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Review Article

Triple-Negative Breast Cancer Treatment Advancements: A Review of Evolving Strategies

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Women around the world are most frequently afflicted with breast cancer, and it is one of the most frequent causes of cancer death in females. Breast cancer is usually classified according to biomarker status, triple-negative breast cancer (TNBC) represents a distinct subtype characterized by immunohistochemical findings that denote negativity for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (Her-2) on cancer tissue. It is more common in younger women than in other subtypes. As an invasive breast cancer subtype with a unique drug-resistant phenotype and metastatic burden, it has limited treatment options, and patients have a poor prognosis with high rates of local, distant recurrence and mortality, and there is still a lack of standardized treatment protocols for TNBC. In this review, we delve into the current treatment strategies for TNBC and explore the potential for new approaches and targets in the future. This trial is registered with NCT03997123.

1. Introduction

As breast cancer continues to be a prevalent and significant issue in global public health, the impact of TNBC cannot be ignored. Patients with TNBC have a poorer prognosis, higher recurrence rates, and increased mortality due to the disease's complex molecular structure and low detection [1]. Comparative rates of this subtype are higher in young females than they are in older women, in contrast to the prevalent hormone-habituated cancers that advance with a lifetime of estrogen intake [2]. In TNBC, breast tumor tissues grow rapidly, and the host produces an immune response that leads to significant lymphocyte inflammation [3]. After tumor tissue expansion, cell adhesion destruction, tumor cell migration, and invasion of blood vessels or lymphatic vessels occur, promoting metastasis in the lungs, liver, and brain. Additionally, lymphatic system involvement is frequent, hinders the treatment of local lesions, and is prone to relapse, further aggravating the clinical condition and greatly reducing the survival rate [4]. Conventional traditional treatments for TNBC such as surgery, radiotherapy, and chemotherapy have not yielded the desired results. Thus, effective and new therapeutic methods are continually being explored to improve the survival rate and prognosis of patients. This article reviews the basic features, subtypes, and recent therapeutic advances of TNBC, including adjuvant chemotherapy, antibody-drug combinations, immune checkpoint inhibitors, PARP inhibitors, new drug development of androgen receptor-targeted drugs, and emerging mRNA therapies [5].

2. Classification of TNBC Subtypes

TNBC is a highly heterogeneous disease, which gives rise to different subtypes with varying outcomes, treatment responses, and overall survival rates. Initially, analysis of a large number of mRNA profiles was used to classify TNBC, which included both intrinsic and extrinsic signals. In 2011,

Lehmann et al. classified TNBC into six subtypes based on gene expression: luminal androgen receptor (LAR), mesenchymal (M), basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), and mesenchymal stem-like (MSL) [6]. However, subsequent studies have shown that two of these subtypes (IM and MSL) are primarily abundant in TNBCs with high numbers of tumor-infiltrating lymphocytes (TILs) and stromal cells and are not distinct cancer cell intrinsic subtypes. Consequently, the TNBC classification was redefined into four subtypes: BL1, BL2, LAR, and mesenchymal cells (MSC) [7]. These four different subtypes differ in terms of treatment, prognosis, and survival. Among them, the basal-like subtype accounts for as much as 75% of TNBC cases [8]. In the LAR subtype, androgen receptor expression is ten times higher than in other subtypes [5]. Tumor cells of the MSC subtype exhibit higher expression levels of cancer stem cell markers, enabling them to more effectively evade treatment and trigger recurrence [9]. Because of the difficulty of treatment and the higher incidence of metastasis and recurrence, TNBC has a poorer prognosis than other types of breast cancer.

3. Chemotherapy and Neoadjuvant Chemotherapy for TNBC

Unlike other forms of breast cancer, TNBC has fewer treatment options and is more likely to recur and spread. This is mostly because TNBC expresses ER, PR, and HER2 negatively, which makes conventional endocrine therapy less effective. Chemotherapy is now a primary option for treating TNBC as a result.

TNBC systemic chemotherapy regimens recommended by the National Comprehensive Cancer Network (NCCN) 2022 breast cancer guidelines include combinations of anthracyclines and paclitaxel: cyclophosphamide, methotrexate and fluorouracil (CMF), cyclophosphamide, Adriamycin and fluorouracil (CAF), cyclophosphamide, epirubicin, fluorouracil and paclitaxel/docetaxel (CEF-T), docetaxel and cyclophosphamide (TC), paclitaxel/docetaxel, Adriamycin and cyclophosphamide (TAC), and Adriamycin and cyclophosphamide (AC) (Table 1).

Neoadjuvant chemotherapy aims to minimize the extent of surgery and has been shown to significantly enhance the prognosis of TNBC patients, as evidenced by recent research and literature. Administering neoadjuvant chemotherapy prior to surgical intervention in TNBC patients aids in reducing the tumor burden [11] and helps to reduce the tumor size. Currently, Adriamycin, cyclophosphamide, and paclitaxel are commonly used as neoadjuvant chemotherapy in TNBC, achieving promising outcomes, these treatments exhibit pCR rates ranging from 35% to 45% [12].

Neoadjuvant chemotherapy is the standard treatment for locally advanced or inoperable TNBC, but up to 30% of patients who do not achieve a complete response will relapse. Despite TNBC's high sensitivity to anthracyclines and paclitaxel, drug resistance can still occur. To develop more effective chemotherapy, a study found that platinum was safe and tolerable to be added to neoadjuvant chemotherapy for TNBC. Platinum drugs enter tumor cells and disrupt DNA double strands, leading to cell death and significant effects on tumors with DNA repair barriers. Moreover, The BRCA genes play a crucial role in maintaining DNA structure, and mutations in BRCA can lead to impaired DNA repair mechanisms. In 15–25% of TNBC patients, BRCA mutations exist, so researchers have explored the role of platinum-based drugs in TNBC chemotherapy [13–15]. Platinum-based drugs can result in pCR rates of 70%–90% in TNBC patients with BRCA mutations. For patients without BRCA mutations, the pCR rate of carboplatin combined with paclitaxel remains high (56%). Patients with wild-type BRCA1/2 seem to benefit from neoadjuvant platinum-based chemotherapy. The administration of platinum salts to patients with DNA repair-deficient cancers undergoing chemotherapy that also contains alkylating drugs like cyclophosphamide is limited in the short term with demonstrated improvement in pCR rate, but the long-term outcome remains an open question [16–18].

4. Advancements in Immunotherapy

Breast cancer can be treated effectively with immunotherapy now, along with surgery, adjuvant chemotherapy, and radiotherapy [19]. In immunotherapy, the immune system is stimulated to generate an antitumor response, with a recent focus on immune checkpoint inhibitors (ICIs). ICIs are cell surface molecules that regulate the immune system, including T-cell activation, and have shown promise as a viable treatment option for TNBC. ICIs have the unique ability to regulate autologous cells, ensuring that immune system activity is within a normal range and preventing excessive immunological activity. Studies have shown varying degrees of effectiveness, ranging from no effect to moderate effectiveness, and some have demonstrated an increase in pathological complete response (pCR) in early stage TNBC. ICIs play a crucial role in preventing autoimmunity and immune system tissue damage from infectious agents [20, 21]. Research on ICIs has led to significant advancements in new therapeutic approaches for TNBC, as these therapies can alleviate immunosuppression and promote cancer patients' antitumor effects of T-cells, potentially improving progression-free survival (PFS) and overall survival. Programmed death receptor 1 (PD-1) and cytotoxic T lymphocyte-associated protein (CTLA-4) are two immunological checkpoints [22], and CTLA-4 antibodies are the first ICIs approved by the FDA for human use.

4.1. PD-1 and PD-L1. PD-1/PD-L1 antibodies are a type of clinical immunotherapy that has been extensively studied and is rapidly growing in popularity (Figure 1). Various immune cells express PD-1, including T cells, B cells, dendritic cells, natural killer (NK) cells, and tumor-infiltrating lymphocytes (TILs) [23] (Table 2). PD-1 includes two ligands, PD-L1 and PD-L2, and both healthy and cancerous cells express PD-L1 more frequently than PD-L2 [29]. In a normal immune system, PD-1 plays a crucial role in maintaining immune tolerance. However, in the tumor microenvironment (TME), PD-1 and PD-L1 interaction can reduce cytokine production, lymphocyte proliferation, and

Table 1: Preoperative/adjuvant therapy regimens [10].

Preferred regimens	First step	Cycle
Dose-dense AC followed by paclitaxel	Doxorubicin 60 mg/m^2 IV day 1 Cyclophosphamide 600 mg/m^2 IV day 1	Cycled every 14 days for 4 cycles
	Paclitaxel 175 mg/m^2 by 3 h IV infusion day 1	Cycled every 14 days for 4 cycles
Dose-dense AC followed by weekly paclitaxel	Doxorubicin 60 mg/m^2 IV day 1 Cyclophosphamide 600 mg/m^2 IV day 1	Cycled every 14 days for 4 cycles
	Paclitaxel 80 mg/m^2 by 1 h IV infusion weekly	12 weeks
TC	Docetaxel 75 mg/m^2 IV day 1 Cyclophosphamide 600 mg/m^2 IV day 1	Cycled every 21 days for 4 cycles
Preoperative pembrolizumab + chemotherapy followed by adjuvant pembrolizumab	Pembrolizumab 200 mg IV day 1 Paclitaxel 80 mg/m^2 IV days 1, 8, 15 Carboplatin AUC 5 IV day 1	Cycled every 21 days for 4 cycles (cycles 1–4)
	Pembrolizumab 200 mg IV day 1 Doxorubicin 60 mg/m^2 IV day 1 or epirubicin 90 mg/m^2 IV day 1	
	Cyclophosphamide 600 mg/m^2 IV day 1	Cycled every 21 days for 4 cycles (cycles 5–8)
	Adjuvant pembrolizumab 200 mg IV day 1	Cycled every 21 days for 9 cycles
Capecitabine	1,000–1,250 mg/m^2 PO twice daily on days 1–14	Cycled every 21 days for 6–8 cycles
Olaparib	300 mg PO twice daily	Cycled every 28 days for 1 y

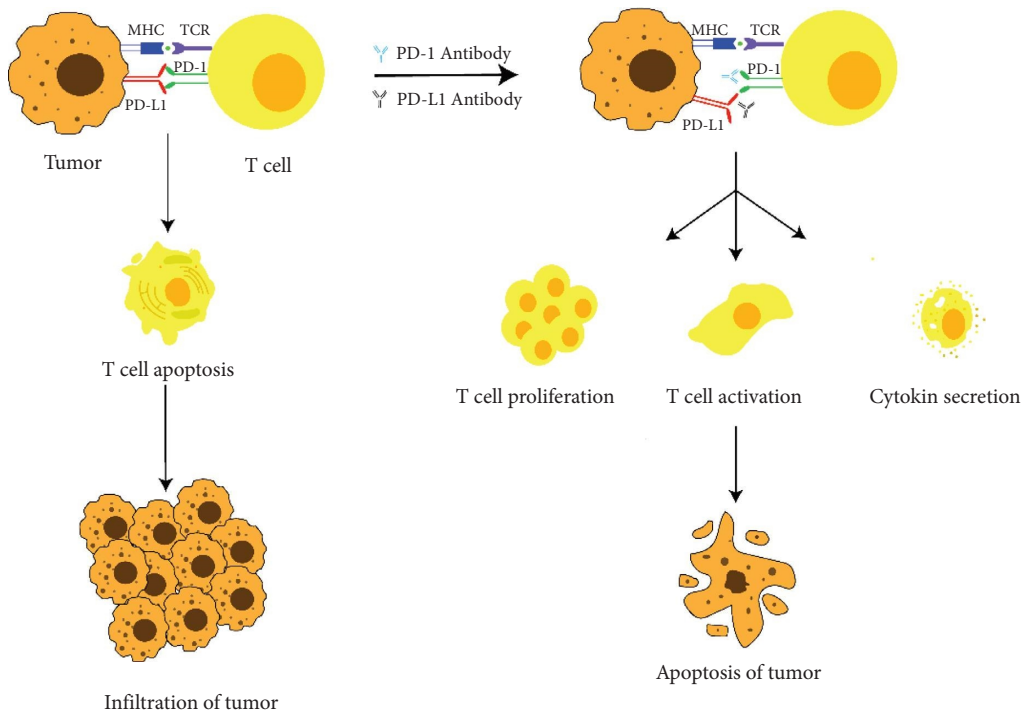

Figure 1: Inhibitors of PD-1 and PD-L1 have an effect. Inhibitors of PD-1 or PD-L1 increase T-cell proliferation, activation, and cytokine release, as well as their capacity to attack tumors. The combination of PD-1 and PD-L1 produces T-cell apoptosis, allowing the tumor cells to infiltrate [15].

cytotoxic T lymphocyte (CTL) activity [30–32], resulting in the demise of tumor-specific T cells [33]. Previous research has demonstrated that a significant portion of TNBC patients express both PD-L1 and PD-1, and that combination treatment utilizing PD-1/PD-L1 inhibitors and chemotherapy is more successful than single-dose ICIs [28] (Table 2). In clinical trials (IMpassion130), PD-L1-positive tumor patients' PFS has been demonstrated to be dramatically improved by pembrolizumab plus chemotherapy, while nab-paclitaxel and atezolizumab in combination have demonstrated encouraging outcomes in terms of PFS and safety profile [25] (Table 2). Moreover, in the same group of patients, the atezolizumab and paclitaxel combination was tried in the IMpassion131 study. The main objective of the study, in contrast to IMpassion130, was to assess investigator-based progression-free survival (PFS) in the PD-L1-positive population. If this assessment proved significant, a secondary goal, overall survival (OS), would be examined only if the PFS results were positive and using an Intent-to-Treat (ITT) analysis. Unexpectedly, the study found no evidence of better PFS in the PD-L1-positive sample (6.0 versus HR 0.82 over 5.7 months, $p = 0.20$). Therefore, atezolizumab should only be administered in combination with nab-paclitaxel. PD-1/PD-L1 inhibitors have limited single-agent efficacy in TNBC, which is in part related to breast cancer resistance to ICIs [26] (Table 2).

4.2. CTLA-4. The latest research suggests that CTLA-4 is upregulated in tumor patients, making it a crucial immune evasion mediator. It functions as a negative regulator, predominantly expressed on T cells [34], and interacts with its ligand CD80/CD86 to suppress T cell responses that are activated when the ligand binds to CD28 [22]. TNBC tumor cells have been shown to express CTLA-4, and anti-CTLA-4 monoclonal antibodies can be employed to block CTLA-4 and PFS and OS [35]. Both drugs have been successful in treating different cancers, so researchers hope they can bring similar benefits to TNBC patients [36]. However, it should be noted that the safety of CTLA-4 inhibitors needs further study, so caution is needed when using them. It is possible to synergistically combine surgical treatment or chemotherapy with immune checkpoint drug therapy in TNBC patients to increase the likelihood of cure. We believe that they have a promising future.

4.3. Antibody-Drug Conjugate (ADCs). ADCs offer a promising avenue for cancer therapy as they can target cancer cells with precision, limiting harm to healthy cells and reducing side effects compared to traditional chemotherapy [37]. The antibodies in ADCs are designed to bind to specific proteins on the surface of cancer cells, delivering a cytotoxic payload directly to the tumor cells. This targeted approach is particularly significant for TNBC, which is known to be highly heterogeneous and challenging to treat with conventional therapies. As a result, ADCs provide a novel strategy for treating this aggressive form of breast cancer. The novel ADC called sacituzumab govitecan (SG) consists of an antitrophoblast surface antigen 2 (Trop-2) linked to the antitumor drug SN-38 [38], the active metabolite of irinotecan (topoisomerase I inhibitor) [39, 40]. It has been shown

Table 2: Key results of the TNBC trial [24].

Trial	Phase	Drug	Key result
IMpassion130 [25]	3	Nab-paclitaxel + atezolizumab Nab-paclitaxel + placebo	PFS: 7.2 vs 5.5 mo HR = 0.80 (0.69–0.92) OS: 21.0 vs 18.7 mo HR = 0.87 (0.725–1.02) PD-L1+: OS 25.4 vs 19.7 mo HR = 0.69 (0.54–0.88) PFS: 7.5 vs 5.3 mo HR = 0.63 (0.50–0.80)
IMpassion131 [26]	3	Paclitaxel + atezolizumab Paclitaxel + placebo	ITT: PFS: 5.7 vs 5.6 mo HR = 0.86 (0.70–1.05) OS: 19.2 vs 22.8 mo HR = 1.12 (0.88–1.43) PD-L1+: PFS: 6.0 vs 5.7 mo HR = 0.82 (0.60–1.12) OS: 22.1 vs 28.3 mo HR = 1.11 (0.76–1.64)
KEYNOTE-119 [23]	3	Pembrolizumab Physician's chemotherapy choice	OS: 9.9 vs 10.8 mo HR = 0.97 (0.82–1.15) PFS: 2.1 vs 3.3 mo HR = 1.60 (1.33–1.92) CPS >10: OS: 12.7 vs 11.6 mo HR = 0.78 (0.57–1.06) PFS: 2.1 vs 4.3 mo HR = 1.14 (0.82–1.59)
KEYNOTE-355 [27]	3	Nab-paclitaxel/paclitaxel/gemcitabine/carboplatin + pembrolizumab	PFS: 7.5 vs 5.6 mo HR = 0.82 (0.69–0.97) CPS ≥10: PFS: 9.7 vs 5.6 mo HR = 0.66 (0.50–0.88) OS: 23 vs 16.1 mo HR = 0.73 (0.55–0.95) CPS ≥1: PFS: 7.6 vs 5.6 mo HR = 0.75 (0.62–0.91)
KEYNOTE-522 [28]	3	Carboplatin + paclitaxel + 4xAC + pembrolizumab ->pembrolizumab in adjuvant Carboplatin + paclitaxel + 4xAC + placebo -> placebo in adjuvant	pCR: 64.8 vs 51.2% $p < 0.001$ PD-L1+: pCR 68.9 vs 54.9% events: 15.7 vs 23.8% HR = 0.63 (0.48–0.82)

that Trop-2 expression is upregulated in all cancer types, especially colon, prostate, breast, lung, and pancreatic cancers. In many epithelial tumors, Trop-2 is overexpressed; as a result, it is a potential therapeutic target [40–42]. One study showed a median PFS of 5.5 months and an OS of 33% with ADC therapy. Based on these results, the ASCENT trial was launched as a phase III study to assess the safety and effectiveness of SG compared to standard chemotherapy administered by physicians for the treatment of relapsed or refractory TNBC. Based on the standard of care, patients were randomly assigned to receive either a dose of SG at 10 mg/kg body weight or a single chemotherapeutic agent on days one and eight of each 21-day cycle. Subsequently, the overall population analysis revealed the effectiveness of SG: patients treated with SG exhibited enhanced median progression-free survival (PFS) (4.8 months vs 1.7 months) and overall survival (OS) (11.8 months, 95% CI: 10.5–13.8 months vs 6.9 months, 95% CI: 5.9–7.7) compared to those receiving chemotherapy [42–44]. These results indicate superior efficacy of SG over chemotherapy. The same side effects: hair loss, neutropenia, diarrhea, nausea, exhaustion, and anemia—were recorded in both groups [45]. Based on the trial's results, the FDA granted accelerated approval to SG for treating patients with metastatic TNBC who had undergone at least two prior treatments for metastatic disease. Studies are currently underway testing the association of SG with pembrolizumab and atezolizumab in metastatic TNBC. This marks the first FDA-approved use of an ADC to treat metastatic TNBC that has relapsed or is refractory.

Ladiratuzumab, a different ADC, combines humanized IgG1 antibodies and monoclonal antibodies that target LIV-1, a transmembrane protein that acts as a zinc transporter and metalloprotease. This protein is expressed in fewer healthy tissues but is found in more than 90% of breast cancer cases. Ladiratuzumab also contains a microtubule inhibitor called MMAE. A phase II clinical trial was conducted to assess the safety and effectiveness of the combination of ladiratuzumab vedotin, pembrolizumab, and the chemotherapy drug eribulin for treating advanced HER2-low TNBC. Preliminary results showed that the overall response rate (ORR) for the ladiratuzumab vedotin combination group was 58.3%, with 12 patients (30%) achieving complete or partial response, compared to an ORR of 25%, and 4 patients (20%) achieving complete or partial response in the eribulin monotherapy group. Furthermore, the ladiratuzumab vedotin combination group also demonstrated a favorable duration of response. Overall, these findings suggest that ladiratuzumab vedotin in combination with pembrolizumab and eribulin is a promising treatment option for HER2-low advanced TNBC patients [46].

There is another type of ADC called trastuzumab deruxtecan (T-Dxd) that targets HER2 and consists of a humanized monoclonal antibody that was generated based on the amino acid sequence of trastuzumab. This is the initial HER2-targeted medication to exhibit favorable clinical antitumor activity and manageable safety in HER2-negative patients. The FDA has approved T-Dxd for the treatment of metastatic breast cancer that is HER2-positive [47]. At present, certain breast cancers that display low levels of HER2 expression (as indicated by IHC1+ or IHC2+/FISH-results) are categorized as HER2-negative. Consequently, some of these cases are managed as TNBC [48]. It is worth noting that T-Dxd has exhibited encouraging effectiveness against tumors in patients with advanced or metastatic HER2-low breast cancer who have undergone extensive prior treatments. HER2-low is defined as having immunohistochemical scores of 2+ or 1+ and no observable ERBB2 amplifications using fluorescence in situ hybridization. These patients include those with TNBC [49]. Unlike traditional chemotherapy, ADCs have distinct side effects. For example, trastuzumab deruxtecan can cause interstitial pneumonia, ladiratuzumab vedotin can cause peripheral neuropathy, and sacituzumab govitecan can cause neutropenia and diarrhea. However, at the same time, ADCs offer precise targeting of tumor cells, and for highly heterogeneous biological TNBC, ADCs are better suited to be used in combination with other targeted agents to enhance synergistic effects, opening up a wide range of research opportunities for the treatment of TNBC.

4.4. PI3K/AKT/mTOR Pathway. The RTK family of cell surface transmembrane enzyme-linked receptors is composed of a protein tyrosine kinase structural domain, a single transmembrane helix, an extracellular ligand binding region, and a paramembrane regulation region. There are 58 different receptors, including AXL, vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), and insulin growth factor receptor (IGF-1R) [50]. Upon ligand interaction and receptor dimerization, RTK activates several downstream pathways, comprising the Janus kinase/signal transducer sub, RTK/Ras/MAPK, PI3K/AKT/mTOR, and transcriptional protein family activator pathways [50, 51] (Figure 2). About 50% of TNBCs show any PI3K pathway abnormalities and the PI3K/AKT/mTOR pathway is necessary for many cellular functions, including metabolism, proliferation, migration, and survival, and it contributes significantly to the survival and chemoresistance of TNBC cells [52]. Dysregulation of this pathway is frequently observed in TNBC [53], with RTK triggering the activation of PI3K, which phosphorylates 4,5-phosphatidylinositol (PIP2) to 3,4,5-phosphatidylinositol (PIP3). PIP3 then binds to AKT and phosphorylates threonine and serine to fully activate AKT [54–56]. There are also other regulators involved in this cellular pathway, such as PTEN, which negatively regulates phosphatase of PI3K signaling and can reduce tumor growth by changing PIP3 to PIP2 [57]. Research has indicated that aberrations in the PI3K/PTEN/AKT pathway, such as activating mutations in PIK3CA and AKT1, loss of PTEN, and activation of mTOR, can be observed in TNBC cells [58–61] and are observed in more than 25% of TNBC patients, making targeting this pathway a promising option for TNBC [58]. In a phase II clinical trial, the effectiveness and safety of combining the chemotherapy drug carboplatin with the mTOR inhibitor everolimus were evaluated for the treatment of advanced TNBC. The results showed that the combination therapy improved patients' PFS, but adverse

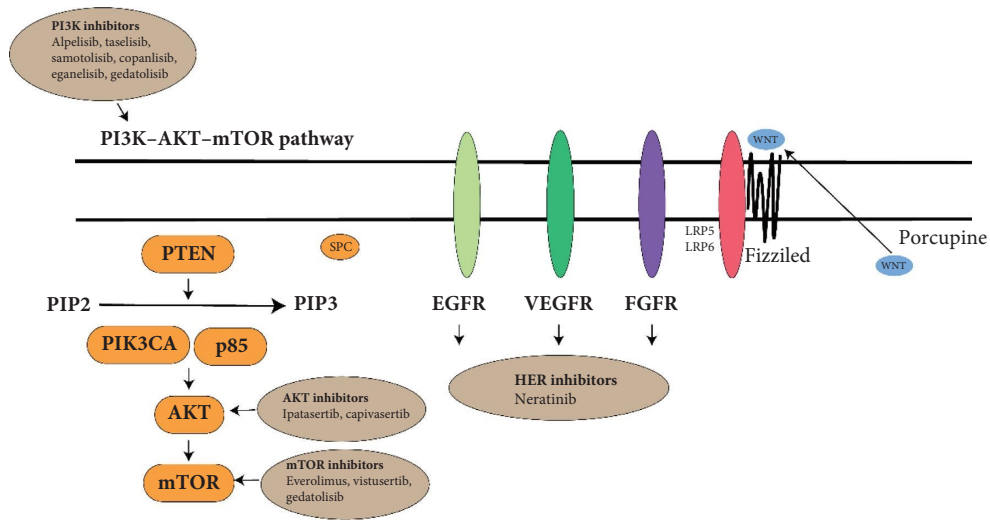

Figure 2: Schematic diagram of PI3K/AKT/mTOR [46].

reactions were relatively common [62]. Another phase II clinical trial was conducted to examine the effectiveness and safety of combining the chemotherapy drug paclitaxel with the AKT inhibitor ipatasertib for the treatment of TNBC. The outcomes demonstrated that the combined therapy markedly increased patients' PFS, and adverse reactions were relatively rare [63]. In cancer models, the highly selective pan-AKT inhibitors capivasertib and ipatasertib, in conjunction with taxanes, have demonstrated synergistic antitumor efficacy, especially in people with PI3K pathway mutations. Capivasertib's anticancer efficacy is being investigated in a comparable research (NCT03997123). In conclusion, although clinical evidence is conflicting, preclinical rationale supports the therapeutic exploitation of PI3K signaling for TNBC.

5. Focused Approach: Targeted Therapy

Compared to chemotherapy, targeted therapy for TNBC has the advantage of being less harmful to healthy cells. Several categories of inhibitors have been explored as possible therapies for TNBC, such as EGFR inhibitors, PARP inhibitors, VEGF inhibitors, PIK3 inhibitors, MEK inhibitors, and AR inhibitors [64].

5.1. Antiandrogen Therapy. Molecular phenotypic analysis of breast cancers has shown that a subset of TNBC resembles LAR tumors, considering downstream effects and androgen receptor activation [65]. This subset of TNBC mediates tumor cell growth through androgen receptor hormone-mediated signaling and plays a role opposite to its role in ER + breast cancers [66]. One study found that androgen receptor (AR) plays a significant role as a possible therapeutic target and is expressed in roughly 35% of TNBC [67]. Compared to AR-negative patients, in patients with AR-positive breast cancer, a high frequency of activating mutations in PIK3CA has been observed. Preclinical studies have demonstrated that combining inhibitors targeting the PI3K pathway with AR antagonists can effectively impede the growth and survival of LAR cell lines [68]. In contrast, another study found a greater dependence of AR-positive TNBC on CDK4/6 phosphorylation. In a phase I/II trial in AR-positive TNBC, the safety and effectiveness of palbociclib (a CDK4/6 inhibitor) and bicalutamide were examined [69]. The clinical trial achieved its primary objective, with a 6-month PFS rate of 33% [27] (Table 2). Another trial called GeparNuevo is for early HER2-positive breast cancer; the trial aimed to evaluate the impact of the three treatment arms on patients' disease-free survival (DFS). The results showed that adding ribociclib to standard targeted therapy significantly prolonged DFS compared to standard targeted therapy alone, while the addition of chemotherapy did not provide additional therapeutic benefits. It suggests that administering ribociclib, a CDK4/6 inhibitor, can enhance the effectiveness of treatment for HER2-positive early breast cancer [70]. Finally, based on the similar effects of immunotherapy and AR inhibitors, it is believed that the two have a synergistic effect, leading to better treatment of the disease. A crucial step in cell growth is mitosis, which depends on the ongoing activation of numerous CDK complexes [71]. Cyclin D, belonging to the cyclin protein family, facilitates the transition of cells from the G1 phase to the S phase of the cell cycle by binding with CDK4/6 kinase and forming a complex [72]. After entering the nucleus, the retinoblastoma protein (Rb) is phosphorylated by the active cyclin D-CDK4/6 complex. Lateral phosphorylation of Rb triggers cell entrance into the S phase, inhibits transcription factors including E2F, and promotes DNA replication [24]. Rb's initial phosphorylation is reliant on the cyclin D-CDK4/6 complex, and hence Rb's tumor suppressor activity is lost when it is hyperphosphorylated. Inhibitors of CDK4/6 can prevent Rb phosphorylation, thereby further preventing tumor cell proliferation. So far, the FDA has authorized three CDK inhibitors for the treatment of HER2+ breast cancer [73–75]. However, TNBC is not allowed to be treated with CDK4/6, and its efficacy, side effects, and prognosis deserve further study. We believe that waiting for new findings from these investigations will result in better tactics for the treatment of TNBC.

5.2. MAPK Pathway. N-Ras, M-Ras, K-Ras, and H-Ras are small GTPases that are first triggered by environmental signals like ligand activation of receptor tyrosine kinases (RTKs) [76]. The signals generated by Ras are then sent to the nucleus by downstream effectors such as Raf, MAPK kinase 1 (MEK), and extracellular signal-regulated kinase (ERK), ultimately promoting cell survival and proliferation [77]. The MEK inhibitor, a crucial element of the Ras/MAPK pathway, has the ability to impede the proliferation of TNBC cell lines. A clinical trial targeting MEK inhibitor selumetinib showed that compared to placebo, patients with TNBC treated with selumetinib had a significant improvement in PFS, indicating that MAPK pathway inhibitors may be an effective treatment option. However, some studies imply that combining therapies may be more effective than using MEK inhibitors alone but clinical outcomes are still immature (Figure 3).

5.3. PARP Inhibitors. Mutations in the breast cancer susceptibility gene (BRCA) are detected in approximately 20% of patients with TNBC, making it one of the most common genetic alterations observed in this patient population [78]. Double-strand breaks in DNA are common DNA damage during tumorigenesis, and BRCA1 and BRCA2 can mend fractures in normal cells [79, 80]. BRCA1 or BRCA2 mutations are present in over 15% of TNBC patients, and there are similarities in clinical and pathological features between TNBC patients and patients with BRCA2 mutations [81, 82]. It has been shown that the DNA repair enzyme PARP is critical for maintaining correct DNA replication and promotes, in the presence of BRCA mutations, the repair of single-stranded DNA breaks, which is a crucial mechanism for repair. Therefore, targeting PARP is a viable option. Damage to PARP can delay DNA repair and make cells more vulnerable to agents that cause DNA breaks [83]. PARP inhibitors can inhibit the DNA repair recombination pathway through polyADP ribosylation or homologs, resulting in cytotoxicity [84]. There are currently four PARP inhibitors approved for marketing, namely, olaparib, niraparib, fluzoparib, and pamiparib [85]. Both monotherapy and combination therapy with olaparib, including chemotherapy, immunotherapy, and radiotherapy, have demonstrated some efficacy in the treatment of breast cancer. In 2017, olaparib was discovered to be functional in people with metastatic breast cancer with mutations [86]. Similar to immunotherapy, PARP inhibitors, having exhibited efficacy against metastasis, were subjected to clinical trials in early stage disease as part of the OlympiA study [87]. The OlympiA trial also evaluated the use of PARP inhibitors in the adjuvant setting, after the completion of neoadjuvant or adjuvant chemotherapy. The decision to test PARP inhibitors as a monotherapy in this setting was based on limited data available on the efficacy of combining PARP inhibitors with chemotherapy. Olaparib has been authorized for use in the OlympiA trial and may eventually replace other treatments for people with BRCA mutations in TNBC. PARP inhibitors serve as one of the most promising treatments for BRCA1/2 mutations in TNBC currently under research, although BRCA mutations are present in only a small percentage of TNBC patients and further research is still needed to address the existing problems.

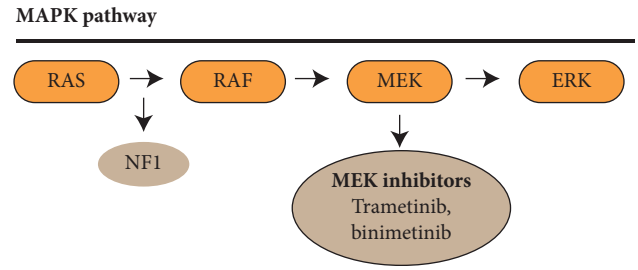

Figure 3: Schematic diagram of MAPK [74].

6. Gene Therapy for TNBC

Gene therapy is one of the extensively researched therapeutic approaches in recent years. RNA-based therapies represent a novel approach to tumor treatment that can target some of the intrinsic tumor pathways that contribute to poor patient prognosis [88]. Two primary categories of noncoding RNAs being investigated are long noncoding RNA and miRNA. miRNA binds to the untranslated region at the 3′ end of mRNA and can degrade mRNA or inhibit translation [89]. LncRNAs are abnormally expressed in TNBC and play crucial roles in biological functions such as regulation of gene expression, cell proliferation, and apoptosis at transcription, posttranscription, and posttranslational modification levels [87]. Therefore, lncRNAs hold promise as potential targets for the treatment of TNBC but need to overcome the limitations that currently exist. RNA interference is a gene-targeting technology that can selectively suppress the expression of specific genes through the interference of RNA molecules. In the treatment of TNBC, some studies are attempting to use RNA interference technology to target genes related to cancer cell proliferation and metastasis, such as FOXC1, CXCR4, and CLDN3. As a transcription factor, FOXC1 is implicated in cancer cell growth and metastasis [90]; CXCR4 is a chemokine receptor that is involved in cancer cell metastasis and invasion [91]; CLDN3 is a cell adhesion protein that has been linked to cancer cell metastasis [92]. Targeting these genes using RNA interference technology can effectively inhibit cancer cell proliferation and metastasis, thus achieving therapeutic effects [93]. The mRNA vaccine immunotherapy is a cutting-edge field in nanomedicine, where RNA vaccines synthesize mRNA via phage RNA polymerase and in vitro transcription (IVT) of template DNA encoding specific antigens [94]. A host immune response is produced by the translation of mRNA transcripts into tumor-specific antigens and their delivery to T cells by antigen-presenting cells. While these new technologies have promising applications, safety issues still need to be addressed before they can be put into clinical practice.

Furthermore, advances in sequencing technology have been able to explain differential gene expression among tumor cell populations. Through whole-genome sequencing of 254

cases of triple-negative breast cancer and classification of tumors using the HRDetect algorithm based on mutation features, it was predicted that 59% of tumors exhibit homologous recombination repair deficiency (HRDetect-high). Various gene alterations associated with HRDetect-high tumors were identified, including BRCA1/BRCA2 mutations, BRCA1 promoter hypermethylation, RAD51C hypermethylation, and PALB2 bilateral loss. A novel mechanism of BRCA1 attenuation was discovered through lineage-specific SINE-VNTR-Alu retrotransposition. HRDetect provides independent prognostic information. HRDetect-high patients show better outcomes in terms of invasive disease-free survival and distant recurrence interval after adjuvant chemotherapy compared to HRDetect-low patients, regardless of the presence of genetic/epigenetic causes [95].

7. Prospect

The methods mentioned above are likely to recur even if the initial treatment of TNBC is successful. Recent studies on TNBC treatment have shown that nanotechnology offers several potential solutions to the problems of TNBC treatment by overcoming the limitations of conventional treatments by increasing the concentration of drugs at the tumor site to decrease the concentration of drugs at other sites [96]. Thus, nanotechnology can achieve the desired therapeutic effect by virtue of a much smaller dose of drug. Nanotechnology holds immense promise in the future treatment of TNBC through advanced drug delivery systems, facilitating precise targeting of tumor sites while minimizing harm to healthy cells [97]. But the reliability and applicability of nanotechnology is yet to be proven, and further research is needed to make them useful for clinical decision making.

Also, mesenchymal stem cells (MSCs) comprise a versatile cell population capable of differentiating into diverse cell types, while also displaying immunomodulatory and anti-inflammatory characteristics. Notably, MSCs showcase remarkable abilities in homing to tumors, allowing them to migrate and gather within neoplastic tissues after systemic administration [98].

One potential application of MSCs in TNBC treatment is through the use of MSC-derived extracellular vesicles (MSC-EVs) as drug delivery systems. MSC-EVs contain therapeutic molecules that can be transferred to tumor cells, mimicking the immunomodulatory and anti-inflammatory properties of MSCs. While MSC-based therapies show promise for enhancing the prognosis of TNBC patients, further research is needed to overcome limitations, refine parameters, and optimize safety and efficacy [99]. The comprehensive understanding of MSC biology and their interactions with TNBC cells is essential for the development of effective stem cell therapies for TNBC.

8. Conclusion

In general, among all breast cancer subtypes, TNBC has the highest aggressiveness, the highest recurrence rate, and the poorest overall prognosis. Despite ongoing research efforts over the last few decades, current therapies are not sufficient to overcome these challenges. However, there have been significant advances in adjuvant chemotherapy for TNBC, improving patient prognosis to some degree. Furthermore, due to the unique characteristics of TNBC, immunotherapy plays an indispensable role in its treatment. Recent developments in ICIs have provided a new direction for TNBC treatment, with CTLA-4 antibodies being authorized for use by the FDA. Moreover, ADCs have entered clinical studies for TNBC, with sacituzumab govitecan being approved by the FDA. Combining immunotherapy with other treatments also shows promise in improving the prognosis for TNBC. Ongoing trials provide hope for further deepening our understanding of TNBC and developing more treatment options to improve patient outcomes. At the same time, the development of nanotechnology has attracted a lot of attention from researchers, but the shortcomings of nanotechnology also need to be constantly improved to play a greater role in the future.

Data Availability

No data were used to support this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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