum activity at SMYD2, whereas post-SET domain are required in enzymatic activity,

for removing entire enzymatic activity [57]. SMYD2 has been suggested as a promising regulator or diagnostic indicator for treatment of BC [58]. In patients, high SMYD2 expression is linked to poor outcomes, whereas lower expression in patients are vulnerable to prognostic condition [59]. Esophageal squamous cell carcinoma (ESCC) are highly expressed in SMYD2 and consider primary tumour where as paediatric acute lymphoblastic leukaemia has been linked to a poor prognosis and survival of patients[60]. The mechanism of the JAK2/ STAT3 signalling pathway is activated when SMYD2 interacts with STAT3 and the p65 isoform of NF-κB [61].

Linda Xiaoyan Li, Julie Xia Zhou *et al*., in the year 2018 reported that SMYD2 is overexpressed in TNBC cell lines; further breakdown of SMYD2 can greatly reduce tumour growth *in vivo*. Through methylation and activation of STAT3 and the p65 isoform of NF-κB, SMYD2 enhances proliferation and survival of TNBC cells[62].

## IV. Immune Checkpoint Inhibitors

4.1 PD-1 and PD-L1 marker

Programmed death-1 (PD-1) is an immunomarker; establish on T-cells and is expressed after activation of T-cells. When PD-1 is activated, it is expressed on double-negative and T cells in the thymus, as well as peripheral T and B cells [63]. PD-1 is a cytotoxic effector T-cell inhibitory surface receptor that is also expressed through B-cells, activated monocytes, natural killer cells, and dendritic cells [64]. Programmed cell death ligand 1 (PD-L1) is an approving ligand of PD-1 that is mostly found in outer surface of tumour and attracts lymphocytes. PD-L1 limits immune system's attack on cancer cells by increasing apoptosis in local T lymphocytes and, as a result it promotes tumour growth[65]. Although PD-L1 testing is suggested in TNBC the checkpoint inhibitors response are used and no such connection was seen in early breast cancer. In TNBC and HER2-positive breast cancer the tumor-infiltrating lymphocytes in the tumour shows great medical condition and proper therapeutic efficacy [66]. PD-L1 expression is significantly linked to high grade abnormal cancer cell and hormone receptor negativity in breast cancer [67]. When two ligands L1 and L2 binds to PD-1 in tumour infiltrating lymphocytes (TILs) it inhibits T cells [68]. PD-L1 expression can be found in both lumps of tissues and monocytes and macrophages as a checkpoint inhibitor, in patients with different tumour types. Anti-PD-1 or anti-PD-L1 antibodies are identified as a responsive biomarker. The safety and efficacy of nivolumab and atezolizumab was demonstrated in early trials as a predictive biomarker for the potential utility of PD-L1 expression [69].

4.1.1 Pembrolizumab

Pembrolizumab is a humanised monoclonal IgG4-K antibody that has excellent affinity and specificity against PD-1 which blocks both L1 and L2 ligands. In normal breast tissue the marker in not detected, but in half of all breast cancers where marker is expressed, including TNBC having the highest level of expression [70]. The anticancer activity of pembrolizumab combination therapy as a neoadjuvant chemotherapy treatment for cancer were studied. More than one-third of patients experienced dose-limiting toxicities (DLTs), the most prominent was febrile neutropenia. The researchers looked into whether connective tissue cell or ligand 1 expression were linked to therapeutic response. Increased PD-L1 expression or stromal TIL levels are important at high pCR rates and closely correlated with each other, with prior investigations [71].Rita Nanda, MD; Minetta C. Liu *et al*., reported in the year 2020 that an immune check point inhibitor pembrolizumab when included with standard neoadjuvant chemotherapy (NACT) displayed better effects over chemotherapy alone in early stage, high-risk and ERBB2-negative breast cancer. Preliminary reports of this therapy in TNBC indicated increased pCR rates through immune check point blockade. However, phase 3 trial is ongoing for this therapy and had a high event free survival rate [72].

4.1.2 Atezolizumab

Atezolizumab is a monoclonal antibody made up of Fc-engineered humanised immunoglobulin G1 that is expressed on cancer cells and tumor-infiltrating immune cells. It connects with programmed death ligand 1 (PD-L1) that prevent from interacting with programmed death 1(PD-1). After combined with taxane treatment, drugs improves immune checkpoint inhibition and may improve toll-like receptor and dendritic-cell function[73]. In the first immunotherapy medication (immune checkpoint inhibitor) the drugs atezolizumab combine with nab-paclitaxel to confirm the therapy for individuals with locally advanced or metastatic TNBC which was unresectable, and that expresses PD-L1 in several countries across the world and the results is sanction based on phase III IMpassion130 trial [74]. Leisha A. Emens, MD, PhD; Cristina Cruz, MD *et al*., reported in the year 2019 that in the phase I trial, 116 people with mTNBC were treated with atezolizumab monotherapy. Furthermore, 78% of people exhibited PD-L1 impression, and practically every patient had adverse event (AE), with grade 3/4 AE accounting for 51% of cases [75].

4.2 Poly-ADP-Ribosyl Polymerase (PARP) Inhibitors

PARP is a superfamily of protein and composed of two ribose moieties and phosphate per unit polymer. PARP1 and PARP2 are enzymes engaged in a DNA repair path that leads for single strand breaks (SSBs) and is essential in the initiation of SSB repair in the DNA via base excision repair [76]. PARP inhibitors remedies used presently in the diagnosis of early-stage BC, where there is unique combinations with patients who do not have gBRCA mutations, that include somatic BRCA mutations along with genetic changes in other DDR chromosomes[77]. PARP1 enzyme is a members of ADP-ribosylating enzymes (ADPRE) behaves in the form of catalyst, transferring NAD+ residues containing ADP-ribose to target enzymes, generating poly ADP-ribose chain that frequently formed in eukaryotic cells. PARP1 is used in repairing DNA and has been linked to nuclear enzymes and chromatin [78]. PARP inhibitors seems to be tiny chemical mimetics of nicotinamide which bind reversely where PARP-1 and PARP-2 have a NAD+ site that inhibits PolyADP-ribosylation and DNA repair processes[79]. PARP1 promotes chromatin structural remodelling by binding directly to DNA and acting as a gene transcription. The function of PARP1 as a regulatory protein for nuclear elements has newly attracted interest due to the role of oestrogen/progesterone and androgen receptors in breast carcinoma[80].

J. Mateo1, C.J. Lord in the year 2019 reviewed that by reducing PARP1 levels in RNA intervention result which helps in decreasing cell existing in BRCA1- and BRCA2- cells. PARP1 inhibitors were effective against carcinoma cells lacking in BRCA1/2 but cells with two different alleles at a particular gene locus of BRCA1/2 genes or without BRCA1/2 gene they aren't sensitive to PARP1 inhibitors [81].

4.2.1 Olaparib

Olaparib is an orally accessible PARP inhibitor which kills cell carrying the BRCA1 & BRCA2 gene [82]. Olaparib is the first drug approved for BRCA mutation carriers in HER2-negative metastatic breast cancer and a history of chemotherapy treatment in the neoadjuvant, adjuvant, or metastatic setting. Olaparib is metabolised mostly through oxidation via hepatic CYP3A4 enzymes, with some metabolites undergoing further glucuronide or sulphate conjugation [83]. It is not recommended to take olaparib with strong or moderate inducers or inhibitors of CYP3A4 enzyme because the enzyme is the key metabolising enzyme of olaparib [82]. Luc Dirix, MD, PhD; Helen Swaisland *et al*., in the year of 2016 demonstrated that the pharmacokinetics of olaparib in the presence of CYP3A4 enzyme inhibitor itraconazole and the CYP3A4 enzyme inducer rifampin was carried in phase I trials twice in people bearing advanced cancerous tumour. Drug was given to the patients either alone or in combination with itraconazole or rifampin. After administration of olaparib with itraconazole the bioavailability of the drug increases which is explained by calculating the treatment ratio of (Cmax) peak concentration and treatment ratio of (AUC) plasma concentration and take the percentage and confidence interval. The mean apparent clearance (CL/F) and apparent volume of distribution (Vz/F) both decreased, in treatment ratio of (Cmax) peak concentration and treatment ratio of (AUC) plasma concentration. Coadministration with rifampin lowered olaparib relative bioavailability by a statistically significant factor. CYP3A4 enzyme inducers and inhibitors shouldn't be used during olaparib administration, according to these data[84].

4.2.2 Veliparib

Veliparib is an orally accessible PARP-1 and PARP-2 inhibitor that has been shown in preclinical models to improve the anti-tumour activity of chemotherapy and radiotherapy (22).

Hidenori Mizugaki, Noboru Yamamoto *et al*., in the year of 2015 investigated that combination of carboplatin and paclitaxel drug doesn't effect on veliparib Tmax, (Cmax) peak concentration and (AUC) plasma concentration in first trial. The pharmacokinetics of veliparib in combination with carboplatin and paclitaxel is investigated in patients with non-small cell lung cancer (NSCLC). Veliparib had no effect on the pharmacokinetics of paclitaxel or carboplatin, according to the study [85].

Lauren Averett Byers, Dmitry Bentsion *et al*., in the year 2021 investigated that in a phase 2, randomized study they investigate veliparib combining with carboplatin and etoposide in hospitalized individuals. They have taken naïve patientsfor extensive-stage small cell lung cancer study who did not show signs of disease progression after completing combination therapy they maintain monotherapy with veliparib 400 mg twice daily (BID) or placebo until intolerable toxicity or illness progression. Individuals are taken on random manner at 1:1:1 ratio in a several different treatment group i.e. veliparib plus chemotherapy, veliparib maintenance, placebo maintenance and placebo plus chemotherapy followed by placebo maintenance therapy, in that combination trial veliparib was administered to individuals with 240 mg dose BID. Statistically this part 2

study shows its primary end point at 2-sided alpha level of 0.2. Veliparib in combination with carboplatin and etoposide, as well as monotherapy, showed no additional safety indications [86].

**Table I:** Common adverse effects of different trial and its class

| Test Drug | Class | Common Adverse Effect |
|---|---|---|
| **Olaparib (OlympiAD)** [87] | Poly-ADP-Ribosyl Polymerase Inhibitors (PARP) | Nausea<br>Anemia<br>Fatigue<br>Neutropenia<br>Diarrhea<br>Headache |
| **Talazoparib (EMBRACA)** [88] | Poly-ADP-Ribosyl Polymerase Inhibitors (PARP) | Anemia<br>Neutropenia Thrombocytopenia<br>Fatigue<br>Nausea<br>Headache<br>Alopecia<br>Vomiting<br>Diarrhea<br>Constipation<br>Decreased appetite<br>Back pain |
| **Buparlisib (BELLE-4)** [89] | Phosphoinositides 3-Kinase inhibitors (PI3K) | Diarrhea<br>Alopecia<br>Rash<br>Nausea<br>Hyperglycemia<br>Fatigue<br>Decreased appetite<br>Neutropenia<br>Stomatitis<br>Depression<br>Peripheral neuropathy<br>Asthenia<br>Constipation<br>Anemia<br>Anxiety |
| **Atezolizumab + nab-paclitaxel (IMpassion130) (11)** | Programmed cell death ligand 1inhibitors (PD-L1) | Alopecia<br>Nausea<br>Cough<br>Neuropathy |

## V. Conclusion

In summary, we shared insights regarding the possible impact of different protein LRRC15, MEX3A, STAT 3 and SMYD2 in tumour cell, cancer pathogenesis, proliferating cells and enrichment networks. LRRC15 correlated with TGFβ signalling pathway plays a vital role in cancer progression via direct impact on cancer cells and other cellular components in the TME. This protein combine with tgfβ pathway and show different cell response. LRRC15 with Wnt/catenin signalling pathway shows the advancement in TNBC with using western

blotting method we can determine the level of LRRC15 which increase and lead to poor prognosis and the way it shows impact in the pathway. MEX3A promotes triple negative breast cancer proliferation and migration via the PI3K/AKT signaling pathway. STAT3 serves distinct role in TME and the protein is upregulated in active TNBC cells, functioning with interleukins enhance tumour progression. SMYD2 protein breaks down and reduce tumour growth. A number of unanswered questions persist about the role of cancer therapy immunotherapy which is newly introduced to diagnose the TNBC where the biomarkers are introduced like immune checkpoint inhibitors and PARP inhibitors. Immune checkpoint inhibitors PD-1 and PD-L1 expressed after activation of T-cells. The checkpoint blockade PD-1 inhibitor and PD-L1 inhibitor promise to improve the response in tumour type and display adaptive resistance. New biomarkers have been proposed to predict survival and response to chemotherapy.

**Conflict of Interest**

There is no conflict of interest.

**Acknowledgement**

I am thankful to my guide, HOD, principal, staff and management of Acharya & BM Reddy College of Pharmacy for providing us with necessary amenities for our study.

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