Molecular targets and therapies associated with poor prognosis of triple-negative breast cancer (Review)

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Abstract. Triple-negative breast cancer (TNBC) is a highly aggressive and heterogeneous subtype of BC characterized by the absence of estrogen, progesterone and human EGFR2 receptors. This lack of receptors renders it unresponsive to standard targeted therapies. Despite advances made in understanding the molecular landscape of TNBC, its poor prognosis and high recurrence rates underscore the urgent need for innovative therapeutic approaches. This review explores the effects of key prognostic markers, such as Ki-67, programmed cell death ligand 1, BRCA1/2 mutations, E-cadherin loss and EGFR alterations. It also examines critical pathways, including the PI3K/AKT/mTOR and mutant p53 pathways, which are prerequisites for TNBC progression and therapy resistance, and discusses the therapeutic potential of directly targeting these key molecules and their associated signaling pathways. In addition, recent advances in targeted therapies were highlighted, such as immune checkpoint inhibitors, and the statuses of emerging strategies were presented, such as chimeric antigen receptor-T cell therapy and small inhibitory RNA-based treatments. Given the molecular heterogeneity of TNBC, the importance of precision medicine was also discussed and it was emphasized that this approach is becoming an increasingly critical aspect of personalized treatment strategies. Resistance to existing therapies presents a major challenge to the effective treatment of TNBC, and thus, the development of future therapeutic strategies requires technical innovations. By integrating these insights, this review aims to provide a comprehensive overview of current and future means of improving TNBC outcomes.

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Abbreviations: TNBC, triple-negative breast cancer; BL-1, basal-like 1; LAR, luminal androgen receptor; MSL, mesenchymal stem-like; M, mesenchymal; IM, immunomodulatory; HER2, human epidermal growth factor receptor 2; ER, estrogen receptors; PR, progesterone receptors; TILs, tumor-infiltrating lymphocytes; Ki-67, antigen kiel 67; PD-1, programmed death 1; PD-L1, programmed cell death ligand 1; BRCA1/2, breast cancer susceptibility gene 1 and 2; EGFR, epidermal growth factor receptor; PI3K, phosphatidylinositol 3-kinases; AKT, protein kinase B; mTOR, mammalian target of rapamycin; IHC, immunohistochemistry; DFS, disease-free survival; OS, overall survival; ICI, immune checkpoint inhibitor; PTEN, phosphatase and tensin homolog; PARPi, poly(ADP-ribose) polymerase inhibitors; EMT, epithelial-mesenchymal transition; LOH, loss of heterozygosity; MEK, mitogen-activated protein kinase kinase; IDC, invasive ductal carcinoma; ERK, extracellular regulated kinase; TKI, tyrosine kinase inhibitor; ORR, objective response rate; NSCLC, non-small cell lung cancer; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PDK, pyruvate dehydrogenase kinase; MDM2, E3 ubiquitin ligase murine double minute 2; LOF, loss of function; RCC, renal carcinoma cells; CRAds, conditionally replicative adenoviruses; ASO, antisense-oligonucleotides; ROS, c-ros oncogene; CAR-T, chimeric antigen receptor-T; ZMCs, zinc metallochaperones; DBD, DNA-binding domain; MK-2206, selective allosteric inhibitor of AKT; SHE78-7, E-cadherin monoclonal antibody; cSNX1.3, peptide-based therapeutic; P53R3, potent p53 reactivator; PRIMA-1, mutant p53 reactivator; APR-246, PRIMA-1 analog; siRNA, small interfering RNA; RTK, receptor tyrosine kinases

Key words: triple-negative breast cancer, Ki-67, PD-L1 expression, BRCA1/2 mutation, E-cadherin, p53 mutation, PI3K/AKT/mTOR

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1. Introduction

Triple-negative breast cancer (TNBC) represents a unique and challenging BC subset, characterized by the absence of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) (1), as the lack of these established hormonal and HER2 targets renders TNBC unresponsive to some of the most effective therapies available for other BC subtypes, such as endocrine therapy and HER2-targeting treatments (2). Consequently, TNBC is often associated with poor prognosis characterized by high rates of early recurrence, metastasis and shorter overall survival (OS) than other BC subtypes (3,4).

TNBC was initially classified into six subtypes based on gene expressions profiles (Fig. 1): Luminal androgen receptor (LAR), mesenchymal (M), basal-like 1 (BL1), BL2, immunomodulatory and mesenchymal stem-like (MSL). However, subsequent studies showed that the IM and MSL subtypes are primarily characterized by high levels of tumor-infiltrating lymphocytes (TILs) and stromal cells and do not constitute distinct cancer cell subtypes. Consequently, the TNBC classification was refined to include four main subtypes (BL1, BL2, LAR and MSC) (1), which differ significantly in treatment response, prognosis and survival rates. Notably, BL1 and BL2 represent ~75% of TNBC cases (5).

The incidence of TNBC depends on demographic factors including age, ethnicity, genetic predisposition and sex. In particular, its prevalence is higher in younger women, African American women and those harboring breast cancer susceptibility gene 1 (BRCA1) gene mutations (6). The aggressive nature of TNBC, in combination with its molecular heterogeneity, complicates treatment and underscores the need to understand underlying biology in depth (7). Over the last two decades, considerable efforts have been directed toward mapping the molecular landscape of TNBC, and as a result, several TNBC molecular subtypes have been identified with unique biological behaviors and therapeutic vulnerabilities. The heterogeneity of TNBC is evidenced by diverse genetic alterations, epigenetic modifications and dysregulated signaling pathways (8). Key molecular aberrations in TNBC include defects in DNA repair mechanisms, alterations in cell cycle regulation and activations of oncogenic signaling pathways, including the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) and JAK/STAT pathways (9). These molecular characteristics not only contribute to the aggressive phenotype of TNBC but also highlight potential targets for therapeutic intervention.

One of the most promising areas of TNBC research involves exploring DNA damage response pathways, particularly in tumors with BRCA1 or BRCA2 mutations (10). Nonetheless, not all TNBCs feature BRCA mutations and resistance to therapies targeting these mutations remains challenging. Thus, the prognosis of patients with TNBC remains poor despite the progress made, particularly in advanced disease stages. Current treatment options are limited and the emergence of resistance to conventional chemotherapies further complicates TNBC management (11). Consequently, there is an urgent requirement to identify novel molecular targets and develop more efficacious therapeutic strategies.

This review aims to provide a comprehensive overview of seven key molecular targets (Table I) related to the poor prognosis of TNBC and to describe current and emerging therapeutic strategies designed to improve patient outcomes (Fig. 2, Table II). By exploring the complex molecular landscape of TNBC and the therapeutic challenges it presents, the current review suggests potential routes for developing more effective treatments for this aggressive form of BC.

2. Key prognostic markers of poor outcomes in TNBC

Ki-67 proliferation index. Ki-67 is considered one of the most promising targets and prognostic markers in TNBC (12). This non-histone nuclear protein was discovered by Gerdes *et al* (13) in 1980 and its encoding gene is situated on the long arm of human chromosome 10q26 (14). Ki-67 is a recognized crucial cell proliferation marker and has been extensively investigated. The expression of this protein provides a reliable and rapid means of assessing malignant cell growth and is strongly correlated with tumor progression, metastasis and local recurrence in various malignancies (15). Thus, evaluations of Ki-67 expression are crucial for assessing tumor cell proliferation, understanding tumor biology and estimating potential risks.

Ki-67 is expressed in all active phases of the cell cycle but is absent in quiescent cells, which makes it a dependable marker of tumor proliferation (16). Furthermore, its expression is tightly regulated by the cell cycle, particularly by E2F transcription factors during the G1 phase. Ki-67 mRNA levels increase during G1, while Ki-67 protein is degraded by the ubiquitin-proteasome system (17,18). Thus, Ki-67 levels vary in cells transitioning from quiescence back into the cell cycle.

Immunohistochemical (IHC) analysis-determined Ki-67 labeling indices have been used as potential predictive and prognostic biomarkers of pathological complete response (pCR) following neoadjuvant chemotherapy in patients with TNBC (19,20). pCR is a critical indicator of a positive response to BC treatment, as it is strongly linked to improved cancer-free and OS outcomes (21). MIB1 (anti-Ki67 antibody) is widely regarded as the 'gold standard' clone for Ki-67 assessment (22,23), though other clones, such as SP6, 30-9, K2 and MM1, are also used (24,25). Notably, rabbit anti-human Ki-67 monoclonal antibody SP6 recognizes the same Ki-67 epitope as MIB1 and has been reported to enhance the sensitivity of quantitative image analysis (26,27).

Elevated Ki-67 levels are linked to increased tumor aggressiveness and have been associated with poorer outcomes in patients with TNBC (28). Studies indicate that patients with TNBC expressing high levels of Ki-67 have poorer prognoses, as evidenced by lower disease-free survival (DFS) and OS rates. According to a study by Goldhirsch *et al* (29), Ki-67 expression of ≥40% above normal significantly increases the risk of recurrence and mortality in TNBC. They proposed a Ki-67 expression cutoff value of 14% for classifying BCs as having a favorable or unfavorable prognosis, such as luminal A BC, and those with a poor prognosis, specifically luminal B BC. However, the applicability of this Ki-67 cutoff to TNBC remains uncertain (30). These findings underscore the significance of Ki-67 as a predictive and prognostic marker in TNBC.

Programmed death ligand 1 (PD-L1) expression. PD-L1 serves as a primary ligand for PD-1, a co-inhibitory receptor that can be constitutively expressed or induced in different cell types, including myeloid, lymphoid, normal epithelial cells and cancer cells (31). Under physiological conditions, the interaction between programmed death 1 (PD-1) and PD-L1 plays a critical role in establishing immune tolerance and facilitating the regulation of immune cell activity to prevent tissue damage and autoimmune responses (32).

PD-L1 is a pivotal biomarker in TNBC and importantly influences cancer cell immune evasion (33). In patients with TNBC, the expression of PD-L1 on tumor and immune cells within the tumor microenvironment has been linked to prognosis and treatment outcomes (34). Oner *et al* (35) recently

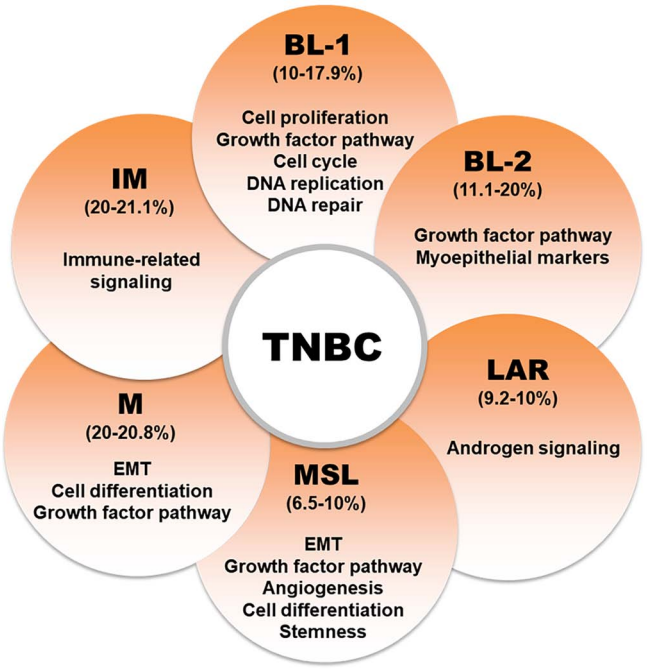

Figure 1. Characteristics and molecular subtypes of TNBC. BL-1, basal-like 1; LAR, luminal androgen receptor; MSL, mesenchymal stem like; M, mesenchymal; IM, immunomodulatory; EMT, epithelial-to-mesenchymal transition; TNBC, triple-negative breast cancer.

observed PD-L1 expression in a subset of TNBC cases and found it to be associated with the ability of tumors to suppress immune responses, and thus, to contribute to the aggressive nature of TNBC. PD-L1 expression is particularly crucial to enable the activities of immune checkpoint inhibitors (ICIs), such as pembrolizumab and atezolizumab, which target the PD-1/PD-L1 pathway. Interestingly, these therapies produced promising results, particularly in PD-L1-positive patients with TNBC, by enhancing the ability of the immune system to identify and eradicate cancer cells (34,36).

PD-L1 regulation is of considerable research interest and is involved in interferon gamma-induced tumor cell surface expression, which inhibits immune responses and oncogenic signaling via the phosphatase and tensin homolog (PTEN)/PI3K pathway (37). PTEN loss or silencing is common in glioblastoma and BC, promotes PD-L1 expression and is associated with PI3K pathway activation (38). In BC, PIK3CA mutations and PTEN loss, which are associated with ER/PR-negative tumors, are present in 30-40% of primary tumors (39). Furthermore, The Cancer Genome Atlas data indicate that basal-like tumors, primarily TNBCs, display PTEN mutation or loss in 35% of cases and that these are correlated with PI3K activation (40).

Patients with TNBC have elevated TIL levels (41). Several studies have explored the relationship between tumor PD-L1 expression and TIL and TNBC prognosis, but the prognostic significance and clinicopathological implications of PD-L1 and TILs remain controversial (42,43). The prognostic values of TILs and PD-L1 were investigated in a meta-analysis of 1,152 patients with TNBC. The analysis revealed no significant association between PD-L1 expression and clinicopathological factors, OS or DFS. Nonetheless, high TIL levels were found to be associated with improved OS [hazard ratio (HR)=0.48] and DFS (HR=0.53). In addition, PD-L1 overexpression was strongly associated with high TIL levels (odds ratio=8.34) (44). These results underscored the prognostic importance of TILs and their relationship with PD-L1 in TNBC.

Clinical studies have shown that patients with TNBC with high PD-L1 expression, particularly those treated with ICIs plus chemotherapy, tend to have better DFS and OS (33,35,36). However, response to ICIs can vary significantly and not all PD-L1-positive patients achieve long-term benefits (36). This variability highlights the need for ongoing research to identify additional biomarkers that predict which patients are likely to benefit from these therapies.

Furthermore, PD-L1 expression has been found to correlate with a higher rate of pCR following neoadjuvant chemotherapy in patients with TNBC and to serve as a surrogate marker of long-term survival (45). While high PD-L1 expression in TNBC is linked to a more favorable response to standard treatments, its role as a standalone prognostic marker has yet to be determined.

BRCA1/2 mutations. BRCA1 and BRCA2 were identified in the 1990s as components of the normal human genome, but their mutations are positively associated with the risk of developing breast and ovarian cancer (46,47). BRCA1 is expressed in endocrine tissues and various cell types, including neuroepithelial cells, during the early developmental stage. Likewise, BRCA2 expression is observed in numerous tissue types, and it is higher in breast and thymus tissues and lower in lung, ovary and spleen tissues (48,49). Of note, BRCA1 and BRCA2 mutations are strongly associated with TNBC. Women harboring BRCA1 mutations are at higher risk of TNBC development because of the role BRCA1 plays in DNA repair. In fact, 15-20% of patients with TNBC harbor mutations in the BRCA1 or BRCA2 genes (50).

BRCA1 and BRCA2 dysfunctions, such as mutations, promoter methylation and diminished protein expression, are alternative causes that impair their activities and contribute to the 'BRCAness' phenotype (51,52). These dysfunctions result in deficiencies in homologous recombination-mediated DNA double-strand break repair. Furthermore, in the absence of functional BRCA1 or 2, cells may depend on more error-prone repair pathways (53). BRCA1 mutations are linked with reduced short- and long-term survival, whereas BRCA2 mutations do not appear to significantly affect survival (52). In addition, BRCA1 methylation has been associated with poor survival in patients with BC (54). However, studies have provided mixed results for different TNBC subtypes, i.e., BRCA1 or 2 mutation carriers had similar or poorer survival than non-mutation carriers (55,56).

BRCA1 mutations are associated with earlier TNBC onset and a more aggressive disease course (57). In addition, patients with BRCA1 mutations exhibit a higher frequency of basal-like TNBC, a more aggressive subtype of TNBC characterized by the absence of estrogen, progesterone and HER2 receptors, making it particularly challenging to treat using conventional therapies. Nevertheless, individuals harboring BRCA mutations may respond better to DNA-damaging agents, such as platinum-based chemotherapies or poly(ADP-ribose) polymerase inhibitors (PARPi), due to defects in homologous recombination repair pathways caused by the mutations (58).

Table I. Key molecular targets related to the poor prognosis of TNBC.

Prognostic biomarker	Mechanism	Approximate prevalence in TNBC, %	(Refs.)
Ki-67 index	Cell proliferation	40-83.3	(28)
PD-L1 expression	Tumor immune surveillance	40-80	(32)
BRCA1/2 mutations	Homologous recombination, DNA double-strand break repair	15-25	(51,52)
Reduced E-cadherin expression	Adherens junctions, Epithelial-to-mesenchymal transition	65.7-73	(60,61)
EGFR mutation and expression	Receptor tyrosine kinase, Cell proliferation/survival	45-76	(78,79)
PI3K/AKT/mTOR pathway	Cell proliferation/survival	7-9	(104-106)
P53 mutation	Transcription factor, Cell cycle arrest	80	(113,114)

Ki-67, antigen kiel 67; PD-L1, programmed cell death ligand 1; BRCA1/2, breast cancer susceptibility gene 1/2; E-cadherin, epithelial cadherin; EGFR, epidermal growth factor receptor; PI3K, phosphatidylinositol 3-kinases; AKT, protein kinase B; mTOR, mammalian target of rapamycin; TNBC, triple-negative breast cancer.

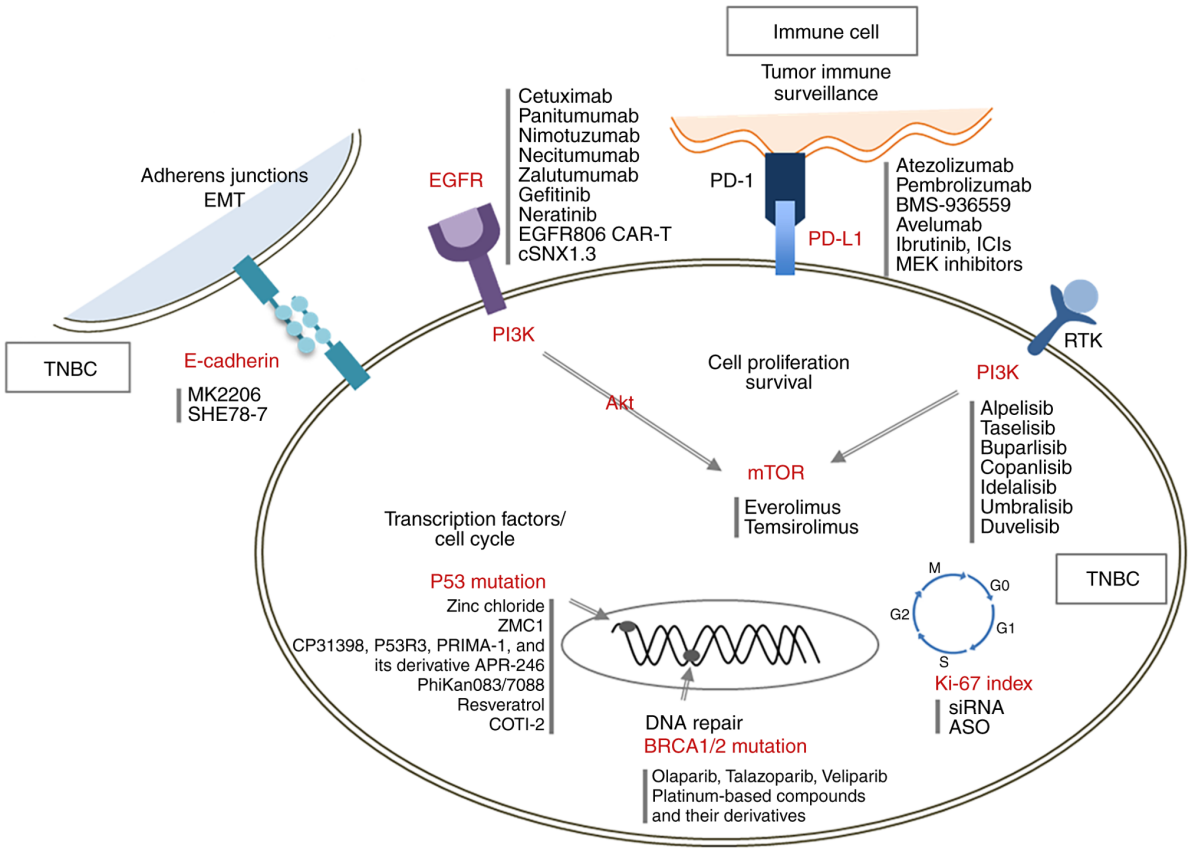

Figure 2. Current therapeutic strategies for metastatic triple-negative breast cancer. TNBC, triple-negative breast cancer; EMT, epithelial-to-mesenchymal transition; ASO, antisense-oligonucleotides; siRNA, small interfering RNA; ICI, immune checkpoint inhibitor; MEK, mitogen-activated protein kinase kinase; PRIMA-1, mutant p53 reactivator; APR-246, PRIMA-1 analog; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinases; Akt, protein kinase B; BRCA, breast cancer susceptibility gene; PD-1, programmed cell death protein1; PD-L1, programmed death-ligand 1; EGFR, epidermal growth factor receptor; RTK, receptor tyrosine kinase; CAR-T, chimeric antigen receptor T-cell; ZNC1, zinc metallochaperones 1.

Although less frequent than BRCA1 mutations in patients with TNBC, BRCA2 mutations are still linked to TNBC. Researchers are now focusing on more personalized management strategies (59).

E-cadherin. Epithelial cadherin (E-cadherin) is a vital component of adherens junctions, which are crucial for cell adhesion and maintaining the epithelial phenotype. The homophilic binding of adjacent cells by E-cadherin is essential

Table II. Molecular targets of TNBC and their inhibitors.

Target molecule	Inhibitor/drug	Mechanism	Outcome	(Refs.)
Ki-67	siRNA	Ki-67 RNA interference	Reduction of cell proliferation and induction of apoptosis	(146)
			Enhanced antitumor efficacy	(147)
	shRNA	ZD55-Ki-67	Induction of apoptosis and inhibit tumor growth	(154)
		G250-Ki-67	Reduced cell proliferation and induced apoptosis	(156)
	ASO	Target pre-mRNA or mRNA degradation	Inhibition of cell proliferation and tumor growth	(162)
			Induction of apoptosis	(163)
PD-L1	Atezolizumab	Anti-PD-L1 antibody	Promotion of neoadjuvant chemotherapy	(36)
	Pembrolizumab	Anti-PD-L1 antibody	Promotion of neoadjuvant chemotherapy	(177)
	BMS-936559	Anti-PD-L1 monoclonal antibody	Continued clinical efficacy	(179,180)
	Avelumab	Anti-PD-L1 monoclonal antibody	Continued clinical efficacy	(181)
	Ibrutinib (+PD-L1/PD-1 inhibitors)	An irreversible potent inhibitor of Burton's tyrosine kinase	Slowed tumor progression and enhanced survival	(183)
	ICIs	Block of immune checkpoint proteins	Enhanced immune clearance	(176)
	MEK inhibitors (+PD-L1/PD-1 inhibitors)		Enhanced anti-tumor immunization response	(182)
BRCA1/2 mutation	Olaparib	PARP inhibitor	Induced synthetic lethality	(184)
	Talazoparib	PARP inhibitor	Improved progression-free survival	(185,186)
	Veliparib	PARP inhibitor	Enhancement of chemotherapy efficacy; Achievement of a pathological complete response	(188)
	Platinum-based compounds and their derivatives	Chemotherapeutic drugs	Cytotoxicity and DNA damage; Destruction of cancer cells by promoting oxidative stress	(196)
E-cadherin	MK2206	A selective allosteric inhibitor of AKT	Reduced cancer cell growth	(197)
	SHE78-7	A monoclonal antibody targeting E-cadherin	Increased cancer sensitivity to chemotherapy drugs; Decreased activity of PKC isoform	(200)
			Increased intracellular drug accumulation	(201)
EGFR	Cetuximab	Anti-EGFR monoclonal antibody	Enhanced chemosensitivity	(93,202)
	Panitumumab	Anti-EGFR monoclonal antibody	Enhancement of chemotherapy efficacy	(93,208)
	Nimotuzumab	Anti-EGFR monoclonal antibody	Improved survival of patients	(208)
	Necitumumab	Anti-EGFR monoclonal antibody	Improved survival of patients	(208)
	Zalutumumab	Anti-EGFR monoclonal antibody	A decreased immunogenic profile with a lower risk of hypersensitivity	(208)
	Gefitinib	Small-molecule TKIs	Poor responses or development of resistance	(93,202)
	Neratinib	Small-molecule TKIs	Poor responses or development of resistance	(93,202)
	EGFR806 CAR-T	High-EGFR-expressing cell recognition	Recognition and cytotoxicity against high EGFR-expressing TNBC	(216)
	cSNX1.3	Block of the interaction between EGFR and sorting Nexin 1	Reduced nEGFR levels	(218)

Table II. Continued.

Target molecule	Inhibitor/drug	Mechanism	Outcome	(Refs.)
PI3K/AKT/mTOR	Alpelisib	Small-molecule inhibitor	Tumor suppression associated with PIK3CA mutation	(219,220)
	Taselisib	Double inhibitors targeting PI3K and AKT	Effective in treating HR-positive breast cancer	(221)
	Buparlisib	Pan-class I inhibitor	Promising anti-tumor activity in KRAS-mutant cancers	(227)
	Copanlisib	Pan-class I inhibitor	Enhanced anti-tumor activity in tumors exhibiting PI3K pathway activation	(227)
	Idelalisib	Pan-class I inhibitor	Inhibition of pAKT levels	(227)
	Umbralisib	Pan-class I inhibitor	Enhanced anti-tumor activity in tumors exhibiting PI3K pathway activation	(227)
	Duvelisib	Pan-class I inhibitor	Reduced off-target toxicities	(227)
	Everolimus	mTOR inhibitor	Improved progression-free survival	(228-231)
	Temsirolimus	mTOR inhibitor	Improved progression-free survival	(228-231)
P53 mutation	Zinc chloride ($ZnCl_2$)	Zinc supplementation	Inhibition of p53 oncogenicity; Activation of apoptotic pathways in mutant p53-expressing cells	(235)
	ZMC1	Reactivation of zinc-free mutant p53	Induction of apoptosis in R175H p53-mutant cells; Structural recovery similar to that of wt-p53	(236)
			Suppression of tumor growth and enhanced survival	(237,238)
	CP31398	Stabilization of mutations in DBD	Strong pro-apoptotic effects	(241)
	P53R3	Stabilization of mutations in DBD	Disrupts mutant p53 aggregation and its prion-like behavior	(241)
	PRIMA-1/its derivative APR-246	Stabilization of mutations in DBD	Pro-apoptotic effects	(242)
			Reduction of the accumulation of mutant p53 aggregates	(242,243)
	COTI-2	Thiosemicarbazone derivative	Anti-cancer activity: Restoration of wt-p53 function and inhibition of the PI3K/AKT/mTOR pathway	(244)
	PhiKan083/7088	Targeting Y220C mutant p53	Induction of cell cycle arrest and apoptosis	(245,246)
	Resveratrol	Inhibition of amyloid protein aggregation, including mutant p53	Reduced p53 aggregation and amyloid colocalization	(247,248)

ICI, immune checkpoint inhibitor; ASO, antisense-oligonucleotides; MK-2206, selective allosteric inhibitor of AKT; SHE78-7, E-cadherin monoclonal antibody; cSNX1.3, peptide-based therapeutic; P53R3, potent p53 reactivator; PRIMA-1, mutant p53 reactivator; APR-246, PRIMA-1 analog; TNBC, triple-negative breast cancer; ZMCs, zinc metallochaperones; siRNA, small interfering RNA; PARP, poly(ADP-ribose) polymerase; PD-1, programmed death 1; PD-L1, programmed cell death ligand 1; ICI, immune checkpoint inhibitor; BRCA1/2, breast cancer susceptibility gene 1 and 2; AKT, protein kinase B; EGFR, epidermal growth factor receptor; PI3K, phosphatidylinositol 3-kinases; mTOR, mammalian target of rapamycin; MEK, mitogen-activated protein kinase kinase; TKI, tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor-T; DBD, DNA-binding domain.

for controlling proliferation contact inhibition, which occurs upon reaching confluence (60). Disruptions or abnormal expressions of E-cadherin/β-catenin complex can lead to epithelial-mesenchymal transition (EMT) and contribute to various malignancies (61). E-cadherin is a pivotal player in TNBC due to its role in cell adhesion and influence on tumor progression. In TNBC, loss of E-cadherin promotes cancer cell detachment, migration and invasion by activating EMT-associated transcription factors such as Snail, Twist and Zeb1. In addition, E-cadherin loss is correlated with elevations in the expression of mesenchymal markers like N-cadherin and vimentin, and thus, further promotes metastasis (62,63).

On the other hand, reduced E-cadherin expression in TNBC is associated with higher tumor grades, larger tumor sizes, increased risk of lymph node metastasis and poorer prognosis (64). A study by Shen *et al* (61) showed that 67.5% of TNBC cases exhibited loss of E-cadherin expression and found it to be correlated with more aggressive tumor features and poorer prognosis. Furthermore, studies suggest that the role of E-cadherin as a prognostic marker in TNBC may be influenced by its interactions with molecular pathways, such as the Wnt/β-catenin signaling pathway (65,66). These findings underscore the importance of E-cadherin as a diagnostic marker and a potential therapeutic target in TNBC.

Several mechanisms have been identified that contribute to the inactivation of E-cadherin in BC, particularly through mutations in the E-cadherin 1 gene (67,68). These mutations are frequently detected in invasive lobular BC (ILC) and were originally found in 55-56% of ILC cases (69). However, subsequent studies reported lower frequencies with mutation rates of 15-27%. These mutations often coincide with loss of heterozygosity (LOH) at the E-cadherin locus, which supports the suggestion it acts as a tumor suppressor gene. Approximately 50% of ILC cases exhibit LOH, leading to protein dysfunction and loss of E-cadherin expression (69).

According to a study by Brouxhon *et al* (70), soluble E-cadherin (sEcad) is a pro-oncogenic protein that interacts with the HER receptor family to promote tumor growth and survival. sEcad is elevated in HER2-positive breast tumors and TNBC and associates with HER1-4 receptors to activate downstream pro-survival pathways, such as the MAPK, inhibitor of apoptosis proteins and PI3K/Akt/mTOR pathways. In addition, sEcad enhances HER2+ cancer proliferation and migration and increases TNBC invasiveness, particularly when combined with HER ligands such as EGF (70). Given its role in activating oncogenic pathways and its correlation with patient outcomes, standard therapies combined with targeting sEcad may provide a novel strategy for BC management.

E-cadherin is a promising biomarker of the responses of specific BC subtypes to mitogen-activated protein kinase kinase (MEK) inhibition (71). Routine breast biopsies aimed at differentiating invasive ductal carcinoma (IDC) from lobular carcinoma (72,73) revealed that E-cadherin is expressed in 90% of IDC cases, which account for 80% of all BC cases (74). The pivotal role played by E-cadherin in tumor progression, metastasis and rapid growth underscores its potential as an oncogene and a critical target for BC therapies (75,76). However, E-cadherin expression is linked with poorer survival in patients with BC, which challenges its classification as a tumor suppressor gene. Studies have also indicated that E-cadherin interacts with epidermal growth factor receptor (EGFR), activates the MEK/ERK pathway and fosters aggressive, proliferative tumor phenotypes in IDC (76). Although MEK inhibitors, such as PD0325901, effectively counter this hyper-proliferative effect *in vitro* and *in vivo*, significant hurdles must be overcome before their clinical deployment.

EGFR mutation and expression. EGFR is present on the surfaces of normal epithelial cells and overexpressed in certain tumors, including brain, lung and ovarian cancer. Furthermore, increased EGFR expression has been associated with tumor cell migration, invasion and prognosis (77). The binding of ligands to EGFR promotes receptor homodimerization or heterodimerization, leading to autophosphorylation of its tyrosine kinase domains and, subsequently, to the stimulation of downstream signaling pathways such as those of PI3K/AKT and Ras/Raf/MEK/ERK (78,79).

EGFR mutations are closely associated with ethnicity, gender, adenocarcinoma and smoking status (80-83). The rarity of activating EGFR mutations in TNBC has been documented in numerous studies that reported different mutation frequencies in East Asians and Caucasians (84,85). These studies conducted in Europe and Australia reported no or low mutation rates, whereas certain Asian studies reported frequencies of 7.7-11.4% in TNBC or basal-like cancers (84,85). However, studies conducted on Japanese and Chinese cohorts detected no activating EGFR mutations. The presence of regional differences in EGFR mutations in TNBC, akin to those detected in lung cancer, remains uncertain. Thus, further investigations are required to determine whether certain patients with TNBC may benefit from tyrosine kinase inhibitor (TKI) therapy.

EGFR mutations occur predominantly in exons 18-21. The most common are exon 19 deletion mutations, the exon 21 L858R point mutation and the exon 20 T790M mutation. These mutations constitute 50-90% of all EGFR mutations and are collectively termed classical mutations (83,86). Other mutations considered rare but clinically meaningful include G719X in exon 18 and L861Q and G719C in exon 21 (87,88). Advances in sequencing and polymerase chain reaction technologies have identified EGFR mutations as predictors of the success of EGFR-TKI targeted therapies (89). For patients with non-small cell lung cancer (NSCLC) with EGFR mutations, the use of EGFR-TKI therapy resulted in an objective response rate (ORR) of 70-80%, a median progression-free survival (PFS) of 9-12 months and an OS of 20-32 months, which established EGFR-TKI as the preferred first-line treatment (90). Clinical trials of EGFR-targeted TKIs in TNBC as monotherapy or in combination with chemotherapy have generally been unfruitful. This contrasts their efficacies in lung cancer, in which activating EGFR mutations drive therapeutic response.

TNBC frequently exhibits EGFR overexpression, which is associated with poor clinical outcomes (91). The prevalence of EGFR overexpression in TNBC varies significantly across studies from 13 to 78% (92). Furthermore, the rate of EGFR protein overexpression in TNBC, as evaluated by IHC, ranges from 13 to 76%, depending on the evaluation methods and antibodies used (93,94). For instance, rates of EGFR expression were reported at 13 and 37% using Novocastra antibodies, 52% with Zymed antibodies and 76% with the EGFR PharmDx Kit (Dako) (95,96). The study that used the PharmDx Kit reported an EGFR protein overexpression rate of 72%, but EGFR mRNA levels varied considerably (97), suggesting post-transcriptional regulation contributes to EGFR protein overexpression in TNBC.

EGFR overexpression has also been associated with poorer DFS and OS in patients with TNBC (98). The use of specific EGFR inhibitors, such as erlotinib, demonstrated promise in preclinical models by inhibiting tumor growth and metastasis, particularly in terms of reducing the EMT frequently

observed in aggressive cancer phenotypes (99). However, the clinical effectiveness of EGFR as a therapeutic target in TNBC remains uncertain due to variable patient responses. This variability may be due to differences in EGFR expression levels and the presence of co-expressed markers that interfere with the efficacy of EGFR-targeted therapies (98). Therefore, optimizing the effectiveness of EGFR-targeted therapy necessitates a patient selection strategy that considers EGFR expression levels and the molecular characteristics and signaling pathways associated with EGFR. Furthermore, additional research is required to assess whether combination therapies involving EGFR inhibitors and other treatments such as immunotherapy or chemotherapy could lead to more favorable outcomes than monotherapy.

PI3K/AKT/mTOR signaling pathway. The PIK3CA gene is located on chromosome 3q26.3 and encodes the catalytic subunit of PI3K, a key enzyme in the PI3K/AKT/mTOR signaling pathway (100). PI3Ks are intracellular signaling enzymes and are divided into three classes in mammals (101). Class I PI3K is the most significant in terms of promoting tumor development and has four catalytic isoforms, which each contain a regulatory subunit (p85α, β or γ) and a catalytic subunit (p110α, β, δ or γ) (100,102). Upon activation by binding of growth factors, such as EGFR and VEGFR, to their respective receptors, a series of downstream signaling molecules are activated. Located in the cytoplasm, PI3K catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate into phosphatidylinositol (3,4,5)-trisphosphate (PIP3) (102,103), which then recruits AKT to the cell membrane, where it becomes activated by phosphorylation. The activated AKT then phosphorylates downstream targets, including mTOR, to initiate a cascade that augments protein synthesis and cell growth (104).

AKT plays a pivotal role in the PI3K pathway (100). Following PI3K activation, PIP3 recruits pyruvate dehydrogenase kinase (PDK)1 and AKT to the cell membrane, where PDK1 phosphorylates Thr308 of AKT and mTORC2 phosphorylates Ser473 to activate AKT fully. In this state, AKT promotes cell proliferation and oncogenic transformation by phosphorylating mTORC1 (105). AKT has three isoforms, viz. AKT1, AKT2 and AKT3. AKT1 is associated with gene amplification and E17K mutations and enhances proliferation while inhibiting migration (105,106). AKT2 supports cell migration and invasion, and thus, contributes to metastasis, whereas AKT3, which is overexpressed in 14% of TNBC cases, primarily drives cell growth (107).

The PI3K/AKT/mTOR signaling pathway plays a vital role in the progression and aggressiveness of TNBC. This pathway contributes to tumor growth, survival, motility and therapy resistance and is frequently dysregulated in TNBC (108,109), and this dysregulation is correlated with poor clinical outcomes in patients with TNBC. Common mutations and alterations in TNBC include the loss of the tumor suppressor PTEN and mutations in PIK3CA, which result in hyperactivation of the PI3K/AKT/mTOR pathway. This hyperactivation promotes oncogenic processes, such as cell proliferation and survival, and facilitates metastasis and chemoresistance (9,110). Furthermore, the pathway has been suggested to contribute to chemoresistance and tumor relapse through an association with cancer stem cells in TNBC (111). Doxorubicin resistance is also promoted by this pathway due to its impact on EMT and the cancer stem cell population (112).

Targeting the PI3K/AKT/mTOR signaling pathway has become a focus for the development of therapeutic strategies for TNBC. However, although PI3K/AKT/mTOR pathway inhibitors produced promising results in preclinical studies, their clinical effectiveness is hindered by obstacles such as drug resistance and toxicity (9,108). Consequently, current research emphasizes refining drug combinations and pinpointing biomarkers to identify patients most likely to benefit from these treatments.

P53 mutation. p53 is a nuclear transcription factor that activates a range of target genes crucial for initiating cell cycle arrest or apoptosis (113,114). Under ordinary conditions, p53 is present at minimal levels due to proteasomal degradation, chiefly controlled by the RING-finger E3 ubiquitin ligase murine double minute 2 (MDM2) (115). When DNA is damaged, p53 accumulates in the nucleus through post-translational modifications like phosphorylation and acetylation, potentially disrupting its interaction with MDM2 and activating p53 (114,116). Once activated, p53 either triggers cell cycle arrest or induces apoptosis, depending on the severity and nature of the damage (114,116). Cell cycle arrest, mediated by p53, provides time for DNA repair, thereby enabling cells to resume normal functioning if the damage is repaired. Alternatively, when the damage is severe, p53 initiates apoptosis to prevent the spread of defective genetic material (117).

P53 is primarily affected by missense mutations or non-synonymous single-nucleotide variants, which frequently occur in the core domain and result in full-length mutant p53 proteins (118). Other mutations, such as synonymous, frameshift, silent and post-translational modifications in TP53, are also observed in various tumors (119). Missense mutations in p53, involving amino acid replacement, are associated with poor prognosis and the pathogenesis of >50% of malignant tumors. Mutated p53 often forms aggregates and is associated with loss of function (LOF), dominant-negative and gain-of-function (GOF) mutations at hotspot regions (120,121). In particular, GOF mutations enhance cancer traits, such as migration, invasion and metastasis, while LOF mutations enhance chemoresistance. There are two categories of missense mutations: Contact mutations (e.g., R248Q, R273H) that enable the protein to retain its conformation but lose its DNA binding ability, and conformational mutations (e.g., R175H, Y220C) that disrupt protein structure and stability (118,122). Furthermore, zinc ion loss resulting from mutations, such as C176F or Y220C, destabilizes the p53 DNA-binding domain, inhibiting tetramer formation and promoting misfolding and aggregation (119,122). For instance, the Y220C mutation exposes hydrophobic regions, thus facilitating amyloid-like aggregation. These changes adequately emphasize the structural and functional instability of mutant p53 during cancer progression (123).

The absence or mutation of p53 in human cancers is linked to increased tumor growth and treatment resistance (122). Mutant misfolded p53 proteins, resulting from dominant-negative TP53 mutations under abnormal conditions, can aggregate with themselves and wild-type p53 and cause endoplasmic reticulum stress and the formation of prion-like

amyloid fibrils. These aggregates bear a GOF phenotype, lack tumor-suppressor activity and promote cancer progression (119,120,124). Mutations in the p53 gene are observed in ~80% of TNBC cases and play a crucial role in driving the aggressive nature and progression of this cancer subtype (125). In addition, they abrogate the tumor-suppressing function of p53, which results in unchecked cell growth, resistance to standard therapies, increased risk of metastasis and poorer prognoses (125,126).

Mutant p53 interacts with other proteins, such as p63 and p73, which also function as tumor suppressors, inhibits their activities and promotes metastasis (127,128). These interactions modulate critical signaling pathways, including the transforming growth factor-β pathway, and facilitate tumor cell migration and invasion through receptors like EGFR and hepatocyte growth factor receptor (129,130). In addition, when affected by p53 mutations, the PI3K/Akt/mTOR pathway enhances tumor growth and invasion (131).

Research into the downstream effects of these mutations is evolving with a focus on ICIs and molecular inhibitors (132). The prognostic significance of p53 expression in TNBC remains under investigation (133). However, studies suggest that BC exhibiting IHC-determined p53 positivity is associated with a more aggressive and metastatic phenotype and unfavorable patient outcomes (134,135). Ongoing research aims to target the p53 pathway in TNBC specifically. Efforts are directed toward developing novel therapeutic strategies that restore wild-type p53 function or target the downstream effects of p53 mutations.

3. Therapeutic strategies targeting TNBC

Ki-67 inhibition. Ki-67 has emerged as a significant therapeutic target and characteristically exhibits high expression in malignant cells and a minimal presence in normal tissues. Retrospective studies explored the possibility of using Ki-67 as a potential marker for assessing cell proliferation and predicting the outcomes of various cancers (136,137). Clinical research increasingly supports the diagnostic utility of Ki-67 in cancer (138). IHC remains the standard method for evaluating Ki-67 expression, and a 10-14% positivity threshold is commonly used to classify patients at higher risk (139). Ki-67 also serves as a biomarker of treatment response and long-term clinical outcome in patients with BC undergoing neoadjuvant endocrine therapy and has been the subject of several prospective trials (140-142). Further, Ki-67 aids the classification of patients with partial responses and identifies those who may benefit from extended systemic therapy or are ready for primary surgery (143). However, variations in Ki-67 measurement limit its consistent application in standard BC IHC workups.

Studies that utilized antisense RNA and RNA interference (RNAi) indicated that Ki-67 knockdown reduces cell proliferation. Furthermore, RNAi has emerged as an effective tool for cancer therapy and small interfering (si)RNAs have been used to target multiple genes and enhance antitumor efficacy (144,145). Recent research demonstrated that siRNA targeting Ki-67 effectively and specifically inhibited the proliferation of human renal cell carcinoma (RCC) cells more than antisense strategies (146). In addition, a pSilencerKi-67 construct using short hairpin RNAs against Ki-67 was developed to overcome the transient effects of siRNAs, and this construct better inhibited cell proliferation and apoptosis induction in 786-O RCC cells than synthetic siRNAs (147).

The clinical application of siRNAs is hindered by off-target effects and immune activation via toll-like receptors (148). To mitigate these issues, approaches such as RNA modification, optimized delivery systems and tumor-specific targeting have been explored (149,150). Among these approaches, oncolytic adenoviruses, which selectively replicate in tumor cells, emerged as promising vehicles for gene therapies, such as siRNA delivery. Conditionally replicative adenoviruses (CRAds) have been engineered to target tumor cells using two strategies, viz. deleting viral elements essential for replication in normal cells or utilizing tumor-specific promoters (151,152). CRAds based on Ad5 have been demonstrated to be effective and safe cancer treatments (153). In this context, researchers developed ZD55-Ki-67, an oncolytic adenovirus that delivers Ki-67-shRNA (154). This construct effectively induced apoptosis in renal cancer cells and curtailed tumor growth in preclinical models (155). To enhance safety, G250-Ki-67 virus with a renal cancer-specific G250 promoter was engineered to ensure replication occurred solely in renal cancer cells. This virus successfully downregulated Ki-67, reduced cell proliferation and induced apoptosis, which highlighted its potential for treating renal clear cell carcinoma (156).

Antisense oligonucleotides (ASOs) delivered systemically without formulation have demonstrated efficacy in treating several non-oncology diseases and are currently being investigated for cancer therapy (157-159). Research has shown that Ki-67-specific ASOs can suppress cancer cell proliferation and reduce tumor growth (160,161). Schlüter *et al* (14) discovered that Ki-67 antisense oligodeoxynucleotides (ASODNs) inhibited the proliferation of human myeloma cells, while Kausch *et al* (162,163) observed similar effects on cancer cells *in vitro* and *in vivo*. Ki-67 ASODNs were also subjected to a phase I clinical trial for bladder cancer (164). Furthermore, recent studies also indicate that methylated oligonucleotides targeting Ki-67 can impede renal carcinoma cell proliferation and induce apoptosis (20).

The clinical application of ASOs is constrained by issues such as low affinity, susceptibility to nuclease degradation and non-specific binding. Peptide nucleic acids (PNAs), i.e., synthetic DNA analogs with a modified backbone, bind to complementary targets with enhanced stability and specificity (165). PNAs have been developed as antisense and antigene agents to control gene expression and have proved to be more effective than ASOs in suppressing human telomerase activity (166). Additional research is needed to improve the clinical utility of these therapies, which may constitute a new paradigm for cancer treatment.

PD-L1 inhibition. PD-L1 is expressed in invasive lobular and ductal BCs, in which it localizes in CD8+ T lymphocytes (167). Overexpression of PD-L1 mRNA is associated with poor prognostic factors, including hormone receptor negativity, HER2 positivity, higher tumor grade, advanced stage and elevated proliferation rates (168). About 20% of TNBC cases exhibit PD-L1 expression due to PTEN loss, which is characterized by significant cytotoxic T-cell infiltration and improved response

to neoadjuvant chemotherapy (34). These findings underscore the potential of anti-PD-1 and PD-L1 inhibitors as treatments for TNBC (169).

PD-1 and PD-L1 inhibitors have demonstrated significant clinical efficacy in lung, kidney, bladder, skin and breast malignancies (170-173). TNBC may exhibit a more favorable response to immunotherapy than other BC subtypes due to higher TIL levels, a greater mutational burden and higher PD-L1 expression (174). Furthermore, elevated TIL levels correlate with enhanced outcomes in patients with TNBC (175). By enhancing immune clearance, ICIs targeting the PD-1/PD-L1 pathway offer a promising therapeutic strategy for TNBC (176). As a result, immunotherapies targeting the PD-1/PD-L1 pathway, which counteract immunosuppression in the TNBC tumor environment, have been developed. In 2019, the US Food and Drug Administration (FDA) approved atezolizumab (an anti-PD-L1 antibody) in combination with nanoparticle albumin-bound paclitaxel as a first-line treatment for TNBC based on the results of the IMpassion130 trial (NCT02425891). This combination therapy has since become the standard of care for patients with PD-L1-positive, unresectable, locally advanced or metastatic TNBC (36). Additionally, in 2017, pembrolizumab (an anti-PD-1 antibody) was approved as a histology-agnostic therapy for tumors with high microsatellite instability or mismatch repair deficiency, marking the first FDA approval of a cancer treatment based solely on a tumor biomarker independently of the primary site (177,178).

Drugs designed to inhibit PD-1 signaling have shown prolonged clinical efficacy against various advanced solid tumors (179). In a phase I clinical trial, the monoclonal antibody BMS-936559 (MDX 1105), which targets PD-L1, demonstrated objective response rates ranging from 6 to 17% in 160 patients with an advanced solid tumor (180). The JAVELIN study evaluated the effectiveness of avelumab, an anti-PD-L1 antibody, across different BC subtypes, regardless of PD-L1 expression levels. In the TNBC group of 58 ER+/HER2-patients, the response rate was 8.6%, and among 72 ER+/HER2-patients and 26 HER2+ patients, the response rates were 2.8 and 3.8%, respectively. Early findings suggest that tumors positive for PD-L1 expression are more likely to respond to treatment (181).

Combinations of MEK inhibitors and PD-L1/PD-1 inhibitors have been reported to enhance antitumor immune response in a BC mouse model (182). A study by Sagiv-Barfi *et al* (183) reported that when ibrutinib plus anti-PD-L1 antibody were administered to mice with TNBC that lacked inherent sensitivity to ibrutinib; tumor progression was significantly decreased and survival increased compared to the effects of either drug used independently.

BRCA1/2 inhibition. Patients with TNBC show a significantly higher prevalence of BRCA1/2 mutations (15-20%) than other BC subtypes (50). The PARPi olaparib, which induces synthetic lethality in tumors deficient in homologous recombination, specifically targets and eliminates tumor cells harboring BRCA1/2 mutations. Results from the phase III olympiAD trial (184) demonstrated that olaparib monotherapy significantly improved PFS in patients with HER2-negative metastatic BC with BRCA1/2 mutations. The ORR in the olaparib-treated group was 59.9%.

Talazoparib, a PARP inhibitor, was approved by the FDA in 2018, as a monotherapy for adult patients with germline BRCA-mutated, HER2-negative, locally advanced or metastatic BC, including TNBC (185). This is the first single-agent therapy to achieve pCR in germline BRCA-positive, HER2-negative early BC (186). Common adverse events included anemia and nausea, which are typical of PARPi (186). These favorable results led to the phase II confirmatory NEOTALA study (NCT03499353), which contains a larger patient cohort.

PARPi has produced promising outcomes when combined with other cytotoxic agents, due to its synergistic effects and potential to enhance chemotherapy regimens (187). For instance, Veliparib has been reported to increase the cytotoxicity of temozolomide and achieve complete response in 50% of women with germline BRCA-associated BC and a response rate of 22% (188). Additionally, combinations of olaparib with cisplatin, carboplatin and topotecan have yielded response rates of up to 73%, where response included stable disease, partial and complete responses (189,190). However, significant hematologic toxicity, including grade 3 neutropenia, was reported when olaparib was combined with paclitaxel (191).

Platinum-based compounds and their derivatives target tumor cells by inducing DNA strand breaks. These compounds also eradicate cancer cells by promoting oxidative stress, altering microRNA regulation and activating protein kinase C (192-194). Cells with BRCA1/2 mutations, which are deficient in DNA repair functionality, are particularly susceptible to DNA-damaging agents (195). Consequently, the relationship between BRCA1/2 mutations and platinum sensitivity in patients with TNBC has emerged as a research topic of particular interest. A meta-analysis of 22 trials indicated that platinum-based therapies are highly effective for patients with BRCA1/2-mutated TNBC. The inclusion of platinum significantly enhanced treatment outcomes, particularly in the neoadjuvant setting and for advanced-stage disease (196).

E-cadherin inhibition. E-cadherin is not yet a direct therapeutic target, but *in vitro* studies have demonstrated that its function can be restored by targeted treatment. As mentioned earlier, loss of E-cadherin activates growth factor signaling, particularly the PI3K/Akt pathway, even in the absence of oncogenic mutations. Lobular BC cells respond well to Akt inhibitors like MK2206, which significantly reduces cancer cell growth (197). Additionally, a synthetic lethal interaction between E-cadherin and c-ros oncogene (ROS)1 has been identified, suggesting that ROS1 inhibitors, such as crizotinib, could effectively treat E-cadherin-deficient tumors (198). A phase II trial is currently investigating this approach in advanced E-cadherin-negative cancers (NCT03620643). The E-cadherin/EGFR heterodimer complex is a promising therapeutic target. Mutations in the extracellular domain of E-cadherin destabilize this complex, enabling EGFR activation by its ligand and the subsequent activation of the Ras homolog family member A signaling pathway, thereby increasing cell motility. Typically, E-cadherin inhibits the kinase activity of EGFR, but mutations diminish binding affinity between E-cadherin and EGFR, allowing EGFR to activate RhoA and further enhancing cell mobility (199). This mechanism is essential for promoting the invasiveness and metastatic

potential of cancer cells. Therefore, therapeutic strategies aimed at regulating the interaction between E-cadherin and EGFR or inhibiting the RhoA signaling pathway may provide the basis for novel cancer treatments.

SHE78-7 is a monoclonal antibody that targets E-cadherin-mediated cell adhesion (200). In HT29 colorectal adenocarcinoma spheroids, SHE78-7 disrupted E-cadherin interactions and thereby enhanced the sensitivity of these spheroids to chemotherapeutics, such as 5-fluorouracil, paclitaxel and etoposide, but not to cisplatin. Furthermore, this antibody diminishes the activity of specific protein kinase C isoforms associated with chemoresistance and facilitates intracellular drug accumulation (201). This study supports the notion that targeting cell adhesion mechanisms may provide a means of overcoming solid tumor resistance. However, further studies are needed to assess its clinical applicability, given the vital role played by E-cadherin in healthy tissue adhesion.

EGFR inhibition. The therapeutic efficacies of anti-EGFR monoclonal antibodies, including cetuximab and panitumumab, and small-molecule TKIs like gefitinib and neratinib, have been explored in clinical trials for TNBC. However, these therapies often yield limited patient responses or are associated with resistance development (93,202), which highlights the need for novel EGFR-targeted therapies.

Cetuximab, the first FDA-approved EGFR-targeted therapeutic antibody (in 2004), inhibits EGFR activation by obstructing its ligand-binding pocket (203). When combined with chemotherapy or radiotherapy, cetuximab has reportedly prolonged median OS by ~3 months in colorectal cancer (204), ~5 months in head and neck cancer (205) and ~8 months in NSCLC (206). Other EGFR-targeting antibodies, such as panitumumab, nimotuzumab, necitumumab and zalutumumab, have demonstrated efficacy in colorectal, head and neck, and biliary cancer, as well as NSCLC (207,208). While most antibodies block EGFR ligand binding, nimotuzumab also elicits immune responses, which enhance its therapeutic impact despite reduced binding efficiency (209). However, these antibodies have only had limited success in TNBC despite achieving high EGFR expression.

EGFR-targeting therapies, including monoclonal antibodies and small molecule TKIs, have been employed to treat TNBC, but numerous patients display poor responses or develop resistance (93). Chimeric antigen receptor-T (CAR-T) technology has recently shown great promise as an immunotherapy for solid cancers by enabling T cells to target tumor-specific antigens through scFv binding domains. In addition, EGFR-specific CAR-T cells exhibited enhanced recognition and cytotoxicity in TNBC cells expressing high levels of EGFR compared to controls, as evidenced by increased cytokine secretion and enhanced cell lysis *in vitro* (210). Furthermore, these cytotoxic effects were significantly increased by promoting EGFR dimerization. These findings indicate that the efficacy of EGFR-specific CAR-T cells is closely associated with EGFR expression levels and underscore their potential as a targeted therapy for TNBC (211).

On the other hand, EGFR CAR-T cells have shown promise in preclinical models of TNBC, but their reliance on cetuximab-based scFv raises concerns about on-target off-tumor toxicity, as they affect EGFR expression in both tumor cells and normal keratinocytes (212,213). To overcome this limitation, a modified CAR-T construct that employs the tumor-specific EGFR mAb806 antibody was developed (214). This antibody selectively targets EGFR, which is linked to oncogene amplification, and in clinical trials, has demonstrated efficacy in eliminating TNBC cells *in vitro* while showing minimal toxicity (215). EGFR806 CAR-T cells are also being investigated in clinical studies for the treatment of pediatric brain tumors (NCT03638167), and no dose-limiting toxicity has been reported to date (216). Also, low EGFR expression in normal adult brain tissue reduces the risk of undesired off-tumor effects, which further highlights its therapeutic potential (217).

The Schroeder lab recently developed a peptide named cSNX1.3 to mimic the interaction domain between endosomal trafficking protein SNX1 and EGFR (218). This end-capped peptide binds to EGFR with an efficiency comparable to SNX1 and reduces nEGFR levels in TNBC cells overexpressing EGFR. Treatment with cSNX1.3 selectively impacts EGFR-dependent oncogenic behaviors such as proliferation, survival, migration and mammosphere formation but has no effect on normal immortalized breast epithelial cells (218).

PI3K/AKT/mTOR pathway inhibition. In precision medicine, therapeutic strategies that target PIK3CA in TNBC aim to inhibit abnormal signaling pathways that drive cancer progression. Significant progress has been made, notably in patients with BC demonstrating heightened sensitivity to PI3K inhibition. A small molecule inhibitor of PI3K p110α, alpelisib, has demonstrated efficacy in clinical trials by effectively suppressing tumors with PIK3CA mutations (219,220). Additionally, dual inhibitors like taselisib, which target PI3K and its downstream effector AKT, have exhibited potential in preclinical studies (221). However, these dual-blockade agents have adverse effects that may limit their clinical benefits. For instance, although AZD2014 (an mTOR catalytic inhibitor) exhibited notable activity in preclinical studies, it was less effective than everolimus in patients with homologous recombination-positive BC in clinical settings (222). Recent clinical studies, such as the BELLE-2 and BELLE-3 studies, have underscored the efficiency of PI3K inhibitors like buparlisib (a pan-class I inhibitor) for treating PIK3CA-mutant homologous recombination-positive BC (223,224). The exploration of combination therapies involving PI3K inhibitors and chemotherapy or immunotherapy is now underway with the aim of improving efficacy. Despite issues like resistance and tumor heterogeneity, continued research into therapies targeting PIK3CA provides a promising route to improving outcomes (219). The complexity of PIK3CA-driven TNBC underscores the need for innovative strategies, though current studies offer a potential means of addressing this aggressive cancer.

Combination therapies are widely recognized as potential means of addressing TNBC, the molecular heterogeneity of which poses significant treatment challenges. Targeting multiple proteins, such as mTOR, AKT and PI3K, often results in feedback mechanisms that restrict the effectiveness of these treatments (225). For instance, mTOR inhibition can lead to the upregulation of downstream receptor tyrosine kinases (RTKs), a class of cell surface receptors that mediate signal

transduction through phosphorylation of tyrosine residues, and cause rebound activation of AKT. Similarly, AKT inhibition can trigger forkhead box O-mediated transcription and subsequent RTK activation (223). Furthermore, PI3K inhibition not only prevents AKT activation but also enhances MAPK signaling. These intricate interactions highlight the complexities of precisely targeting cancer pathways and the potential for developing resistance (226). To address these challenges, research is underway to combine PI3K inhibitors with conventional chemotherapy or ICIs to achieve synergistic therapeutic benefits. Currently, five FDA-approved PI3K inhibitors are available (copanlisib, idelalisib, umbralisib, duvelisib and alpelisib), which paves the way for further investigation into new, more effective inhibitors with improved safety profiles (227).

mTOR inhibitors, including everolimus and temsirolimus, have been demonstrated to be effective BC treatments. Studies like BOLERO-2, PrE0102 and GINECO have demonstrated that combining everolimus with endocrine therapy significantly improves PFS in postmenopausal patients with homologous recombination-positive, HER2-negative advanced BC (228,229). Furthermore, the BOLERO-4 and BOLERO-5 studies confirmed that everolimus plus letrozole or exemestane prolonged PFS, and the MIRACLE study reported their effectiveness in premenopausal patients with metastatic BC (230). Additionally, a phase I trial of temsirolimus and everolimus in combination with liposomal doxorubicin and bevacizumab in patients with metaplastic TNBC demonstrated an ORR of 21% [complete response (CR)=4 (8%); partial response (PR)=7 (13%)], with enhanced efficacy observed in patients with PI3K pathway activation. However, subsequent trials were discontinued (231).

P53 inhibition. Developing p53-targeted drugs poses significant challenges due to the necessity to selectively target mutant p53 in cancer cells while sparing wild-type p53 in healthy cells and is further complicated by the structural diversity of mutant p53 proteins due to various mutations (232). Therapeutic strategies targeting p53 are generally classified as strategies that restore wild-type p53 function or eliminate mutant p53 (233).

Several studies have focused on the use of zinc ions to reactivate mutant p53 function. When mutant p53 binds zinc, it regains its wild-type conformation and DNA-binding abilities, which trigger target gene activation and inhibit tumor growth (234). Zinc supplements, such as zinc chloride, have been shown to suppress p53 oncogenicity, restore binding to target promoters and activate apoptotic pathways in mutants, including H175 and H273 (235). Zinc ion treatments also enhance the functions of p53 and p73 by restoring their interactions with gene promoters (122). In addition, zinc metallochaperones (ZMCs), such as ZMC1, have been developed to reactivate zinc-deficient mutant p53, and thus, promote the apoptosis in R175H p53 mutations and restore a wild-type-like structure (236). Furthermore, targeting p53 and BRCA1 using ZMCs has been suggested as a promising therapeutic strategy for BCs in which these tumor suppressors are inactivated (237). Albumin nano vector formulations have also been suggested for the effective delivery of ZMC-based drugs (237). Studies show combining ZMC1 with zinc ions can suppress tumor growth and enhance survival, particularly in zinc-deficient and BRCA1-deficient BC models (238). In addition, ZMC1 acts synergistically with PARPi olaparib, even in olaparib-resistant tumor cells. Despite these encouraging results, further investigations are required to evaluate the safety and efficacy of these strategies in clinical settings (238).

The structural reversibility of mutant p53, particularly in temperature-sensitive variants, enables the restoration of wild-type activity under specific conditions (122). DNAJA1 (DnaJ heat shock protein family member A1), a chaperone protein, prevents the proteasomal degradation of misfolded mutant p53 and contributes to tumor suppression (239). It has also been suggested inhibiting DNAJA1 would promote the degradation of mutant p53 and reduce the malignant potential of cancer cells (240). In addition, compounds such as PLINH, derived from plumbagin, have been shown to suppress the growth and migration of cancer cells by depleting mutant p53 through DNAJA1 inhibition. However, DNAJA1 inhibitors are not yet clinically available and further research is required to confirm their safety and efficacy (240).

Compounds such as CP31398, P53R3 and PRIMA-1, and a derivative APR-246 (Eprenetapopt), can stabilize mutations in the DNA-binding domain (DBD) of p53, prevent p53 aggregation and restore its tumor suppressor function (241). APR-246 is the most advanced and extensively studied of these compounds and exhibits pronounced pro-apoptotic effects, particularly in mutated p53-containing cancers like TNBC (242). APR-246 interacts synergistically with chemotherapeutics such as eribulin but with cell-dependent variable efficacy. Reactivation of p53 by PRIMA-1 and its active metabolite, 2-methylene-3-quinuclidinone, can restore misfolded p53 mutants to their native conformation, thereby inducing apoptosis and activating multiple p53 target genes. Furthermore, anti-amyloid oligomer antibody assays demonstrated that PRIMA-1 reduces the accumulation of mutant p53 aggregates in breast and ovarian cancer cell lines (242,243). These compounds represent promising therapeutic options for targeting p53 mutations in TNBC.

COTI-2 was identified using the CHEMSAS® platform and demonstrates anti-cancer activity in xenograft models, including MDA-MB-231 BC cells, by restoring wild-type p53 function and inhibiting the PI3K/AKT/mTOR pathway (244). Other p53-reactivating compounds, such as PhiKan083 and PhiKan7088, specifically target Y220C mutant p53 and induce cell cycle arrest and apoptosis through p21 and NADPH oxidase activator 1 activation (245). PhiKan7088 synergizes with nutlin-3a to enhance p53 activity in various cancers and is effective in combination with carboplatin for TNBC (246). These findings highlight promising therapeutic strategies for targeting mutant p53 in cancer.

Resveratrol, a natural compound sourced from plants such as berries, peanuts and grapes, has demonstrated the ability to target cancer signaling pathways and inhibit amyloid protein aggregation, including mutant p53 in BC models (247). A study from 2018 demonstrated that resveratrol prevents aggregation in the DBD region of wild-type and mutant p53 (R248Q) dose-dependently and that mutant p53 BC cell lines (HCC-70 and MDA-MB-231) were more responsive to treatment than wild-type p53 cells (247). Furthermore, resveratrol reduced p53 aggregation and amyloid colocalization in mutant cell lines and tumor models (248). Additionally, small-molecule

inhibitors targeting the inositol-requiring enzyme 1α and PRKR-like ER kinase enzyme active sites, particularly those based on salicylaldehyde, have been shown to effectively enhance response to chemotherapy and reduce tumor cell secretions in TNBC xenograft models (248).

Synthetic siRNA delivery offers a promising strategy for p53-targeted genetic therapy by mitigating the GOF effects of mutant p53 while preserving wild-type p53 functionality (249). Interestingly, specific siRNAs designed to target hotspot p53 mutations have effectively reduced tumor viability in patient-derived xenografts without impacting wild-type p53 or inducing organ toxicity (250). In TNBC cells, siRNA-mediated suppression of mutant p53 expression led to the activation of pro-apoptotic genes, such as caspases, BCL-2 family members and death receptors, and the downregulation of anti-apoptotic genes, thus promoting cell death (251). Although the development of siRNA-based therapies is in the preliminary stage, advancements in RNA delivery technology hold substantial promise for the treatment of mutant-specific cancer (249).

4. Conclusions

TNBC remains one of the most aggressive and challenging subtypes of BC due to its molecular heterogeneity, lack of specific therapeutic targets and poor clinical outcomes. Despite the significant progress made in understanding the biology of TNBC, including the identification of key prognostic markers, such as Ki-67, PD-L1, BRCA1/2 mutations, E-cadherin loss and EGFR alterations, therapeutic advancements have been constrained by issues such as drug resistance and tumor complexity. The PI3K/AKT/mTOR pathway and mutant p53 remain critical molecular targets for intervention, and ongoing research continues to explore their potential to enhance patient outcomes. Innovative approaches such as ICIs, CAR-T cell therapies, siRNA-based treatments and zinc metallochaperones offer promise for the management of TNBC. These strategies leverage advancements in molecular biology to tackle the unique challenges posed by the heterogeneity and resistance mechanisms of TNBC. Nonetheless, their clinical efficacies and safety profiles require further validation through comprehensive trials. Combination therapies that target multiple pathways, including DNA damage repair and immune modulation, are gaining traction to counteract treatment resistance and improve therapeutic efficacy. Furthermore, the integration of targeted therapies with conventional treatments, such as chemotherapy and radiotherapy, also holds promise due to observed synergistic effects.

Although TNBC remains a challenging subtype, ongoing advancements in immunotherapy, targeted therapy and antibody-drug conjugate treatments are promising. The development of novel biomarkers, the application of precision medicine and the optimization of combination therapies are anticipated to enhance TNBC treatment outcomes. Overcoming treatment resistance and establishing personalized therapeutic strategies are pivotal in advancing the treatment of this formidable disease.

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