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Review Article

Understanding Triple Negative Breast Cancer: A Review on Molecular Signaling Pathways

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ABSTRACT

Triple negative breast cancer (TNBC) is a divergent disease which lacks receptor for estrogen (ER), progesterone (PR) and human epidermal growth factor receptor 2 (HER2). It constitutes about 15-20% of total breast cancer cases globally which mainly strikes younger women. Due to its aggressive nature, the standard choice of treatment for TNBC is chemotherapy, but the same has very poor prognosis due to risk of tumor recurrence, metastasis and death. To direct the line of research to get pathological Complete Response (pCR) and increase the quality of life (QOL) years of cancer patients, it is necessary to understand the molecular pathways and their down signalling pathways which can be targeted. Triple negative breast cancer involves several signaling pathways leading to tumor initiation, proliferation, and metastasis such as Ras/Raf/MEK pathway, PI3/AKT/mTOR pathway, DNA repair pathway, Wnt/ β -catenin Pathway, Hedgehog pathway, Notch signalling pathway and immune pathway. Currently available treatment for triple negative breast cancer comprises chemotherapy in combination which includes anthracyclines, platinum compounds, folate antagonist, taxanes, cyclophosphamide and others. The present review focuses on the molecular aspect of TNBC subtypes and targets. Also, the ongoing clinical trials along with the completed clinical trials targeting different pathways for the treatment of TNBC patients are discussed.

INTRODUCTION

Breast cancer is the most prevalent cancer worldwide affecting 2.3 million women in 2020.^[1] When breast cancer lacks the expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), it refers to triple-negative breast cancer (TNBC). TNBC accounts for 10–20% of breast cancer cases diagnosed worldwide.^[2] TNBC is heterogeneous and aggressive among all breast cancer subtypes with six TNBC subtypes such as luminal androgen receptor (LAR) type, basal-like 1 & 2 (BL1, BL2), mesenchymal (M) type, mesenchymal stem cell (MSL) type and immunomodulatory (IM).^[3] Lehmann *et al.* confirmed four TNBC subtypes using 198 TNBC cell lines namely luminal androgen receptor (LAR) type, basal-like/Immune activated (BLIA), basal-like/immune-suppressed (BLIS) and mesenchymal (M) type.^[4] Further

gene expression analysis helped in the identification of cell lines representative of each TNBC subtype for the evaluation of therapeutic treatment and targets.

BL1 tumors consist of genes responsible for cell proliferation such as v-Myc avian myelocytomatosis viral oncogene homolog (c-MYC), NRAS, Aurora A/B (AURKA/B), TTK protein kinase (TTK), polo-like kinase 1 (PLK1) and baculoviral inhibitor of apoptosis repeat-containing 5 (BIRC5) accompanied by elevated DNA-damage response pathway genes such as Checkpoint Kinase 1 (CHEK1), RAD51 recombinase (RAD51), nibrin gene (NBN), mutS homolog 2 (MSH2) and DNA repair and recombination protein RAD54 homolog B (RAD54B). High expression of Ki-67 protein makes BL1 the most aggressive subtype. The BL1 tumors are more sensitive and responsive to antimitotic agents like taxanes^[5,6] and platinum compounds. Basal like-2 tumors are characterized by

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genes involving growth factor signaling such as epidermal growth factor receptor gene (EGFR), hepatocyte growth factor receptor gene (MET), ephrin type-A receptor 2 gene (EPHA2) and have origin from basal/myoepithelial due to high levels of myoepithelial markers tumor protein p63 (TP63) and common acute lymphocytic leukemia antigen (CD10). Mesenchymal-like tumors are enriched with genes for ECM (extracellular matrix) receptor interaction, cell differentiation pathways (like Wnt pathway and TGF- β (transforming growth factor- β signaling)) and also cell motility pathway. They are more sensitive to PI3K/mTOR inhibitors as they have deregulated PI3K pathways. MSL tumors are characterized by genes associated with epithelial-mesenchymal transition (EMT), cell differentiation pathway, angiogenesis, growth factor signaling pathway and immune signaling. They have low expression of proliferation genes and are enriched for genes related to stem cells. MSL tumors have low expression of claudin 3, 4 and 7, cytokeratin (KRT7/8/18/19) and the cluster of differentiation (CD24) expression. They are sensitive to sarcoma family kinase (SRC) PI3K/mTOR inhibitors. Both *in-vivo* and *in-vitro*, deregulation of the TGF- β receptor is responsible for migration and invasion of MSL cell lines. IM tumors are characterized for genes involved in immune response such as immune cell signaling, antigen processing and presentation as well as cytokine signaling which overlaps with medullary breast cancer. LAR tumors are characterized by hormonally regulated pathways such as androgen receptor signaling and are positive for PI3KCA mutations. LAR express luminal patterns and have highly expressed genes such as forkhead box protein A1 (FOXA1), keratin 18 (KRT18) and X-box binding protein 1 (XBP1). They are sensitive to androgen receptor antagonists like bicalutamide and dual PI3K/mTOR inhibitors like dactolisib.^[7,8]

Younger premenopausal women, shorter duration of breastfeeding, obesity and young age at full-term pregnancy are the risk factors for basal-like breast tumors.^[9] TNBC patients have reduced cancer-specific survival as compared to luminal tumors. There are increased chances of recurrence in TNBC patients during the first three years of therapy with a rapid decline thereafter. TNBC has a poor pathological complete response (pCR) outcome but it is not resistant to chemotherapy.^[10] Among various breast cancer subtypes, basal-like (85%) and HER2-positive (70%) tumors showed the highest response rates as compared with luminal (47%) when treated with neoadjuvant AC (Adriamycin and Cyclophosphamide) chemotherapy. In another study involving anthracycline/taxane-based neoadjuvant strategies, from over 1000 patient population, TNBC patients showed higher pCR than ER-positive breast tumors with increased overall survival at three years compared to those with residual disease (RD). Although TNBC is highly responsive to anthracyclines and anthracycline/taxane chemotherapy, if a residual

tumor is present, then there is a high risk of relapse.^[11] Due to the aggressive nature of TNBC, its management involves polychemotherapy with anthracycline (such as doxorubicin or epirubicin) and taxane (paclitaxel or docetaxel) in various well-described regimens. Almost 70% of breast cancers with BRCA mutation are of triple-negative type.^[12] Tumors with BRCA mutation and TNBC subtype are sensitive to DNA-damaging agents such as platinum compounds and PARP inhibitors.^[13] Hence for targeting TNBC, a brief insight into signaling pathways is obligatory for identifying an operative therapeutic target.

MOLECULAR SIGNALING PATHWAYS FOR TNBC

Ras/Raf/MEK/ERK Pathway

Ras/Raf/MEK/ERK pathway is responsible for cell proliferation, survival, differentiation and metastasis in TNBC.^[14] Due to the activation of RTKs, growth-factor-receptor-bound protein 2 (Grb2) molecules are recruited to the plasma membrane and binds directly to RTKs. Another way is Grb2 activates protein SRC homology and collagen protein (Shc) which in turn helps in Son of Sevenless (SOS) protein recruitment to the plasma membrane. Grb2 also generates phosphatidic acid by activation of PLD2 (phospholipase D2) which causes recruitment of SOS to the plasma membrane by interacting with SOS. Grb2 associated with SOS then converts inactive guanosine diphosphate associated Rat sarcoma (GDP-Ras) to active guanosine triphosphate associated Rat sarcoma (GTP-Ras). Ras, small GTPases such as Harvey sarcoma virus (HRAS), Kirsten sarcoma virus (KRAS), neuroblastoma RAS viral oncogene homolog (NRAS), muscle RAS oncogene homolog (MRAS) are activated indirectly via external stimuli (ligand-dependent activation of RTKs).^[15] NF1 (neurofibromin 1) keeps the Ras activation at check by catalyzing the conversion of GTP-Ras to GDP-Ras and hence controls the pathway.^{[16][17][18]} Serine/threonine kinase, Rapidly Accelerated Fibrosarcoma kinase (Raf), is activated as a result of Ras activation and in turn activating mitogen-activated protein kinase kinase (MEK 1/2). This activation of MEK1/2 is modulated by various scaffolding proteins like RKIF (Raf kinase inhibitor protein), KSR (kinase suppressor of Ras), MP1 (MEK partner 1) and MKPs (MAPK phosphatases). Activation of MEK1/2 leads to phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2) that results in activation transcription factors v-fos FBJ murine osteosarcoma viral oncogene homolog (FOS), v-myc avian myelocytomatosis viral oncogene homolog (MYC), v-ets avian erythroblastosis virus E26 oncogene homolog 1/2 (ETS1/2), ETS transcription factor ELK1 (ELK-1) responsible for cell proliferation, differentiation and survival. Deregulation of dual-specificity phosphatase 4 (DUSP4) gene whose hypermethylation is responsible

for decreased messenger RNA (mRNA) expression is also implicated in TNBC.

Further, as compared to other breast cancer subtypes, the Ras/Raf/MAPK pathway is additionally activated in TNBC.^[19] Ras/Raf/MAPK pathway is also involved in EMT (epithelial-to-mesenchymal transition) which leads to metastasis in TNBC through elevated activation of ERK1/2 due to deviation from normal Ras function. After chemotherapy treatment in TNBC patients, activation of the Ras/Raf/MAPK pathway relates/correlates to its aggressive nature. Treatment with MEK inhibitors can help in restoring the sensitivity of tumor cells to cytostatic agents.^[20] CDK4/6 inhibitors currently approved for treating breast cancer are abemaciclib, palbociclib and ribociclib. Lapatinib blocks phosphorylation of EGFR, ERK1/2 and Akt kinases. It also inhibits cyclin D protein levels in tumor cells. Table 1 represents the clinical trials of drugs targeting the Ras/Raf/MEK pathway in TNBC patients (Fig. 1).

PI3K/Akt/mTOR Pathway

In resting cells with inactive phosphoinositide 3-kinase (PI3K), phosphatidylinositol 3-kinase regulatory subunit alpha (p85) suppresses phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (p110 α) of PI3K/Akt pathway. PI3K is responsible for tumor proliferation,

growth, motility, survival and angiogenesis.^[22] Due to extracellular ligand-dependent activation of RTKs, PI3K becomes active due to the interaction of p85 with tyrosine residues, non-RTKs and adaptor protein like insulin receptor substrate 1 (IRS1) with its Src Homology 2 (SH2) domains. The activity of PI3K can be modified by GTP-Ras and SFKs (Src family kinases) on the intracellular membrane.^[23] Phosphatidylinositol 4,5-bisphosphate (PIP2) is converted into phosphatidylinositol (3,4,5)-trisphosphate

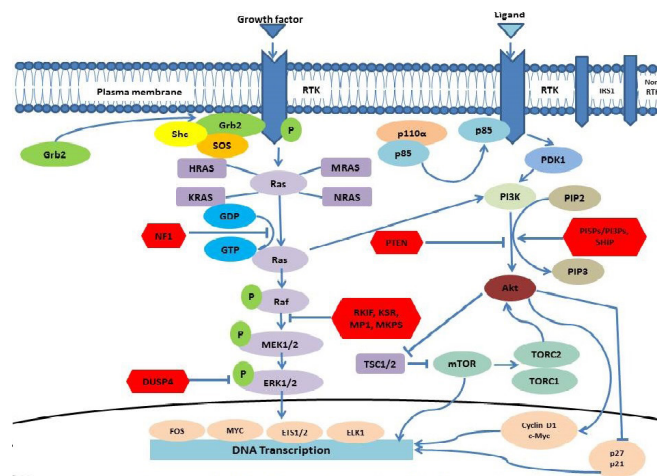


Fig. 1: Ras/Raf/MEK/ERK pathway and PI3K/Akt/mTOR pathway in TNBC.

Table 1: Clinical trials involving drugs targeting Ras/Raf/MEK/ERK pathway in TNBC patients

Drug	Combination	Target	Phase	Status	Primary outcome	Clinical trial number ^[21]
Selumetinib (AZD6244)	Vistusertib (AZD2014) (mTOR inhibitor)	MEK inhibitor	Ib	Recruiting	Efficacy, progression-free survival, duration of response and overall survival	NCT02583542
Cobimetinib	Paclitaxel	MEK inhibitor	II	Completed	Progression-free survival and overall response rates	NCT02322814
Selumetinib	Docetaxel	MEK inhibitor	II	Recruiting	Increase in survival of patients	NCT02685657
Trametinib (GSK1120212)	Uprosertib (GSK2141795) (Akt inhibitor)	MEK inhibitor	I	Completed	Determine dose and regimen for combination	NCT01138085
Trametinib	Uprosertib (GSK2141795) (Akt inhibitor)	MEK inhibitor	II	Completed	Stop tumor growth	NCT01964924
Trametinib (GSK1120212)	Buparlisib (BKM120) (PI3K inhibitor)	MEK inhibitor	Ib	Completed	Dose determination, safety pharmacokinetics and pharmacodynamics	NCT01155453
Binimetinib (MEK162)	Dactolisib (BEZ235) (PI3K/mTOR inhibitor)	MEK inhibitor	Ib	Completed	Incidence of dose limiting toxicities	NCT01337765
Binimetinib (MEK162)	Buparlisib (BKM120) (PI3K inhibitor)	MEK inhibitor	Ib	Completed	Incidence of dose limiting toxicities	NCT01363232
Binimetinib	Palbociclib	MEK inhibitor	I II	Recruiting	Progression-free survival	NCT04494958
Trilaciclib (G1T28)	Gemcitabine Carboplatin	CDK4/6 inhibitor	II	Recruiting	Number of treatment related adverse events	NCT02978716



(PIP3) with the help of active PI3K by Phosphatidylinositol 5-phosphate (PI5Ps) or Phosphatidylinositol 3-phosphate (PI3Ps), SH2-containing Inositol Phosphatase (SHIP), phosphatase and tensin homolog (PTEN) and others.^[24] Due to the generation of membrane-associated phospholipids, there is recruitment of signaling molecules with Pleckstrin homology domain (PH) domain of non-RTKs, Ras GTPase-activating proteins (RasGAP), phosphoinositide phospholipase C γ (PLC γ), IRS, growth factor receptor-bound protein 7 (Grb7), phosphoinositide-dependent kinase-1 (PDK1) and protein kinase B (Akt) adjacent to the plasma membrane.^{[25][26][27]} Due to signal propagation of PI3K/Akt pathway, GTP-Ras activation of Ras/Raf/MAPK pathway is also affected, this signifies the cross-talk between two pathways.^[28]

Activation of Akt inhibits repression on mammalian target of rapamycin (mTOR) by Tuberous sclerosis proteins 1 and 2 (TSC1/2). mTOR after activation forms two complexes with proteins such as mTOR Complex 1 (TORC1), responsible for growth stimulatory effects of mTOR, and mTOR Complex 2 (TORC2), for further stimulation of Akt. Activated Akt is also involved in angiogenesis and EMT leading to cell migration.^[29] Activated Akt then moves to cytoplasm and nucleus thereby phosphorylating target proteins and is responsible for apoptosis, DNA repair, cell division and metabolism.^{[30][31]} Akt also acts by reducing cell cycle inhibitors expression (p27 and p21) and promoting c-Myc and cyclin D1. Phosphatidylinositol-4,5-bi-

phosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations or loss of PTEN activity leads to PI3K/Akt pathway activation and mTOR activity in TNBC.^[32] It limits programmed cell death and increases cellular survival by influencing Bcl-2 family member, Bad. mTOR sends the signal for increasing mRNAs translation encoding proteins required for cell growth and cell cycle progression.^[33] The extracellular ligand RTK may be HER2 on which trastuzumab, lapatinib, neratinib, pertuzumab, margetuximab and tucatinib may bind extracellularly on HER2 receptor and inhibit phosphorylation RTKs and reduction in the signaling of proteins intracellularly. Alpelisib is the PI3K inhibitor approved for the treatment of breast cancer in the clinical setting. A phase Ib/II study evaluating safety and efficacy of iniparib (GDC-0941) in combination with cisplatin on TNBC patients was terminated due to excessive toxicities and lack of efficacy. (NCT01918306) A phase II study treating TNBC patients with Akt inhibitor (MK220) before conventional surgery for evaluating changes in the levels of pAkt, pS6 and Ki67 expression was terminated due to toxicity. (NCT01319539) Table 2 represents ongoing and completed clinical trials involving drugs targeting PI3K/Akt/mTOR pathway.

DNA Repair Pathway

In a cell, DNA repair is done by either mismatch repair (MMR), base excision pair (BER) and double-strand break repair (DSR). When DNA double-strand breaks repair

Table 2: Clinical trials involving drugs targeting PI3K/Akt/mTOR pathway

Drug	Combination	Target	Phase	Status	Primary Outcome	Clinical Trial Number ^[21]
Temsirolimus	Cisplatin Erlotinib (receptor tyrosine kinase inhibitor)	mTOR inhibitor	I	Completed	To find out Maximum Tolerated Dose in combination	NCT00998036
CUDC-907	---	PI3K/HDAC inhibitor	I	Completed	Safety, Tolerability and Pharmacokinetics	NCT02307240
BKM120 (Buparlisib)	Olaparib (PARP inhibitor) and olaparib with BYL719 (aplesilib)	PI3K inhibitor	I	Completed	Evaluated for safety combination	NCT01623349
AZD5363 (Capivasertib)	Paclitaxel	Akt kinase inhibitor	II	Recruiting	Progression free survival	NCT02423603
AZD2014 (Vistusertib)	Olaparib (PARP inhibitor)	mTORC1/2 inhibitor	Ib	Recruiting	Evaluated for maximum tolerable dose in combination	NCT02208375
AZD5363 (Capivasertib)		Akt inhibitor				
Apatinib (YN968D1)	----	Tyrosine kinase inhibitor	II	Completed	Disease control rate and Progression Free Survival	NCT01176669
Ipatasertib (GDC-0068)	Trastuzumab Pertuzumab	Akt inhibitor	I	Recruiting	To define the Recommended Phase 2 Dose (RP2D) of ipatasertib when used in combination with HP (+/- ET)	NCT04253561
Eganelisib (IPI-549)	Etrumadenant Pegylated liposomal doxorubicin (PLD)	PI3K inhibitor	I	Completed	Incidence of adverse events and dose limiting toxicities	NCT03719326

is done, it is toxic to cells. They are repaired by error-prone non-homologous end-joining (NHEJ) and error-free homologous recombination (HR).^[34,35] Homologous recombination (HR) is dependent on BRCA 1/2 DNA repair associated (BRCA1/2) pathways and breast cancer gene (BRCA) is responsible for the maintenance of genomic stability.^[36-38] Cells lacking BRCA1/2 to repair these breaks, are susceptible to more error-prone mechanisms, resulting in an increased risk of breast cancers.^[39] In error-free HR, the repair is carried out by a group of enzymes, poly (ADP-ribose) polymerases (PARPs), involved in genomic stability, DNA repair, cell cycle and apoptosis.^[40,41] Hence PARP inhibition will lead to apoptosis and cell death. Genes participating in DNA repair pathway are mainly partner and localizers of BRCA2 (PALB2), BRCA1-associated RING domain protein 1 (BARD1), BRCA1 Interacting Protein C-terminal Helicase 1 (BRIP1), RAD51 paralog C/D (RAD51C/D), RAD50 double-strand break repair protein (RAD50) and X-Ray Repair Cross Complementing 2 (XRCC2), which accounts for the highest proportion in TNBC.^[42] Impairment in BRCA1/2 function like BRCA1/2 mutation, methylation of the promoter, decreased expression of protein contributes to BRCAness of cancer.^[43] BRCA1 mutation leads to decreased short-term and long-term survival as compared to BRCA2 mutation due to the involvement of different pathways of BRCA1/2 in pathogenesis.^[44] Most of the tumors with BRCA1 mutation identified by immunohistochemistry have a negative expression for ER, PR and HER2 and overexpression of EGFR along with tumor protein p53 (TP53) mutation.^[45-47] Olaparib and talazoparib (PARP inhibitors) are currently used targeted therapies for the treatment of breast cancer clinically. Table 3 represents ongoing and completed clinical trials involving drugs targeting PARP.

Wnt signaling pathway

Three different Wnt (wingless/integrated) signaling pathways namely canonical Wnt pathway (Wnt/ β -catenin pathway), non-canonical planar cell polarity pathway (β -catenin independent pathway) and Wnt/ Ca^{+2} pathway can be activated after binding of Wnt ligand with frizzled (Fz) receptors.^[48] Canonical Wnt pathway (Wnt/ β -catenin pathway) is responsible for gene transcription regulation.^[49] The non-canonical planar cell polarity pathway is responsible for cellular and cytoskeleton organization whereas Wnt/ Ca^{+2} pathway regulates cell adhesion and migration by regulating calcium level.^[50,51] In Canonical Wnt pathway, Wnt ligand binds with frizzled (Fz) receptors and lipoprotein related protein 5/6 (LRP5/6) and activates Dishevelled (Dvl) protein. In absence of Wnt, Axin and APC (adenomatosis polyposis coli) destruction complex with β -catenin initiates phosphorylation of glycogen synthase kinase-3 (GSK-3) and casein kinase-1a (CK1) which in turn leads to degradation of β -catenin. Activated Dvl protein interacts with Axin and APC destruction complex leading to increased levels of free β -catenin in the cytosol. Free cytosolic β -catenin then translocates to the nucleus and binds to TCF/LEF (transcription activation complex with T-cell factor/lymphoid enhancing factor) and displaces Groucho which is a transcription repressor.^[52] β -catenin binding to TCF/LEF leads to transcription of fibroblast growth factor 20 (FGF20), dickkopf-related protein 1 (DKK1), WNT1-inducible-signaling pathway protein 1 (WISP1), MYC and CYCLIN-D1.^[53,54]

In the non-canonical planar cell polarity pathway, the Wnt5a ligand binds to frizzled (Fz) receptors with co-receptors like retinoic acid receptor-related

Table 3: Clinical trials involving drugs targeting PARP on TNBC patients

Drug	Combination	Target	Phase	Status	Primary outcome	Clinical trial number ^[21]
Fluzoparib	Apatinib (VEGFR inhibitor)	PARP inhibitor	I	Recruiting	For evaluating the mechanism of action of drug	NCT03075462
Niraparib	Pembrolizumab	PARP inhibitor	I/II	Completed	Evaluating safety and efficacy	NCT02657889
TAK-228 (Sapanisertib)	Cisplatin and nab paclitaxel	Inhibiting Homologous Recombination (HR)	II	Recruiting	Assess the objective response rate associated with sequential treatment	NCT03193853
TAK-117 (Serabelisib)						
BSI-201 (Iniparib)	Gemcitabine plus carboplatin	PARP1 inhibitor	II	Completed	pathologic complete response	NCT00813956
E7449 (Stanoparib)	Alone and in combination with temozolomide or with carboplatin and paltaxel	PARP 1/2 inhibitor	I II	Completed	Maximum tolerated dose	NCT01618136
Veliparib	Cisplatin	PARP inhibitor	II	Recruiting	Progression free survival	NCT02595905
SHR3162 (Fluzoparib)	Famitinib	PARP inhibitor	I II	Recruiting	Objective response rate	NCT03805399
Rucaparib	---	PARP inhibitor	Early I	Recruiting	Measurement of expression of PD-L1 by IHC	NCT03911453



orphan receptor (ROR), related to receptor tyrosine kinase (RyK) and protein tyrosine kinase receptor (PTK). Due to the binding of ligand, the Dishevelled protein is activated and interacts with Ras-related C3 botulinum toxin substrate 1 (Rac1) and the Dishevelled-associated activator of morphogenesis 1 (DAAM1). Rac1 leads to actin polymerization by activating c-Jun N-terminal kinase whereas DAAM1 leads to cytoskeletal arrangements by activation of Rho and Rho-associated protein kinase (ROCK) in sequence.^[55,56] In Wnt/Ca²⁺ pathway, the Wnt ligand binds to the Fzd receptor which activates the G-protein and Dvl protein leading to activation of cGMP-specific phosphodiesterase or Phospholipase C (PLC) that increases the concentration of calcium in the cytoplasm. Increased concentration of calcium causes activation of downstream signaling protein-like protein kinase C (PKC), Calcineurin and Ca²⁺/calmodulin-dependent protein kinase II (CAMKII).^[57] Wnt5a ligand binding with the Fzd receptor activates CAMKII which phosphorylates TGF- β activated kinase and in turn Nemo-like-kinase.^[58] Nemo-like-kinase phosphorylates transcription factor 4 (TCF4) that inhibits interaction with β -catenin, thereby inhibiting the canonical Wnt pathway. Hence, Canonical Wnt signaling is also negatively regulated by the Wnt/Ca²⁺ pathway. *In-vitro* studies and *in-vivo* mouse cancer models of TNBC have shown that accumulation of β -catenin in the nucleus is responsible for cell migration, resistance to chemotherapy and stem cell-like features of TNBC cells suggesting canonical Wnt signaling, as a major driving force of TNBC development.^[59] TNBC and its poor clinical outcomes are due to the over-activation of Wnt/ β -catenin signaling.^[60,61]

Dysregulation of the non-canonical Wnt signaling pathway is responsible for metastatic behavior of TNBC cells and its cancer stem cells (CSC) through aberrant activation of JNK (c-Jun N-terminal kinase).^[62] Inhibition of β -catenin-mediated transcription in *in-vitro* studies on TNBC cell lines and *in-vivo* patient-derived xenograft models resulted in inhibition of stem cell proliferation and tumor volume reduction, respectively.^[63] A dose-escalation phase I study is recruiting patients with metastatic TNBC for determining the safety of combination getatolisib and PTK7-ADC (cofetuzumab pelidotin) showed better tolerability and promising clinical activity. Cofetuzumab pelidotin is an antibody-drug conjugate targeted to PTK7 protein (Wnt pathway co-receptor) with an auristatin payload.^(NCT03243331) Another dose escalation study is recruiting patients with selected solid malignancies including TNBC for evaluating safety and efficacy of LGK974 (a porcupine inhibitor) in combination with spartalizumab (anti-PD-1 immune checkpoint) ^(NCT01351103) (Fig. 2).

Hedgehog Signaling Pathway

Hedgehog (Hh) signaling pathway, Hh ligand binds with Patched1 transmembrane protein and subsequently

activates the Smoothed (SMO) transmembrane protein. The activated SMO releases transcription factor glioma-associated oncogene homolog 1 (GLI1) which gets translocated to the nucleus and leads to transcription of target genes responsible for metastasis, apoptosis and angiogenesis resulting in the development of TNBC.^[64] Activated SMO further activates v-myc myelocytomatosis viral related oncogene, neuroblastoma derived (MYCN), by increasing expressions of cyclin D and FOXM1, responsible for the development and progression of TNBC.^[65] FOXM1 controls the expression of genes essential for DNA synthesis and mitosis.^[66,67] Hence, SMO and Patched1 can be beneficial targets for the effective treatment of TNBC. Currently, drugs under clinical investigation comprise Hh-targeted therapies, specifically SMO inhibitors. SMO inhibitors have been proved clinically beneficial for basal cell carcinoma and medulloblastoma but not in the case of colorectal, pancreatic, lung cancer and metastatic castrate-resistant prostate cancer.^[68-73] Deregulation of the Hh pathway is due to multiple pathway activation including SMO-dependent and SMO-independent signaling via direct regulation of GLI1 expression. The mechanisms of the Hh pathway downstream activation of SMO includes loss of tumor suppressor genes, Teashirt zinc finger homeobox 2 (TSHZ2), Liver kinase B1 (LKB1), or Single-minded-2s (SIM2s) leading to limited application of any drug against TNBC.^[74] A phase I study involving R04929097 (gamma-secretase/Notch signalling pathway inhibitor) and vismodegib (SMO inhibitor) in combination for evaluation of safety and efficacy was terminated. (NCT01071564) Another phase II study is evaluating safety and efficacy of vismodegib (SMO inhibitor) in combination with chemotherapy comprising of paclitaxel, epirubicin and cyclophosphamide in TNBC patients (NCT02694224) (Fig. 3).

Notch signaling pathway

Notch signaling pathway gets activated when Notch ligand such as Delta-like (Dll) 1, 3, 4 and JAG ligands (Jagged 1, 2)

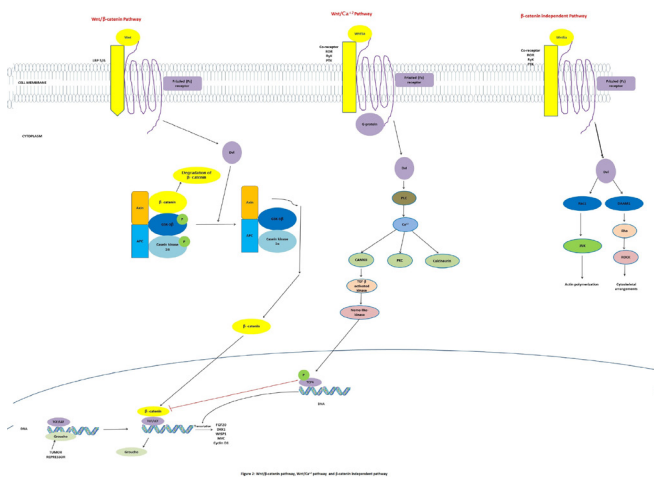


Fig. 2: Wnt signaling pathways.

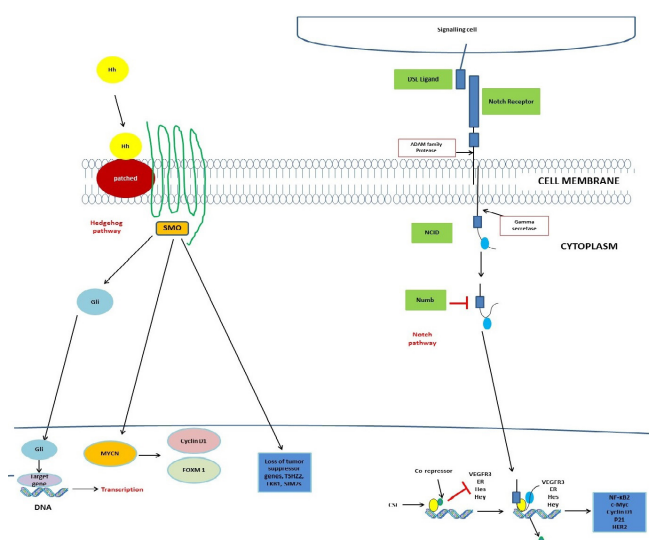


Fig. 3: Hedgehog and notch signaling pathway in TNBC.

bind to Notch receptors (Notch1,2,3 and 4) expressed in tumor, normal and endothelial cells. Extracellularly, notch extracellular truncation (NEXT) is formed with the help of disintegrin and metalloprotease (ADAM/TACE) proteases by cleavage of notch ligand-receptor complex. Intracellular notch intracellular domain (ICD) is formed by gamma-secretase (γ -secretase) which then translocate from cytoplasm to nucleus. This, in turn, activates an activation initiator CBF1, Suppressor of Hairless, Lag-1 (CSL) complex from a transcriptional repressor leading to activation genes such as vascular endothelial growth factor receptor 3 (VEGFR3), ER, Hairy Enhancer of Split (Hes) and Hairy/Enhancer of Spit related with YRPW motif (Hey). Targets of notch signaling pathway include Nuclear Factor Kappa B Subunit 2 (NF- κ B2), c-Myc, cyclin D1, cyclin-dependent kinase inhibitor 1 (p21), HER2 and regulators of angiogenesis and apoptosis.^[75] Directing antibodies towards notch receptors has been proven to be beneficial in decreasing tumor growth by inhibiting

Table 4: Clinical trials involving drugs targeting immune pathway for TNBC patients

Drug	Combination	Target	Phase	Status	Primary Outcome	Clinical Trial Number ^[21]
KY1044 (Alomfilimab)	Atezolizumab	Inducible T cell CO-stimulator	I II	Recruiting	Safety, tolerability, overall response rate and incidence of dose limiting toxicities	NCT03829501
SI-B003	----	A PD-1/CTLA-4 bispecific antibody	I	Recruiting	Dose limiting toxicity, maximum tolerated and administered dose, adverse events and recommended dose determination for phase II	NCT04606472
XmAb@22841 (Pavunalimab)	Pembrolizumab	CTLA-4 and LAG-3 bispecific antibody	I	Recruiting	Safety and tolerability profile of XmAb22841 assessed by rates of treatment-related adverse events (AEs)	NCT03849469
CX-2009 (Praluzatamab)	CX-072 (pacmilimab)	Probody drug conjugate (PDC) conjugated with DM4	II	Recruiting	Objective response rate	NCT04596150
Retifanlimab	Pelareorep	PD-1 monoclonal antibody	II	Recruiting	To determine the efficacy of the combination of retifanlimab (INCMGA00012) and pelareorep for patients with metastatic triple negative breast cancer in the second and third line setting along with safety, tolerability and feasibility	NCT04445844
Toripalimab	Nab-paclitaxel	Anti-PD-1 antibody	II	Recruiting	Pathologic complete response	NCT04418154
Nivolumab	Capecitabine	Anti-PD-1 antibody	II	Recruiting	Disease free survival	NCT03818685
Ipilimumab						
Durvalumab	Paclitaxel Epirubicin Cyclophosphamide	PD-L1 inhibitor	I II	Recruiting	Adverse events and pathological response	NCT03356860
Carelizumab	Nab-paclitaxel Apatinib	PD-1 immune checkpoint inhibitor	III	Recruiting	Progression-free survival	NCT04335006
Daratumumab	Nivolumab	CD38 PD-1	I II	Completed	Incidence of adverse events and Grade of laboratory abnormalities and establish tolerability	NCT03098550



angiogenesis in several preclinical models.^[76] It has been reported that Jagged1 and Delta Like Canonical Notch Ligand 4 (DLL4) ligands influence angiogenesis by independent mechanisms. Jagged1 ligand influences tumor angiogenesis by activating the Notch pathway.^[77] Combination therapy targeting VEGF plus DLL4 ligand is used for treatment as vascular endothelial growth factor (VEGF) induces expression of later in cancer cells and its activation leads to down-regulation of vascular endothelial growth factor receptor 2 (VEGFR2). Hence, blocking of DLL4 may up-regulate VEGFR2 leading to sensitization of the VEGF signaling due to an increase in angiogenesis.^[78] A variety of γ -secretase inhibitors (GSIs) have proved to be effective by increasing the sensitivity of tumor cells towards chemotherapy and radiation. A phase II study recruiting TNBC patients is evaluating overall response rate, progression-free survival and safety of AL101 (a γ -secretase inhibitor). (NCT04461600)

Immune Pathway

TNBC, with high genomic instability and burden, generates neoantigens recognized as 'non-self' antigen by the immune system. Cytotoxic T lymphocytes (CD8+ T-cell) recognize this antigen on tumor cells presented by Major Histocompatibility Complex-1 (MHC1). Antigens expressed in some TNBC cells are glycosylated form of mucin 1 (MUC-1), melanoma-associated antigens (MAGE-A), mesothelin and cancer/testis antigen 1 (NY-ESO-1).^[79-81] Due to neoantigens, there is the recruitment of tumor-infiltrating lymphocytes (TILs) with high expression of programmed cell death 1 ligand 1 protein (PD-L1) as compared to other breast cancer subtypes in TNBC. The high amount of TILs in the tumors provides a better prognosis to the cancer treatment and also the risk of relapse is reduced. Better prognosis is possible due to upregulation of genes induced by TIL for markers like programmed death-ligand 1 (PD-L1), programmed cell death protein 1 (PD-1), CTLA-4 (cytotoxic T lymphocyte antigen 4) and Type I iodothyronine deiodinase (DIO1).^[82,83] TNBC can also be targeted by blocking immune-checkpoint receptors preventing immune activation such as CTLA-1, B- and T-lymphocyte attenuator (BTLA), PD-1 along with its ligands PD-L1/2, T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) and lymphocyte-activation gene 3 (LAG-3). The immune system can also be targeted by immunosuppressive factors, by activating co-stimulatory receptors which induce the generation of tumor-reactive T-cells and transferring genetically engineered tumor-reactive T cells.^[84] In addition, the strong association between increased PI3K/AKT/mTOR signaling and the presence of PD-L1 is reported, as the loss of PTEN expression is associated with overexpression of PD-L1 ligand. Pembrolizumab, dosarlimab, atezolizumab approved for breast cancer treatment, are humanized monoclonal antibodies that act by blocking the PD-L1 receptor and preventing binding and

activation of PD-L1 and PD-L2. Various clinical trials with drugs targeting anti-PD-L1 and CTLA-4 inhibitors involved in breast cancer are listed in Table 4.

CONCLUSION

The heterogeneous nature of TNBC makes it the most aggressive of all breast cancer subtypes. The poor clinical outcome of the chemotherapy in TNBC is due to tumor recurrence, metastasis and mortality. It is worthwhile to explore various signaling pathways in detail and identify the molecular targets for the treatment of TNBC. Numbers of trials are ongoing and new targets are discovered but they do not see the daylight. This keeps the burning desire in the researchers to continuously explore various signaling pathways and find a way out for treating TNBC with promising drugs having pCR. Currently, clinical studies are ongoing for TNBC patients for evaluating the safety and efficacy of various drugs targeting different pathways in combination and results are still awaited.

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