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REVIEW ARTICLE

Targeting Different Pathways Using Novel Combination Therapy in Triple Negative Breast Cancer

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Abstract: Triple negative breast cancer (TNBC) is one of the most aggressive subtypes of breast cancer accounting for 15-20% of cases and is defined by the lack of hormonal receptors viz., estrogen receptor (ER), progesterone receptor (PR) and expression of human epidermal growth receptor 2 (HER2). Treatment of TNBC is more challenging than other subtypes of breast cancer due to the lack of markers for the molecularly targeted therapies (ER, PR, and HER-2/ Neu), the conventional chemotherapeutic agents are still the mainstay of the therapeutic protocols of its patients. Despite, TNBC being more chemo-responsive than other subtypes, unfortunately, the initial good response to the chemotherapy eventually turns into a refractory drug-resistance. Using a monotherapy for the treatment of cancer, especially high-grade tumors like TNBC, is mostly worthless due to the inherent genetic instability of tumor cells to develop intrinsic and acquired resistance. Thus, a cocktail of two or more drugs with different mechanisms of action is more effective and could successfully control the disease. Furthermore, combination therapy reveals more, or at least the same, effectiveness with lower doses of every single agent and decreases the likelihood of chemoresistance. Herein, we shed light on the novel combinatorial approaches targeting PARP, EGFR, PI3K pathway, AR, and wnt signaling, HDAC, MEK pathway for efficient treatment of high-grade tumors like TNBC and decreasing the onset of resistance.

Keywords: Breast cancer, TNBC, drug resistance, combination therapies, PARPi's, Wnt/β-catenin, Hsp90.

1. INTRODUCTION

Cancer is the major cause of morbidity and mortality worldwide and is the second leading cause of death in United States [1]. Breast cancer is the most common cancer type worldwide that affects women with nearly 1.67 million cases diagnosed annually, and approximately 1 in 37 women succumb to breast cancer [2]. According to recent epidemiologic studies, there has been a 20% rise in the number of reported breast cancer patients globally, which resulted in 522000 deaths since 2008 [3, 4]. Based on gene expression profiling, Perou *et al.* and Sorbie *et al.* identified five molecular subtypes of breast cancer with distinctive clinical behaviour and outcome: Luminal A, Luminal B, HER2 enriched, Normal-like and Basal-like [5, 6]. Another subtype of breast cancer, Triple negative breast cancer (TNBC), accounting for 15-20% cases is an aggressive subtype and is associated with higher recurrence rates as compared to other subtypes [7]. According to the survey conducted by the American society surveillance Research (2017), the female breast cancer incidence rates by subtype and Race/ethnicity are shown below in Fig. (**1**). Triple negative breast cancer is commonly characterized by the lack of expression of estrogen (ER) and Progesterone receptors (PR) as well as the absence of human Epidermal Growth Factor receptor 2 (HER2) amplification [8]. Among breast cancer subtypes, TNBC has a higher proliferative rate and is poorly differentiated, with higher incidence of distant metastasis, poor overall survival and high recurrence rates. The disease recurrence and progression typically occur within the first 3-5 years after diagnosis, while distant metastasis present to the brain and lung much more commonly in TNBC [9, 10]. About 70-80% of TNBCs are basal-like, while about 70% of basal-like tumors are triple-negative [11]. Recently, a TNBC subgroup lacking basal markers was identified called, the claudin-low molecular subtype, that represents the tumors enriched for stem cell and epithelial-mesenchymal transition (EMT) markers supporting the heterogenous nature of TNBC [12]. Despite being an aggressive subtype of breast cancer, triple negative breast cancers (TNBCs) show a good initial response to chemotherapy, but it has been well established that patients with residual TNBC disease have a worse prognosis, after treatment with neo-adjuvant chemotherapy than those presenting with non-TNBC [13]. A general chemotherapy treatment based on the combination of 'Anthracyclines' and 'Taxanes', that is part of the standard chemotherapy, although sensitized TNBC patients, but with poorer overall survival and disease recurrence [14], TNBC treatment is quite challenging. In TNBC patients with BRCA or BRCAness phenotypes, a significant increase in pCR rates has been shown by the addition of platinum agents to neoadjuvant chemotherapy. Only limited progress in systemic treatment of TNBC has been possible as a result of poor response, toxicity and eventual multidrug resistance [15, 16]. Additionally, due to the inter-patient heterogeneity and complex biology, it is difficult to target and manage TNBC [17]. Some FDA-approved

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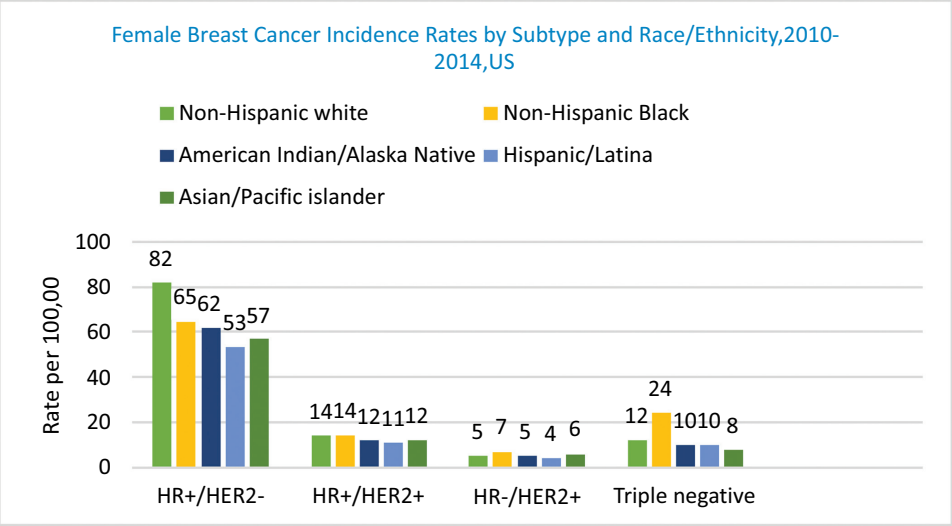

Fig. (1). Representing the incidence of female breast cancer cases according to subtypes and race/ethnicity. HR=hormone receptor, HER=Human Epidermal Growth factor Receptor2. Rates are age adjusted to the 2000 US standard population. Adapted from NAACCR, 2017. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

targets are under investigation for the treatment of TNBC as represented in Table **1** [18].

Table 1. Some FDA-approved targets in TNBC.

Biomarkers	Examples Include	Reference
Blood biomarkers	Vascular Endothelial growth factor (VEGF) Vascular endothelial growth Receptor IL-8	Roberti *et al.* [21] Chen *et al.* [22]
Cell Surface biomarkers	EGFR Insulin-like growth Factor binding protein c-kit c-Met PD-L1	Cheang *et al.* [23] Sohn J *et al.* [24] Zhu Y *et al.* [25] Johansson *et al.* [26] Yi YW *et al.* [27] Soliman H *et al.* [28]
Cytoplasm biomarkers	PIK3CA PAKT/S6/P4E-BPI pTEN ALDH1 PIK3CA/AKT/mTOR-related metabolites	Shah SP *et al.* [29] Baxi SM [30] Dean *et al.* [31] Ohi *et al.* [32]
Nucleus biomarkers	BRCA1 TP53 Ki67	Xu *et al.* [33] Foedermayr *et al.* [34] Urruticoechea *et al.* [35]

2. TNBC: EPIDEMIOLOGY

The management of TNBC is challenging due to its molecular heterogeneity. The original six-way molecular classification of Lehmann *et al.*, [19] based on the gene expression profiling has recently been refined into four: basal-like1 (BL1), basal-like 2 (BL2), Luminal androgen receptor (LAR) and mesenchymal (M) as shown in Fig. (**2**). By single-cell genomic analysis, it has been seen that these four subtypes can co-occur within given tumors [20]. Thus, TNBC can be significantly heterogeneous, making it essential to focus simultaneously on more than one subtypes expressing different pathways, so that the effective management of TNBC could be made possible (Fig. **3**). Therefore, simultaneously targeting more than one pathway, using novel and combinational therapies, is an emerging therapeutic strategy to treat TNBC.

2.1. Strategies to Target TNBC

For better management of TNBC, new treatment strategies are needed immediately. From the last five years many reviews have focused on this topic from different angles [36-39]. Here, we evaluate the recent progress in the development of novel modalities in therapeutics with an emphasis on combination therapies.

3. POLY ADP RIBOSE POLYMERASE INHIBITORS (PARPI)

PARP are a family of proteins that are components of the DNA base excision repair pathway (BER). PARPs lead to the activation and recruitment of repair enzymes at the site of single strand DNA breaks (SSBs). PARP inhibition blocks the BER pathway to repair SSBs, leading to the persistence of DNA single-strand breaks that collapse replication forks resulting in double-strand breaks [40]. These lesions repaired by the high-fidelity homologous recombination (HR) requires the presence of functional BRCA genes. If the cells are BRCA-deficient, the double-strand breaks are repaired by an alternative error-prone non-homologous repair process like Non-Homologous End-joining, which results in chromosomal instability, cell cycle arrest and apoptosis as shown in Fig. (**4**) [41, 42]. A concept known as Synthetic lethality arises if the unrepaired DNA damage accumulates and leads to cell death [43]. Thus, for the treatment of BRCA-deficient cancer PARP inhibition is a model of 'synthetic lethality' therapeutic strategy [41].

Various PARP inhibitors like olaparib, veliparib, talazoparib have been evaluated in clinical trials on TNBC patients as mono-therapies and/or combination therapies. Initially the use of PARPIs was hampered after the inhibitor Iniparib combined with (gemcitabine+ carboplatin) did not show any significant improvement in progression-free survival (PFS) and (OS) at phase 3 trial [44]. However,

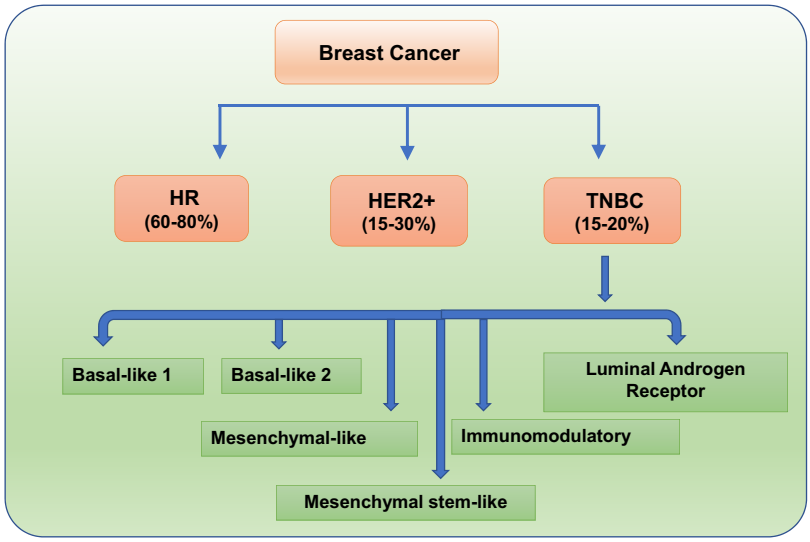

Fig. (2). Classification of TNBC. Six different subtypes of TNBC were identified by Lehmann *et al.* [20] such as: Basal-like1, Basal-like2, mesenchymal-like, mesenchymal stem-like, Immunomodulatory type and Luminal Androgen receptor type. This classification was later refined by these authors into four subtypes (Basal-like1, Basal-like2, mesenchymal-like and Luminal Androgen Receptor (LAR). The percentage of TNBC and other subtypes of Breast cancer is depicted in this figure.

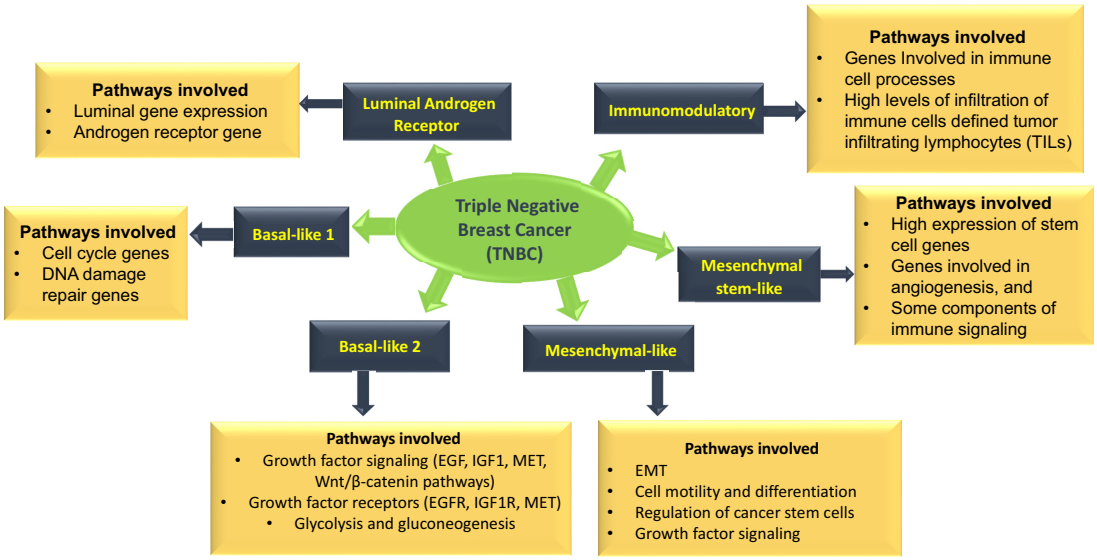

Fig. (3). Gene expression profiling of TNBC subtypes: expression of different pathways according to the TNBC subtypes.

Olaparib has been successful as it showed a response rate of 88%, when used in combination with paclitaxel, cisplatin [45]. In a phase II clinical trial, the combination of olaparib and eribulin showed a response rate of 37.5%, a median PFS of 4.2 months and a median overall survival (OS) of 14.5 months in mTNBC patients previously treated with anthracyclines and taxanes. This combination showed significant tolerance and proved to be a promising strategy allowing further investigations [41, 46]. Thus, combination of PARPIs with chemotherapy appears to be a promising approach both to increase the efficacy of PARPIs and to sensitize wild type BRCA patients, as wild type BRCA patients previously showed poor response to PARPIs alone [47]. Veliparib, an oral PARPI investigated by Rodler *et al.* for combinatorial studies showed an encouraging response rate at 300mg when combined with cisplatin and vinorelbine. On these promising results, a phase 2 randomized trial has been planned to assess veliparib's contribution to cisplatin chemotherapy in BRCA mutated breast cancer and TNBC [48]. Furthermore, in TNBCs with wild-type BRCA, a combination of veliparib + cisplatin + vinorelbine provided an ORR of 53% [49]. In order to sensitize wild-type BRCA patients to PARPIs, another novel approach is to co-target other complexes in DNA repair pathways, such as cyclin dependent kinase1 (CDK 1). As BRCA1 forms foci at areas of DNA damage, on phosphorylation by CDK1, the combination of olaparib + CDK1 inhibitor (RO3306) resulted in additive growth inhibition of MDA-MB-231 and HCC1937 cells [50]. A clinical trial of the CDK inhibitor dinaciclib + veliparib is underway [47].

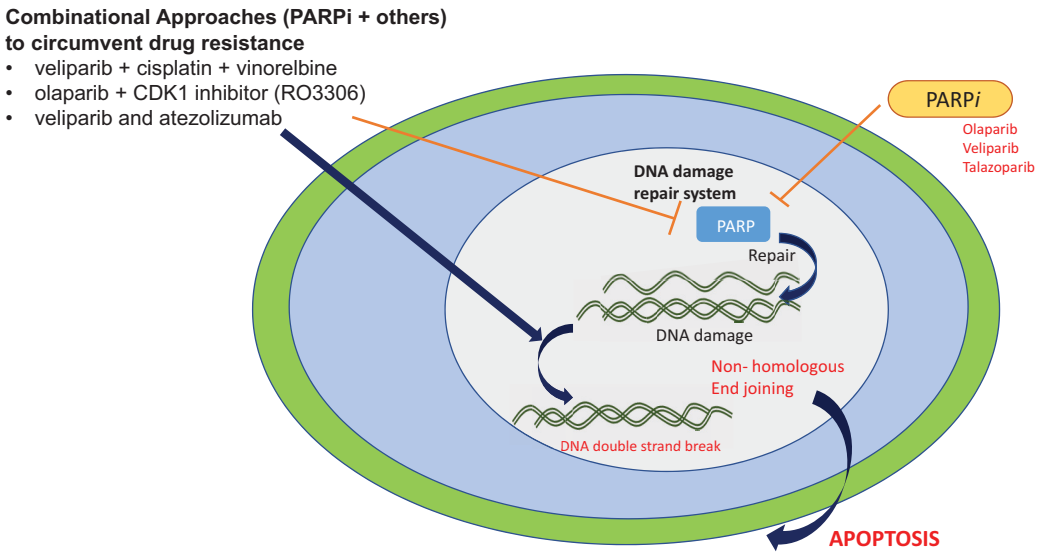

Fig. (4). Mechanism of PARP action and effect induced by PARPi as single agent or in combination. PARPi as a single agent has reduced efficacy due to resistance mechanisms, whilst PARPi's in combination with other emerging therapies provide promising evidence to combat resistance in TNBC cell lines and therefore prove effective.

With the emergence of immunotherapy as a new target for cancer therapy and the recent approval of therapeutic antibodies that block PD-1, PDL1 and CTLA-4, the combination of PARPIs with immunotherapy is being evaluated clinically for the expansion of clinical applications for PARP inhibitors. Some preclinical pieces of evidence suggested that the upregulation of PD-L1 expression in tumor cells is connected with the attenuation of PARPi efficacy. Thus, provided evidence that the inhibition of PD-L1 might restore the attenuated anti-tumor immunity and potentiate PARPi in tumor suppression [51]. Furthermore, there has been evidence that BRCA1/2 deficient cancers are more immunogenic, as they express higher levels of neoantigens. Also in various preclinical studies, a combination of PARPi with CTLA-4 antibody have shown synergistic activity [52]. Furthermore, many clinical trials are under investigation to test the efficacy of PARPIs in combination with immunotherapy, including; a phase 2 trial (NCT03167619) investigating the efficacy of olaparib in combination with durvalumab in advanced TNBC, a phase ½ trial (NCT02657889) studying niraparib combined with pembrolizumab in advanced TNBC, a phase 2 trial (NCT02849496) focusing on the use of veliparib and atezolizumab either alone or in combination treating patients with stage III-IV TNBC, and a phase 1b/2 study (NCT03330405) is going onto test talazoparib in combination of avelumab in advanced solid tumors [53].

4. EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR)

Epidermal Growth Factor Receptor (EGFR) belongs to the family of transmembrane tyrosine kinase receptors and is involved in the regulation of cell-proliferative growth, differentiation and survival [54]. EGFR expression is a common phenomenon in TNBC. Its occurrence has been reported in up to 89% of TNBC specimens, thus evidently appears as a promising therapeutic target [55]. Activation of EGFR by either EGF ligand, or cytoplasmic EGFR tyrosine phosphorylation, triggers downstream signaling through the PI3K-AKT-mTOR and Ras-MEK pathways, promoting cell proliferation and survival (Fig. **5**) [56]. Furthermore, overactivation of EGFR promotes primary tumorigenesis and metastasis by invasion, migration, angiogenesis, proliferation and epithelial-mesenchymal transition (EMT) [57, 58]. Nuclear EGFR expression is correlated with more aggressive clinical behaviour and resistance to chemotherapy and radiotherapy [59, 60]. *In vitro*, the nuclear EGFR expression also showed resistance to an EGFR tyrosine kinase inhibitor, Gefitinib [61]. Anti-EGFR therapies in TNBC include the tyrosine kinase inhibitors (TKIs)-erlotinib and lapatinib and the monoclonal antibodies (mAbs)-panitumumab and cetuximab [62-67]. Given the strong expression of EGFR, pre-clinical trials of EGFR-TKIs and mAbs against TNBC have been disappointing [68]. Also in phase 2 studies, cetuximab and panitumumab (mAbs) exerted only a small inhibitory effect when applied as monotherapies [69, 70].

Novel strategies for improving the efficacy of EGFR inhibition include a combination of TKI + mAb therapies. For example, in a phase 2 study, a combination of cetuximab with carboplatin against TNBC showed a response rate of about 16% compared with the use of cetuximab alone, with only 6% response [71]. Besides, a recombinant human p53 adenovirus (Ad-p53) + Gefitinib could enhance EGFR inhibition [72]. It was also reported by Yi *et al.*, that the combinatorial use of EGFR inhibitors with PI3K inhibitors might prove to be an attractive therapeutic strategy against TNBC [73]. In addition, antibody-drug conjugates (ADCs) represent a potential therapeutic approach in TNBC treatment. ADCs are a class of rapidly growing cells that combine the targeting property of mAbs with the anti-proliferative effects of cytotoxic drugs [74]. For example, ABT-414, an ADC (monomethyl auristatin F (MMAF), a potent microtubule inhibitor + EGFR-targeted humanized mAb) [75], selectively inhibits the growth of tumor cells overexpressing wild-type or mutant forms of EGFR and has shown complete tumor regression and cure in most

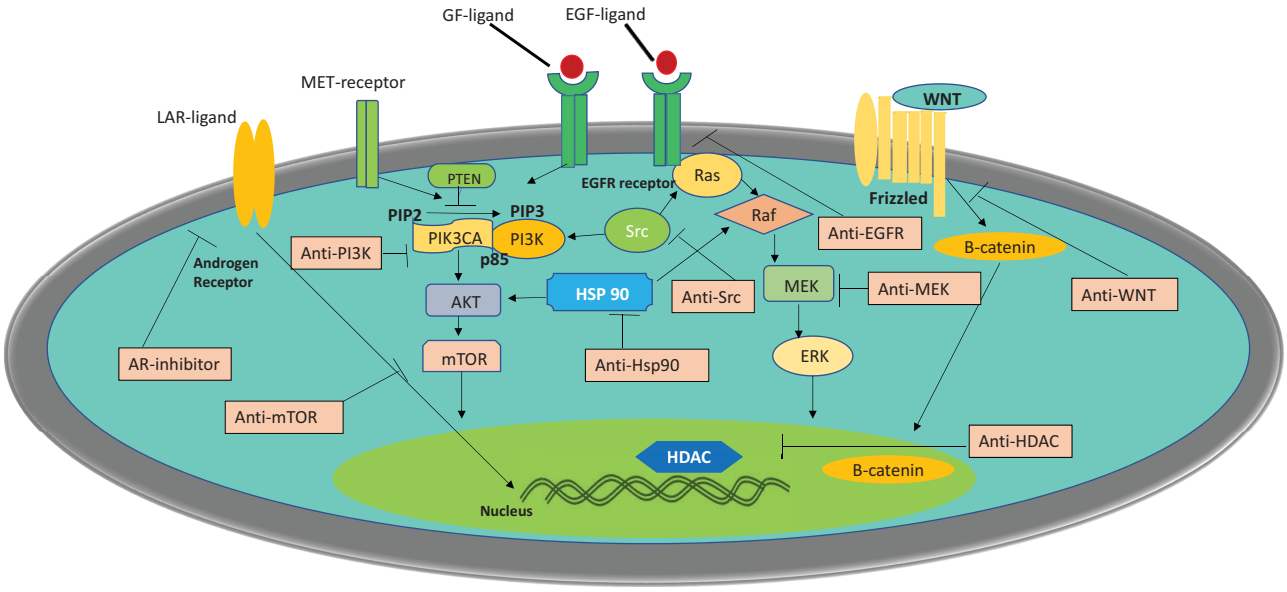

Fig. (5). Signaling pathways and other entities involved in TNBC. This diagram represents the inter-linkage of various pathways and provides us with an insight into targeting more than one pathway by combining different inhibitors.

sensitive models [76]. Another ADC includes Sacituzumab-govitecan (IMMU-132), targeting Trop-2 (a protein over-expressed in more than 80% of TNBC) for the selective delivery of SN-38, an active irinotecan metabolite. In a phase II trial, sacituzumab-govitecan induced an overall response rate of 30% with mild toxicity less than shown by the chemotherapeutic agent, Irinotecan alone. Due to these promising results, a confirmatory phase III trial is now recruiting to further explore its effectiveness [77]. Also, a combination of Sacituzumab-govitecan + PARPi (Olaparib or talazoparib) showed a decrease in the tumor volume in TNBC-derived cell xenograft as compared to the respective monotherapies, irrespective of BRCAness phenotype. This study evokes the need for further evaluation of Sacituzumab-govitecan + PARPi combinations in clinical trials [78]. In conclusion, monotherapy may not be a suitable therapeutic strategy for targeting EGFR. However, targeting EGFR with combinational therapy such as, TKI-mAb combinations, ADCs or in combination with other emerging modalities including PARPIs appears more promising. Additionally, patient heterogeneity and their responsiveness to certain specific modalities must be taken into consideration for an effective treatment against TNBC.

5. PI3K/AKT/MTOR PATHWAY

In TNBC, the PI3K/mTOR/AKT pathway is commonly over-expressed and hence represents an emerging multi-target of drugs. It is likely that blockade of this pathway can lead to amplified anti-tumor activity in TNBC [79]. Increased signaling through the PI3K/AKT/mTOR pathway is commonly found in breast cancer types, including TNBC [80]. PI3Ks, the critical molecules in the pathway, lead to tumor-cell growth. PI3Ks are heterodimers composed of regulatory (p85) and catalytic sub-unit (p110) subunits and exist in 4 isoforms (α, β, γ and δ) [81]. The stimulation of tyrosine kinase receptors, a growth factor receptor triggers the activation of this signaling pathway, which in turn triggers the activation of PI3K, the activated PI3K phosphorylates the serine/threonine protein kinase, AKT. This reaction is antagonized by the phosphatases PTEN (Phosphatase and Tensin Homolog) and INPP4B (Inositol polyphosphate-4-phosphatase type II) (Fig. **5**). mTOR is a downstream serine/threonine protein kinase formed of two complexes: mTORC1 and mTORC2. mTORC1, primarily regulates protein translation, while mTORC2 mediates the activation of AKT. mTORC2 is under negative feedback regulation by mTORC1 [82]. In TNBC, rather than mutations in PIK3CA, mutations in PTEN or INPP4B are the major cause of aberrant PI3K/AKT/mTOR activity [83, 84]. In multiple TNBC cell lines, the inhibition of mTOR with rapamycin or everolimus boosted the cytotoxicity of various chemotherapy agents [85, 86]. However, an open label phase II trial of everolimus with a standard neoadjuvant chemotherapy (paclitaxel) did not result in a significant increase of pCR (pathologic Complete Response) rate [87], might be due to the selective inhibition of mTORC1 by everolimus, resulting in the release of the feedback inhibition of mTORC2, causing continued activation of AKT [88]. One hopeful solution to this problem may be the use of dual mTORC1/2 inhibitors and pre-clinical studies have shown reduced activation of p-AKT by mTORC1/2 inhibitor AZD2014 as compared with everolimus [83]. Furthermore, mTOR inhibitors have also shown synergistic effects with many emerging therapies such as PI3K inhibitors or EGFR-TKIs [89, 90]. Trials of combined mTOR + PARP inhibitors and dual mTOR/PI3K inhibitors on TNBC are ongoing in Table **2**.

In pre-clinical models, PI3K inhibition fails to prevent tumor progression [91], which might be due to the result of PI3K inhibitor-induced activation of parallel signaling pathways (*e.g.* Notch and Wnt/β-catenin pathways) and HER-family RTKs (*e.g.* HER2/3, IGF1R) [92]. So, to improve response to PI3K inhibition, co-targeting these "resistant mechanisms" could prove to be a novel combinatorial therapeutic approach [93]. Notably, PI3K inhibition sensitizes

Table 2. Clinical trials of emerging novel combinational therapies in TNBC.

Class of Agent	Agent	Phase	Combinatorial Agents	Clinical Participants	Trial No.
PARPi	Olaparib	3 1 1b	- BKM120 or BYL719 (PI3K inhibitors) AZD2014 (mTORC1/2 inhibitor) or AZD5363 (AKT inhibitor)	Either TNBC or HER2-negative hormone receptor-positive BCa; must have germline BRCA1/2 mutation Recurrent TNBC, or high grade serous ovarian cancer Recurrent TNBC, endometrial, ovarian, peritoneal or fallopian tube cancer	NCT02032823 NCT01623349 NCT02208375
	Talazoparib	2	Irinotecan	Invasive BCa with prior no cytotoxic treatment	NCT01042379 (I-SPY2)
	Veliparib	1	Dinaciclib (CDK inhibitor)	Advanced solid tumors (BRCA-deficient and BRCA-proficient cohorts)	NCT01434316
PI3K inhibitor	Buparsilib	2 2	Selumetinib (MEK inhibitor) -	mTNBC mTNBC	NCT01629615 NCT01790932
AKT inhibitor	Ipataserib	2 2	Paclitaxel Paclitaxel	Stage Ia-IIIa TNBC Locally advanced TNBC or mTNBC	NCT02301988 NCT02162719
mTOR inhibitor	AZD2014	1/2	Selumetinib (MEK inhibitor)	TNBC, non-small cell lung cancer	NCT02583542
Dual PI3K/mTOR inhibitor	PQR309	1/2	Eribulin	Locally advanced/metastatic HER2-negative BCa	NCT02723877
AR antagonist	Bicalutamide	2	-	AR-positive mTNBC	NCT02353988
	Enzalutamide	2 2 2 1/2	Paclitaxel - - Taselisib (PI3K inhibitor)	Primary AR-positive TNBC Primary AR-positive TNBC Stage I-IIIAR-positive TNBC AR-positive mTNBC	NCT02689427 NCT02676986 NCT02750358 NCT02457910
	VT-464 (CYP17A1 inhibitor)	1/2	-	Advanced ER-positive BCa; advanced AR-positive TNBC	NCT02580448
HDAC inhibitor	Entinostat	2	Azacitidine	Locally advanced TNBC or mTNBC or HER2-negative BCa	NCT01349959
	Romidepsin	1/2	Cisplatin	Locally recurrent TNBC or mTNBC; locally recurrent or metastatic BCa with BRCA	NCT02393794
Hsp90 inhibitor	Onalespib	1	Paclitaxel	Locally advanced TNBC or mTNBC	NCT02474173
		1	Olaparib	Patients with solid tumors that are metastatic or cannot be removed with surgery, with expansion to recurrent TNBC	NCT02898207
Src inhibitor	Dasatinib	2	Durvalumab (anti-PD-L1)	n EGFR positive, stage I-III TNBC	NCT02720185
β- AR antagonist	Propranolol	2	Nab-paclitaxel Nab-paclitaxel + dose dense doxorubicin/cyclophosphamide	Stage I-III BCa planning to undergo definitive surgery	NCT02596867
	Propranolol	2	Regimen1: paclitaxel (may be given with nab-paclitaxel) or regimen 2: doxorubicin + cyclophosphamide	Newly diagnosed Breast cancer	NCT01847001
	Propranolol	2	-	Locally recurrent or metastatic solid tumors which cannot be removed by surgery, including TNBC	NCT02013492

Abbreviations: mTNBC: metastatic TNBC, AR: Androgen receptor, BCa: Breast cancer, β-AR: β-Adrenergic receptor, nEGFR: nuclear Epidermal Growth Factor Receptor, HER2: Human Epidermal Growth Factor Receptor2.

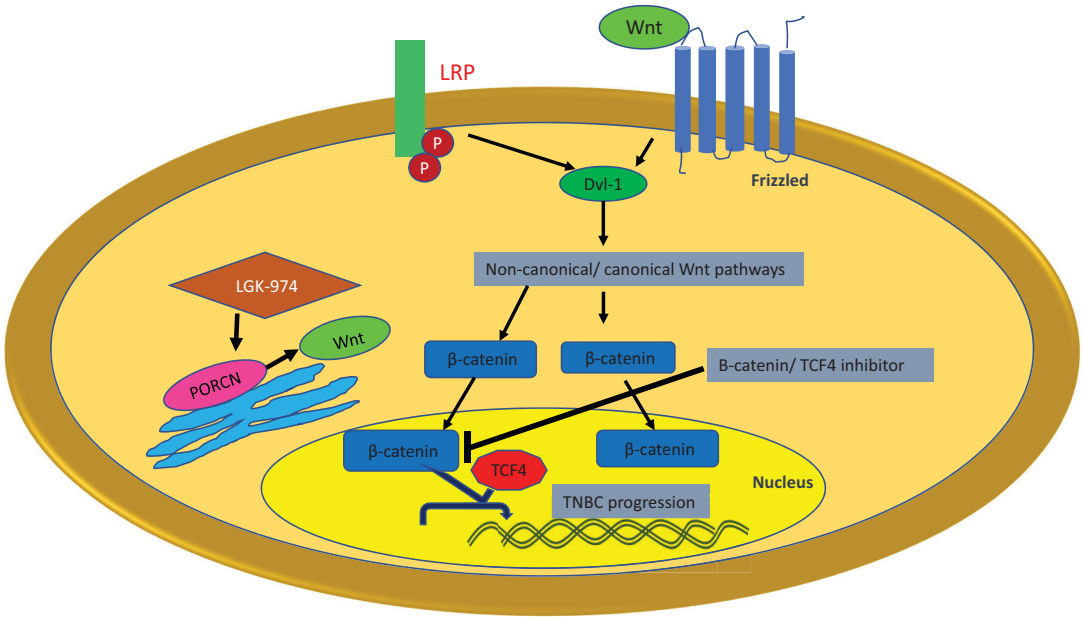

Fig. (6). Overview of Wnt/β-catenin signaling pathway and its role in tumor progression. CWP232228, a small molecule selectively blocks the interaction between β-catenin and T-cell factor, hence blocking Wnt pathway. Dishevelled (Dvl-1); LRP (LDL-receptor-related protein), TCF-4 (T-cell receptor 4).

BRCA-proficient tumors to PARP inhibition by downregulating BRCA1/2 and promoting HR deficiency [94]. Accordingly, a phase I study of buparlisib (BKM120), a pan-PI3K inhibitor in combination with olaparib is currently under evaluation (Table **2**) [95]. Preclinical data on AKT inhibition has been promising enough. In a phase II LOTUS trial, the addition of ipatasertib, an oral AKT inhibitor to paclitaxel therapy significantly improved the median PFS (Proliferation Free Survival) compared to placebo alone in the metastatic TNBC patients, especially in the patients with PIK3CA/AKT/PTEN-alteration [41]. Several other AKT inhibitors, AZD5363, MK-2206 is currently under clinical development as monotherapy and/or in combination with chemotherapy or targeted agents against TNBC [79, 96, 97].

A combination of MK-8669, an mTOR inhibitor with MK-2206, an AKT inhibitor significantly improved the average percentage of tumor growth inhibition compared to either one alone [98]. On the basis of these findings, new combinations concurrently targeting diverse components of the PI3K/mTOR/AKT pathway continue to be developed. For example, a combination of Gedatolisib, an equipotent PI3Kα/mTOR inhibitor + PTK7 antibody-drug conjugate (NCT03243331) is currently under development for TNBC treatment [98].

6. ANDROGEN RECEPTOR

Androgen receptor (AR) expression has been reported in about 13% to 37 % of TNBC patients and is particularly classified as a LAR-subtype. LAR undergoes dimerization upon ligand binding and is translocated to the nucleus, regulating genes that promote growth and survival [99, 100]. LAR-positive TNBC is more common at an older age [101]. It has been observed that AR-positive TNBC is resistant to chemotherapy [102], and hence relative to other subtypes, TNBC has lower survival rates [103]. *In vitro* studies suggested that targeting AR with anti-androgen inhibitors bicalutamide and enzalutamide inhibited proliferation, anchorage-independent growth, invasion, migration and enhanced apoptosis in various TNBC cell lines [104, 105]. PIK3CA mutations have been reported in about 40% cases of AR-positive TNBC patients than AR-negative TNBC and hence showed sensitivity to PI3K inhibitors [106, 107]. Based on this finding, for a response to other therapies, AR may prove to be a "surrogate biomarker" [108]. In AR-positive, MDA-MB-453 and CAL-148 xenografts, a combination of bicalutamide + GDC-0941 (a pan-PI3K inhibitor) or GDC-0980 (a PI3K/mTOR inhibitor) has shown improved growth inhibition [109]. A combination of enzalutamide + taselisib (a PI3K inhibitor) in clinical trial is ongoing. Furthermore, tamoxifen, an anti-estrogen repressed recurrence rates only in AR-positive TNBC patients, as previously it was believed to be ineffective in TNBC [110]. From these findings, it may be proposed that tamoxifen interacts with AR and/or some components of this signaling pathway, thus demanding further investigation to treat TNBC patients with AR expression. Combining anti-androgens and immunotherapy could be another possible approach to treat TNBC patients that co-express AR and PD-L1 [111]. In a phase II proof-of-concept study, a combination of abiraterone acetate (a selective inhibitor of cytochrome P450) + prednisone reached positive results, thus merits further clinical investigation [112]. Presently, combination of palbociclib and ribociclib + bicalutamide, an AR antagonist are in trials against AR-positive TNBC [113].

7. WNT/β-CATENIN PATHWAY

The role of Wnt/β-catenin signaling has been associated with embryonic development and homeostasis in adult stem cells [114, 115]. In BCSCs, the significance of Wnt/β-catenin has been confirmed in several experimental models

[102, 116]. This pathway has also been found to be linked with stemness, tumor initiation and metastatic spread [117]. Furthermore, the activation of Wnt/β-catenin signaling pathway is associated with the accumulation of nuclear β-catenin, its nuclear accumulation promotes cell migration, colony formation, stem-like features and chemoresistance of TNBC cells and hence suggesting that Wnt/β-catenin signaling is a major driving force in TNBC tumorigenesis [118, 119]. Therefore, Wnt/β-catenin signaling represents a major reasonable therapeutic target in battling TNBC tumorigenesis. Several studies have confirmed the importance of using Wnt/β-catenin inhibiting agents as novel benzimidazole compounds, SR133576 and SR135889 inhibited this pathway by producing pro-apoptotic effects in TNBC cell lines [120]. Both *in vivo* and *in vitro* studies in TNBC xenografts have shown that a small molecule CWP232228, selectively inhibits Wnt signaling pathway by blocking nuclear β-catenin interaction with T-cell factor, as shown in Fig. (**6**) and therefore, shows a strong effect against chemoresistant breast CSCs [121]. Also, Clofazimine showed reduction in the expression of ABC transporters by downregulating the pathway through negative obstruction of the accumulation of β-catenin in the cytosol. Besides, it also showed a synergistic effect with doxorubicin with a tremendous toxicity profile [122]. It has been seen that the combined inhibition of tankyrase-1, an antagonist of the destruction complex + polo-like kinase 1 also reduced the invasiveness and survival of TNBC cell lines [123]. Furthermore, both *in vivo* and *in vitro* studies suggested that a novel recombinant human Frizzled-7 protein antagonist suppressed the proliferation, invasion and angiogenesis, and also sensitized TNBC cells to docetaxel [124]. Currently, a small molecule LGK974, that blocks Wnt ligand secretion in patients with Wnt-ligand dependent malignancies, including TNBC (NCT01351103) is under investigation. Additionally, a phase I study verified vantictumab, an antibody that blocks several Frizzled receptors, together with paclitaxel in advanced or metastatic breast cancer (NCT01973309). Although, formal results have not yet been made available. Additionally, a combination therapeutic in metastatic TNBC, PTK7-ADC, an antibody-drug conjugate is currently under investigation (NCT03243331).

In summary, significant progress has been made in the realization of the structure and interaction of the Wnt/β-catenin signaling pathway. Various Wnt/β-catenin targeted inhibitors were designed as monotherapies and/or combinational therapies have been developed in the wake of this knowledge. Further elucidation and characterization of the components in this pathway may provide opportunities for the development of novel future therapeutics.

8. HISTONE DEACETYLASE INHIBITORS (HDACI'S)

HDAC (Histone deacetylase) is a vital player involved in epigenetic modification by regulating the proteins that are critical for homologous recombination repair of DNA. Consequently, the inhibition of its activity in the cells can improve the efficacy of drugs that are involved in causing DNA damage in the affected cells [125]. HDAC exercises effect non-histone proteins that control cellular homeostasis, such as cell cycle progression, differentiation and apoptosis [126]. Additionally, the acetylation of lysine residues in histones disrupts the structure of chromatin to facilitate gene transcription. Therefore, hypoacetylation caused by the aberrant expression of HDAC, resulting in amplification of genes and is associated with tumorigenesis by inhibiting the expression of tumor suppressor genes, including DNA repair genes [127, 128]. In view of that, HDAC inhibitors (HDACi's) have been seen to induce a HR deficiency-like gene expression profile in multiple wild-type TNBC cell lines and have shown to cause reductions in cell *via*bility, when used in combination with genotoxic agents such as cisplatin or PARPi's [129-131]. A further investigation of HDACi's combined with both DNA methyltransferase inhibitors and cisplatin is ongoing.

9. MEK PATHWAY

MEK (a mitogen-activated protein/extracellular signal regulated kinase), a component of RAS/MEK/ERK pathway plays a vital role in response to mitogens, oncogenes, stress and inflammation, besides the regulation of proliferation and survival. Therefore, anomalous regulation of this signaling pathway can lead to tumorigenesis by contributing to uncontrolled proliferation, invasion, metastasis and angiogenesis as well as reduced apoptosis [132, 133]. Furthermore, analysis of TNBC tumor specimens showed high levels of activation of the RAS/MEK/ERK pathway, supporting MEK as a suitable target for therapeutic intervention in a subset of TNBC (Fig. **5**) [134]. Preclinical data suggest that upregulation of MAPK/ERK pathway is a potential mechanism of resistance to taxanes, a frequently occurring phenomenon in TNBC patients. Therefore, a combination of taxane-based chemotherapy with MEK inhibitors could be an effective chemotherapeutic approach to treat TNBC patients. For instance, a combination of cobimetinib (a highly selective MEK inhibitor) + paclitaxel as compared to placebo + paclitaxel showed promising therapeutic effect [135]. Clinical data on use of MEK inhibitors in TNBC are inadequate, however a complete response was reported in a TNBC patient receiving the MEK inhibitor trametinib + gemcitabine in a phase 1b trial [136]. Additionally, clinical exploitation of MEK inhibition might thus consider combination therapies co-targeting IGF1R, EGFR or mTORC1. Certainly, combinations like these have shown the anti-proliferative effects of MEK inhibition in multiple TNBC cell lines [137-139]. For instance, the combination of selumetinib (MEK inhibitor) + Gefitinib (EGFR-TKI) in selumetinib sensitive TNBC cells (SUM149-EGFR+) induced a substantial G0/G1 cell cycle arrest and apoptosis. Also, a combination of Dactolisib (PI3K and mTOR inhibitor) + MEK 162 (MEK inhibitor) for TNBC treatment is currently under investigation [140].

10. MET RECEPTOR

MET (Methyl Erythritol Tyrosine kinase) is a cell surface receptor tyrosine kinase, which activates multiple downstream effectors including Src, AKT, ERK and RAS involved in cell proliferation, migration and survival. MET activation can occur either by ligand-independent activation through EGFR transactivation, or by endogenous ligand which is a hepatocyte growth factor (HGF). There is a strong pre-clinical evidence showing the increased expression of MET in TNBC, further MET expression in TNBC tissues is

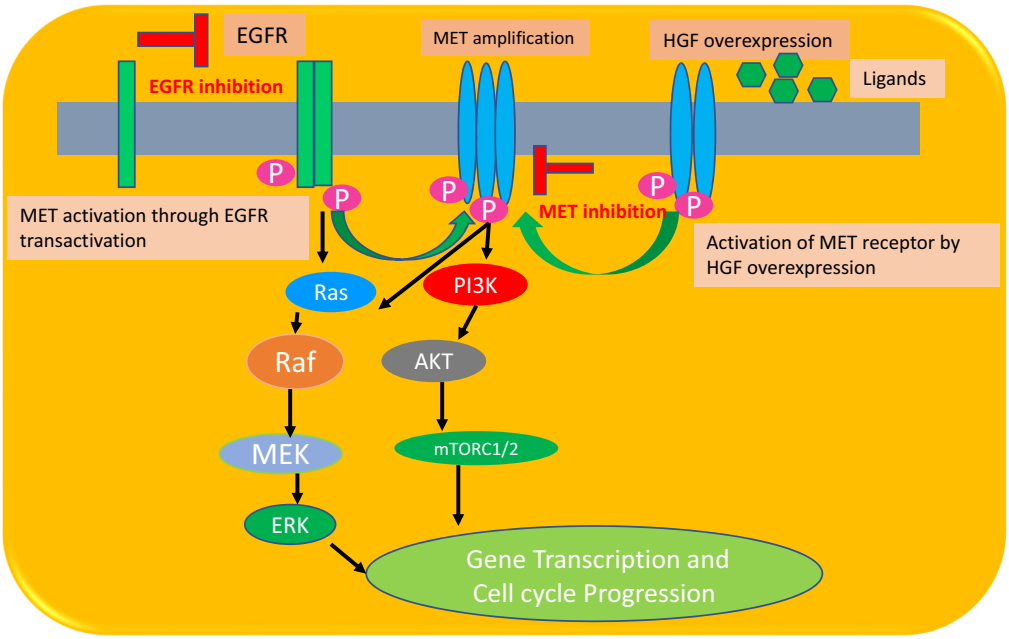

Fig. (7). Overview of cross-talk between MET and EGFR. MET is overexpressed either by ligand-dependent HGF (Hepatocyte Growth Factor) overexpression or by EGFR transactivation. A combination of EGFR and MET inhibitor representing a valid strategy to combat TNBC.

related with poor overall survival. In addition, MET expression strongly correlates with the expression of EGFR (Fig. **7**). TNBC patients co-expressing MET and EGFR show lower disease-free survival (DFS) as compared to those expressing EGFR alone [141]. Also, the presence of significant "cross-talk" between MET and EGFR found *in vitro* to a degree explains the restricted effectiveness of MET and EGFR inhibition as monotherapies [142]. For instance, in the most drug-resistant TNBC cell line (MDA-MB-468), silencing of EGFR enhanced their sensitivity to MET inhibitor (PHA-665752). Also PHA-665752 showed synergy with the EGFR inhibitor erlotinib in reducing the *via*bility of MDA-MB-468 cells [142]. Moreover, Mueller *et al.* reported that MET expression participates in the resistance mechanism in SUM229 breast cancer cells despite treatment with EGFR-TKI gefitinib. Both of these studies suggest that a combination of MET + EGFR inhibition can be a valid strategy for the treatment of TNBC [143]. Additionally, both *in vivo* and *in vitro* studies showed that various combinations of MET + PARP inhibitors synergistically reduced MDA-MB-231 and HCC1937 cell growth [144].

In summary, despite the fact that MET inhibition as monotherapy does not seem *via*ble for TNBC treatment, the combination of MET inhibitors with EGFR-TKIs and/or PARPIs provides promising preclinical evidence demanding further investigation.

11. HSP 90

Hsp 90 (heat shock protein 90) is a conserved molecular chaperone involved in the regulation, stability, activation and maturation of various 'client proteins' including receptor tyrosine kinases (EGFR, MET, HER2, IGF-1R), transcription factors (HIF1, TP53), cell cycle regulatory proteins (CDK4, CDK6) and signalling proteins (AKT, SRC). Subsequently, Hsp90 provides the potential stance of targeting multiple oncogenic pathways simultaneously (Fig. **4**) [145-148]. Over-expression of Hsp90 is associated with poor prognosis and worse recurrence-free survival in TNBC patients [149-151]. Preclinical studies have demonstrated that Hsp90 inhibitors show significant anti-cancer activity, resulting in simultaneous degradation of oncogenic client proteins and tumor growth inhibition [152-154]. The most advanced Hsp90 inhibitor, Ganetespib, caused the downregulation of multiple client proteins, G2/M phase cell cycle arrest, inhibition of metastasis and tumor growth in TNBC [155, 156]. Furthermore, several clinical trials have shown anti-tumor activities in TNBC patients. In spite of these promising responses, not all patients responded to the treatment, due to the development of resistance to Hsp90 inhibitors [157-160]. A combination of ganetespib and LY2784544 (an inhibitor of JAK2) showed increased apoptosis and enhanced cytotoxicity in Hsp90 inhibitor-resistant clones. Another combination of JAK2 inhibitor (AZD1480) also showed increased sensitivity to Hsp90 inhibitor resistant clones [161]. Phase I clinical trials evaluating the combination of Hsp90 inhibitors with paclitaxel and/or olaparib are under investigation in Table **2**.

12. SRC ONCOPROTEIN AS TARGET

The Src oncoprotein is a key member of the sarcoma family of non-receptor tyrosine kinases. It plays a vital role in multiple signaling pathways (Fig. **4**) and participates in processes such as regulating invasion, metastasis, angiogenesis and proliferation [162]. Many studies have indicated that TNBC shows higher sensitivity to the Src inhibitor than other breast cancer subgroups [163]. However, clinical trials of Src inhibitors bosutinib, saracatinib and dasatinib did not offer significant clinical benefit in combating TNBC [164-

166]. Nonetheless, combinational therapies may improve the therapeutic potential of Src inhibitors. Some reports suggested that a combination of dasatinib + cisplatin + cetuximab improved the inhibition in multiple TNBC cell lines [167, 168]. Furthermore, Src activity promotes cetuximab resistance by increasing EGFR nuclear translocation [61]. Therefore, a clinical trial is under investigation to evaluate if dasatinib could certainly thwart nuclear translocation of EGFR (Table **2**).

CONCLUSION

Despite the fact that TNBC is a complex group of heterogenous diseases characterized by several genetic alterations and a lack of validated biomarkers. Based on its molecular subtypes, that can co-occur within tumors, the inherent heterogeneity restricts the treatment efficacy. Moreover, lack of effective targeted therapy is equally challenging. Further, the development of 'resistance-mechanism' in TNBC is proving to be quite challenging for the treatment of TNBC. Monotherapies targeting the particular pathways are proving to be less effective because of poor overall survival and low response rates. However, various clinical trials targeting more than one pathway simultaneously brings into consideration a more promising approach to treat TNBC. Combinational therapies are proving to enhance and increase the effectiveness of various drugs used as single agent. Comparable clinical trials that take advantage of similar strategies are underway. Significantly, a diverse range of novel combinational targets is also emerging preclinically. These may aid as novel biomarkers and may form the firm basis for future therapies.

EXPERT OPINION

Breast cancer is the second leading cause of death worldwide and the most effective treatment for diagnosing this disease is to target the overexpressing hormone receptors like Estrogen receptor (ER), Progesterone receptor (PR) and HER2 (Human Epidermal Growth Factor receptor (HER 2). Breast cancer has various subtypes but among those subtypes, Triple Negative Breast Cancer (TNBC) is the most lethal and aggressive subtype. Like other subtypes, TNBC cannot be treated with the treatment option applied for treating other breast cancer subtypes, because of the absence of hormone receptors which include Estrogen receptor (ER), Progesterone receptor (PR) and HER2 (Human Epidermal Growth Factor receptor) due to which chemotherapy remained the sole impactful treatment option for TNBC treatment. Initially, TNBC patients showed a good initial response to chemotherapy but after treatment with neoadjuvant chemotherapies like 'Anthracyclines' and 'Taxanes', it has been seen that TNBC have a worse prognosis, mainly because of the development of resistance. Furthermore, chemotherapy targets the growing cells irrespective of differentiating whether the cell is a normal growing cell or a cancerous cell thereby affecting the patient's health eventually. Hence, making it essential to focus on targeted therapy in completely treating TNBC disease. Various biomarkers are under investigation that are involved in this disease which include: VEGF (Vascular Endothelial Growth Factor), IL-8 (Interleukin-8), EGFR (Epidermal Growth Factor Receptor), PI3KCA, ALDH1 (Aldehyde dehydrogenase 1), TP 53, *etc.* Furthermore, the molecular characterization has revealed many pathways and the molecules involved in these pathways that are over-expressed in TNBC, paving the way as targets by which TNBC can be targeted and treated. Studies have revealed some of the pathways that are overexpressed in TNBC which include: PI3K/AKT/mTOR, Wnt/β-catenin pathway, MEK pathway, *etc.* Despite these findings, the complete cure for TNBC has not been achieved yet, the main reason being the development of resistance in TNBC patients and also molecular heterogeneity existing between affected individuals.

In order to diagnose this disease, approaches should be made to subside resistance by combating the same ways a drug is used and also take into consideration the differences in the molecular heterogeneity of TNBC patients before prescribing a drug or any medication, as prescribing medicine on generalized terms could also lead to the development of drug hence specifying the individual needs and this could stop the development of resistance in patients that is "specific drugs on specific targets" to a large extent could help eradicate resistance among patients. However, many studies have revealed that targeting any one over-expressing pathway has proved to be of less significance in treating TNBC patients, generating an urgent need to focus on targeting more than one pathway simultaneously.

Taking into consideration the inter-patient heterogeneity and complex biology, the treatment of TNBC is difficult. One approach is to target the pathways in TNBC patients according to their over-expression in different TNBC subtypes. Therefore, targeting simultaneously more than one subtype of TNBC expressing different pathways, using novel combination therapies could prove to be an effective way to treatment. Furthermore, many clinical trials have supported the use of combinational approach in bringing improvement in TNBC patients generating a need on further studies.

LIST OF ABBREVIATIONS

Akt	=	Protein kinase B
BCa	=	Breast Cancer
BCSCs	=	Breast Cancer Stem Cells
CSCs	=	Cancer Stem Cells
DFS	=	Disease Free Survival
EGFR	=	Epidermal Growth Factor Receptor
ER	=	Estrogen Receptor
HDACi's	=	Histone Deacetylase inhibitors
HER2	=	Human Epidermal Growth Factor Receptor2
Hsp90	=	Heat Shock protein 90
MEK	=	Mitogen activated protein/extracellular signal regulated kinase
MET	=	Methyl erythritol Tyrosine Kinase
mTNBC	=	metastatic Triple Negative Breast Cancer
mTOR	=	mammalian Target of Rapamycin
ORR	=	Overall Response Rate
OS	=	Overall Survival

PARPi's	=	Poly ADP Ribose Polymerase
pCR	=	pathologic Complete Response
PFS	=	Progression Free Survival
PI3K	=	Phosphatidyl inositol 3-kinase
PR	=	Progesterone Receptor
Src	=	Protein oncogene tyrosine protein kinase/cellular sarcoma
Wnt	=	Wingless-related integration site

AUTHORS' CONTRIBUTIONS

MAM initiated the study, designed the plan and edited the manuscript. HQ and MAM wrote the manuscript and designed the figures and tables. NW and UM reviewed the manuscript and arranged the references. MAM, NW, HQ, UM and SN read and approved the final manuscript.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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