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Facts and challenges of immunotherapy in triple-negative breast cancer

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Abstract

Triple-negative breast cancer (TNBC) is an aggressive but common cancer subtype in clinical practice. Immune activation has been observed in a subgroup of TNBC, suggesting that immunotherapy may be a potential therapeutic option. With the widespread use of monotherapy, specific immune checkpoint inhibitors (ICIs) such as avelumab, pembrolizumab, and atezolizumab have made significant contributions to improving outcomes in both early and advanced TNBC. In addition, the expressions of immune regulators such as cytotoxic T-lymphocyte-associated protein 4, programmed cell death 1 (PD-1), and programmed cell death-ligand 1 (PD-L1), which are influenced by tumor-infiltrating lymphocytes (TILs), are also critical factors in determining the effect of immunotherapy in TNBC. This review focuses on the updates on the biological underpinnings of TNBC and the associated treatment advances. We present the current landscape of well-known immune regulators and widely used ICIs for TNBC and highlight the future directions that are significant for further improving the efficacy and effect of targeted therapeutic strategies to immunotherapy in TNBC and more reliable prognostic predictions for tailored therapy in the future.

Keywords: Triple-negative breast cancer; Immunotherapy; Immune checkpoint inhibitors; Programmed cell death 1/Programmed cell death-ligand 1; Cytotoxic T-lymphocyte-associated protein 4

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1. Introduction

Fifteen to twenty percentages of all human breast cancers (BCs) are triple-negative breast cancer (TNBC). TNBC is characterized by the absence of expression of human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER), and progesterone receptor (PR). TNBC frequently exhibits aggressive characteristics, including early recurrence and metastasis[1]. With regard to overall survival (OS), if a patient is found to have stage 1 TNBC, the 5-year survival rate of the patient is nearly 94.7% due to good immune condition and nutrition absorption. The 5-year survival rate of patients with stage 2 TNBC, where the cancer continues to spread but is still confined within the breast or has only affected adjacent lymph nodes, is about 86.37%. In stage 3 TNBC, the cancer has expanded past the tumor's local vicinity and may have even infiltrated adjacent muscles

and lymph nodes, but it has not yet reached distant organs. The 5-year survival rate of patients with stage 3 TNBC is 84%. Stage 4 BC indicates that the cancer has metastasized (spread to other areas of the body), and patients with stage 4 TNBC have only about a 10% chance of survival[2,3]. After all, TNBC is curable when it is diagnosed in the first three stages. The life expectancy and survival rate for stage 3 TNBC are constantly improving[4,5]. At present, there are many treatments available for BC, including surgery, chemotherapy, targeted therapy, and radiotherapy, among which chemotherapy is the primary systemic treatment for the majority of metastatic TNBC (mTNBC) patients[6]. However, responses are frequently transient, and patients have median OS of 12 – 18 months. Moreover, traditional chemotherapy drugs, including paclitaxel, anthracycline, and alkylating agents, are likely to cause side effects and systemic toxicity[4,7]. Therefore, the demand for better therapeutics is increasing.

Based on the expression of ER, PR, and HER2, BC can be classified into four intrinsic subtypes: luminal A, luminal B, HER2+, and TNBC. In most cases, these subtypes have specific immunological characteristics, with different expression levels of tumor-infiltrating lymphocytes (TILs)[8]. In recent years, researchers have found that BC is immunogenetic regardless of its subtype. Lymphocyte-predominant BCs that have stromal or intratumorally lymphocytes make up more than 50 – 60% of the tumor tissue[9,10]. Given that immunotherapy has improved survival in other solid tumors, it may also be a viable option for TNBC treatment. Immune checkpoint inhibitors (ICIs), which inhibit immunosuppressive receptors such as programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) to increase the cytotoxicity and proliferation of tumor-infiltrating cells, are the most effective immunotherapy drugs. ICIs, such as pembrolizumab, nivolumab, atezolizumab, durvalumab, and avelumab[11], which are monoclonal antibodies against PD-1, programmed cell death-ligand 1 (PD-L1), and CTLA-4, have produced long-lasting responses in a variety of tumor types[12-15].

Compared with other subtypes, TNBC is more likely to react to immunotherapy due to a number of factors. First off, TNBC contains higher levels of TILs than other BC subtypes, which have been found to be associated with more significant responses to ICIs and a better prognosis for TNBC in its early stages[16]. Second, TNBC has significantly different levels of PD-L1 expression on both immune and cancer tissues[17], making it a direct target for ICIs and correlating with how well those treatments work in treating other malignancies[4]. Third, a better anti-tumor immune response has been mounted by neoantigen-specific T-cells when TNBC has a notable frequency of non-synonymous gene mutations, which lead to tumor-specific neoantigens[16]. These neoantigen-specific T-cell responses can be amplified by ICIs[17,18].

This review offers a framework for comprehending the most recent clinical data relating to immune checkpoint blockade (ICB) and other new immunotherapy drugs for TNBC. Future directions for the development of immunotherapy in TNBC are also explored, along with the development of immunotherapy biomarkers (Tables 1 and 2).

2. Immunotherapy in triple-negative breast cancer

2.1. Triple-negative breast cancer characteristics

TNBC accounts for 15 – 25% of all BCs and is widely recognized as the worst BC among all the subtypes of BC, posing a huge threat to patients diagnosed with BC[1]. TNBC can be classified into four robust subtypes based on their different transcriptomic characteristics: basal-like (BL), immunomodulatory (IM), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR)[30]. A large number of studies have indicated that age, sex, and even race can be risk factors of TNBC. According to research, BRCA and basal TNBC, as well as apocrine and neuroendocrine TNBC, are more common in younger and older women compared to the same age groups in men. It has been documented that Hispanic and African American women are at a higher risk of TNBC and have a poorer prognosis than other populations. In a case study, there was a 2.5% increased risk of TNBC in 187 TNBC patients who had taken oral contraceptives for more than a year, the risk of TNBC was 4.2% for women under the age of 40, and it was discovered that the risk rose as the duration of oral contraceptive use increased[17]. In the United States, TNBC accounts for 12% of BC cases, with 8 – 16% 5-year survival rate.

Other than the four robust subtypes of TNBC, which can be detected at the transcriptomic level, there are four discrete subtypes: LAR, mesenchymal (MES), basal-like immune suppressed (BLIS), and basal-like immune activated (BLIA)[18]. LAR represents TNBC tumors with the lowest genomic complexity, with mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*), AKT serine/threonine kinase 1 (*AKT1*), neurofibromatosis type 1 (*NF1*), GATA binding protein 3 (*GATA3*), and cadherin-1 (*CDH1*)[12-15]. The mesenchymal subtype is characterized by lower genomic complexity and activation of PI3K pathway[31]. BLIA represents the majority of TNBCs with a complex genomic profile, having *TP53* mutations in more than 90% of cases

Table 1. Avelumab, pembrolizumab, and atezolizumab in TNBC treatment

Antibody	Target	Patient population	Sample size	ORR (%)	References
Avelumab	PD-L1	Uncertain breast cancer	168	3.0	Dirix *et al.*[11]
		PD-L1-positive breast cancer	12	16.6	
		PD-L1-negative breast cancer	124	1.6	
		Uncertain TNBC	59	5.2	
		PD-L1-positive TNBC	9	22.2	
		PD-L1-negative TNBC	39	2.6	
Pembrolizumab	PD-1	PD-L1-positive TNBC	27	18.5	Nanda *et al.*[19]
		Uncertain TNBC	170	5.3	Adams *et al.*[20]
		PD-L1-positive TNBC	105	5.7	
		PD-L1-negative TNBC	64	4.6	
		PD-L1-positive TNBC first line	84	21.4	Adams *et al.*[20]
Atezolizumab	PD-L1	Uncertain TNBC	115	10.0	Emends *et al.*[21]
		PD-L1-positive TNBC	91	11.0	
		PD-L1-negative TNBC	21	0.0	
		Uncertain TNBC first line	21	24.0	
		Uncertain TNBC ≥ second line	94	6.0	

ORR: Objective response rate, PD-1: Programmed cell death 1, PD-L1: Programmed death-ligand 1, TNBC: Triple-negative breast cancer

Table 2. Availability of immunotherapy for prevalent cancers

Cancer type	Availability
Bladder cancer	Immune checkpoint inhibitors, T-cell transfer therapy, monoclonal antibodies, treatment vaccines, and immune system modulators[22]
Breast cancer	Immune checkpoint inhibitors, monoclonal antibodies, treatment vaccines, and immune system modulators[23]
Cervical cancer	Immune checkpoint inhibitors, therapeutic vaccines, engineered T-cells, and antibody-drug conjugates[24]
Colorectal cancer	Immune checkpoint inhibitors and monoclonal antibody therapies[25]
Esophageal cancer	Immune checkpoint inhibitors and monoclonal antibody therapies[26]
Head and neck cancer	Immune checkpoint inhibitors[27]
Kidney cancer	Interleukin-2, alpha-interferon, and immune checkpoint inhibitors[28]
Leukemia	Allogeneic bone marrow transplant, therapeutic cancer vaccines, T-cell therapies, monoclonal antibody therapies, and donor lymphocyte infusions[29]
Glioblastoma	No
Ovarian cancer	No

and a high frequency of homologous recombination DNA repair deficiency (HRD). BLIS also shows a high mutation rate in *TP53*, complex genomic profiles, and an HRD-associated signature but are associated with significantly lower TILs[32]. The most noticeable feature about these subtypes is that BLIA and BLIS subtypes are, respectively, associated with the best and the worst disease-free survival. To make a more vivid comparison among the subtypes, the LAR subtype displays mutations similar to those detected in luminal B cancers, and its microenvironment is described as "cold," with low TILs, in comparison with the "desert" microenvironment in the MES subtype and the "hot" microenvironment in the BLIA subtype[33]. However, it should be noted that in these gene expression classification systems, the vast majority of TNBCs analyzed were of high grade; hence, it remains unclear as to how the low-grade forms described above would fit into this taxonomy or if these low-grade forms would constitute completely different entities at the transcriptomic level[34].

The risk factors of TNBC are discussed below. The first is related to age, in which 80% of BC cases (including TNBCs) are older than 50 years old[6]. Due to different sex hormonal stimulation, female sex is considered a higher risk for TNBC compared to male sex. In addition to these two factors, race is also associated with TNBC, in which the incidence of TNBC remains high among Caucasian non-Hispanic women[35]. With regard to breast tissue density, as per clinical practice, breasts can be categorized into low-density breasts, fatty breasts, and high-density breasts[36]. In postmenopausal and premenopausal women, breast density affects the risk of cancer, that is, the higher the

density, the higher the risk of BC[37]. Breast tissue density screening could be a promising and quick approach for rational surveillance. According to several epidemiological studies, obesity is a potential risk factor for BC[38,39]. Hence, engaging in physical activity is considered the best way to prevent BC. Alcohol and alcoholic beverages can also increase the risk of malignancy[40].

2.2. Triple-negative breast cancer microenvironment

The tumor microenvironment (TME) contains various cell types, including fibroblasts, TILs, and lymphatic vascular channels. The active interaction between tumor cells and the microenvironment affects the pathogenesis and development of tumor. Research has indicated that high levels of TILs, especially in the IM subtype, are associated with better prognosis and response to chemotherapy in both neoadjuvant and adjuvant contexts[1,4]. Later, research has revealed that variations in gene overexpression of IM and MSL subtypes are derived from the TME, including infiltrating immune cells and tumor-associated mesenchymal tissue, respectively[41,42]. Intriguingly, and in agreement with the aforementioned findings, these genes are not expressed in cell lines when tests are conducted *in vitro*, where the microenvironment is absent. It is evident that TME has a significant influence on the development of tumor as well as the response and resistance to treatment. Furthermore, the elevated expression of immune regulators such as CTLA4, PD-1, and PD-L1 in TNBC, brought on by lymphocyte infiltration of the tumor, is likely linked to a response to ICIs. Several studies have purported the possibility that TILs may be a marker for improved survival outcomes[43-45]. All the preceding evidence suggests that focusing on TME in TNBC and further exploring the biomarker landscape are promising efforts for better immunotherapy.

2.3. Specific biomarkers

Due to the underlying heterogeneity of TNBC, there is a need for efficient biomarkers that can guide doctors in determining the best course of action. Therapeutic trials have been conducted on several suggested biomarkers for TNBC, with limited clinical benefits so far. Breast cancer gene (*BRCA1*/*BRCA2*) mutations have been found to be predictive of the effectiveness of poly (ADP-ribose) polymerase (PARP) inhibitors, and changes to other homologous recombination-related genes appear promising in this context[46-49]. It is possible to use the expression of PD-L1 protein in either immune cells (ICs) or tumor cells, or both, as a biomarker to predict how well an immune checkpoint inhibitor would work[15]. TILs are also considered an important prognostic factor in TNBC. Up to 15 studies have shown that 11% (median; range, 5 – 26%) of breast cancers are lymphocyte-predominant breast cancers (LPBCs), among which TNBC accounts for the highest incidence (20%; range, 4 – 37%)[50]. Moreover, $CD8^+$ T-cell infiltrates have been observed in 60% of TNBC cases[41]. Various tests that employ different antibodies and scoring methods are commercially available. There is an ongoing debate over the optimal assay for TNBC and whether the findings hold for all ICIs.

2.4. Drugs

ICIs, especially for CTLA-4, PD-L1, and PD-1, have made great contributions to cancer therapy. The five drugs in TNBC immunotherapy include avelumab, pembrolizumab, and atezolizumab, ipilimumab, and tremelimumab.

2.4.1. Programmed cell death 1/programmed cell death-ligand 1 inhibitors

Avelumab, a complete monoclonal antibody of the isotype IgG1 that binds to PD-L1 and prevents binding to its receptor PD-1, acts as a checkpoint inhibitor, and is being utilized in the immunotherapy for various types of advanced or metastatic cancers[51,52]. In the TNBC subgroup treated with avelumab, there were three partial responses (PRs), giving TNBC patients an objective response rate (ORR) of 5.2% (95% CI, 1.1 – 14.4%). The disease control rates (DCRs) were 28% (47/168) and 31% (18/58) for the overall population and the TNBC subgroup, respectively. Both the overall population and the TNBC subgroup showed a tendency toward higher ORRs in patients with PD-L1 expression in tumor-associated ICs (10% cutoff), with ORRs of 16.7% (2/12 patients) and 22.2% (2/9), respectively, for PD-L1-positive disease and 1.6% (2/124 patients) and 2.6% (1/39 patients), respectively, for PD-L1-negative disease[53].

A humanized antibody, pembrolizumab, is used in cancer immunotherapy to treat melanoma, lung, head and neck, stomach, cervical, and breast cancers, as well as Hodgkin lymphoma. Pembrolizumab is slowly injected into a vein. The IgG4 isotype antibody blocks the defense mechanism of cancer cells, thus enabling the immune system to eliminate them. Pembrolizumab targets the lymphocyte PD-1 receptor and functions by concentrating on the PD-1/PD-L1 biological pathway, which is present in some cancer cells and immune cells in the body[6,54-61]. The PD-1 antagonist pembrolizumab, in the KEYNOTE-012 trial, which studied the safety and antitumor efficacy of pembrolizumab monotherapy in patients with advanced PD-L1-positive solid tumors, was initially assessed in PD-LI-positive advanced TNBC patients. PD-L1 expression was prescreened in 111 patients with advanced TNBC, in which 58.6% of them tested positive for PD-L1. The median number of prior therapies for advanced illness

was two among 32 treated TNBC patients (range, 0 – 9). Of these, 27 patients had their clinical responses evaluated. With 1 complete response (CR) and 4 PRs, the ORR was 18.5% (95% CI, 6.3 – 38.1%), and the DCR was 25.9% (95% CI, 11.1 – 46.3%)[62].

By preventing the interaction of PD-L1 with PD-1 and CD80 receptors (B7-1Rs), atezolizumab can be used to treat dysplastic carcinoma, hepatocellular carcinoma (HCC), non-small-cell lung cancer (NSCLC), small-cell lung cancer (SCLC), and TNBC[63,64]. Atezolizumab is a monoclonal antibody of the IgG1 isotype that has been fully humanized and engineered to target the protein PD-L1[13,65-67]. In the PCD4989g trial, atezolizumab was tested in patients with advanced malignancies[68], including 116 patients with advanced TNBC, 115 of whom had an objective response assessed. After the enrollment of the initial 25 patients, the eligibility was changed to permit the enrollment of patients with any PD-Ll status. These patients displayed PD-LI in IC, occupying <5% of the tumor area. With 58% of patients having received at least two prior lines of therapy for an incurable illness, the enrolled patients were severely treated[68,69].

2.4.2. Cytotoxic T-lymphocyte-associated protein 4 inhibitors

Ipilimumab is a monoclonal antibody that works to activate the immune system by targeting CTLA-4, a protein receptor that downregulates the immune system. It boosts the immune response against cancer cells and prevents the inhibitory interruption of cytotoxic T-lymphocytes (CTLs), which can recognize and destroy cancer cells[70]. In a study on early-stage BC, 12 of 18 women received a single dose of neoadjuvant ipilimumab alone or with additional cryoablation; the other six patients received cryoablation alone. T-cell density was found to be significantly correlated with TIL count by hematoxylin and eosin (H&E). It was shown that about 5/6 patients who received ipilimumab alone had increased T-cell density in contrast to the decrease in the cryoablation group[71,72].

Tremelimumab blocks the binding of antigen-presenting cell ligands B7.1 and B7.2 to CTLA-4, resulting in the inhibition of B7-CTLA-4-mediated downregulation of T-cell activation. Tremelimumab has been evaluated in various types of tumors. Experiments with tremelimumab in combination with exemestane have been carried out. Among 26 patients who received tremelimumab (3 – 10 mg/kg) and exemestane (25 mg/kg daily), five patients developed dose-limiting toxicity when the dose of tremelimumab with 25 mg/day exemestane was about 6 mg/kg Q90D, four of which were diarrhea. Up to 42% of patients had stable disease for at least 12 weeks. The percentage of $CD4^+$ and $CD8^+$ T cells expressing inducible T-cell costimulator (ICOS) increased in all patients[73].

2.4.3. Neoadjuvant ipilimumab

These groundbreaking studies offer solid proof in favor of using PD-1/PD-L1 and CTLA-4 inhibitors in both early and advanced TNBC. The FDA has authorized the use of pembrolizumab in conjunction with chemotherapy for the treatment of PD-L1-positive advanced TNBC, and health authorities now recommend the combination of atezolizumab and nab-paclitaxel[55]. To further understand the immunobiology of both early and late TNBC, well-controlled translational studies may be conducted using the data sets and tissue samples from these trials[49,60]. By identifying TNBC as a tumor that can react to immunotherapy, these studies collectively pave the way for the testing of cutting-edge ideas that can successfully harness the immune system to improve clinical outcomes for patients with this arduous condition (Table 3).

3. Challenges of immunotherapy in triple-negative breast cancer

3.1. Unclear mechanism of tumor-infiltrating lymphocytes

It is essential to consider whether the number of TILs expressed in the primary tumor and the metastatic sites can affect the prognosis of patients with TNBC. Another issue is whether the heterogeneity of TILs at the original sites, the occurrence of residual invasive disease (RD) following the completion of neoadjuvant chemotherapy (NAC), and the metastatic locations can influence the choice of follow-up therapy options in TNBC[2,54]. Despite the fact that the discovery of biomarkers has given individuals who are looking to advance their skills an effective tool, one of the main limitations of the use of TILs at the moment is their reliance on manual measurement, which is subject to potential human error[41]. Surprisingly, there are many opportunities to employ computational techniques that extract spatial-morphologic predictive elements, thus making it possible for computer-aided diagnostics.

We, now, need to figure out how to assess TILs in combination with other biomarkers to direct a more focused course of treatment, as they have been established as distinct biomarkers in the early TNBC. In addition, it is still worthwhile to advocate the current belief that TILs serve as the starting point for the expression of additional biomarkers[16,51].

In terms of immunomodulatory mechanisms, whether negative immunomodulatory regulation, as part of a standard feedback loop, has a positive and persistent

Table 3. Randomized phase III clinical trials of PD-1/PD-L1 blockade for metastatic TNBC

Trial	Sample size	Key eligibility	Intervention	ORR	Median PFS	Median OS	Reference
IMpassion130 Randomized 1:1, double-blind, placebo-controlled	902	1st line mTNBC TFI ≥ 12 months Any PD-L1 status	Atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel	ITT 56% versus 46% PD-L1-positive IC 59% versus 43%	ITT 7.2 versus 5.5 months PD-L1-positive IC 7.5 versus 5.0 months	ITT 21.0 versus 18.7 months PD-L1-positive IC 25.4 versus 17.9 months	Schmid *et al.*[69] Miles *et al.*[74]
IMpassion130 Randomized 2:1, double-blind, placebo-controlled	651	1st line mTNBC TFI C mTNBC :1, Any PD-L1 status	Atezolizumab + paclitaxel versus placebo + nab-paclitaxel	PD-L1-positive IC 63.4% versus 55.4% ITT 53.6% versus 47.5%	PD-L1-positive IC 6.0 versus 5.7 months ITT 5.7 versus 5.6 months	PD-L1-positive 28.3 versus 22.1 months I ITT 22.8 versus 19.2 months	Miles *et al.*[74]
KEYNOTE-119 Phase III, randomized 1:1, open-label	622	2nd or 3rd line mTNBC Prior A and T Any PD-L1 status	Pembrolizumab monotherapy versus chemotherapy of physician's choice*	ITT 9.6% versus 10.6% CPS ≥ 1 12.3% versus 9.4% CPS ≥ 10 17.7% versus 9.2% CPS ≥ 20 26.3% versus 11.5%	ITT 2.1 versus 3.3 months CPS ≥ 1 2.1 versus 3.1 months CPS ≥ 10 2.1 versus 3.4 months CPS ≥ 20 3.4 versus 2.4 months	ITT 9.9 versus 10.8 months CPS ≥ 1 10.7 versus 10.2 months CPS 2 months versus 11.6 months CPS ≥ 20 months versus 12.5 months	Oki *et al.*[75]
KEYNOTE-355 Phase III, randomized 2:1, double-blind, placebo-controlled	847	1st line mTNBC TFI C mTNBCrandoany PD-L1	Pembrolizumab + chemotherapy# versus placebo + chemotherapy	NR	ITT 7.5 versus 5.6 months	NR	Cortes *et al.*[76]

A: Anthracycline, CPS: Combined positive score, IC: Immune cell, ITT: Intent-to-treat, mTNBC: metastatic TNBC, NR: Not reported, ORR: Objective response rate, OS: Overall survival, PD-L1: Programmed death-ligand 1, PFS: Progression-free survival, T: Taxane, TFI: Treatment-free interval. *Chemotherapy of physician's choice could be capecitabine, eribulin, or gemcitabine. #Chemotherapy of physician's choice could be paclitaxel, nab-paclitaxel, or gemcitabine + carboplatinum

effect on tumor immune response is worth discussing. Furthermore, more exploratory work needs to be done to determine whether the possible mechanism above potentially defines a more immunogenic tumor. At the same time, we should continue to focus on the heterogeneity of TILs, the subpopulation classification of T cells, and how their respective molecular pathways regulate immunity[44,73].

3.2. Unpredictable personal benefits

For the purpose of selecting patients who are most likely to benefit from immunotherapy and the development of combination treatments to overcome drug resistance, tumor molecular profiling is significant. Through gene expression profiling analysis of TNBC tumor samples, abnormal cell cycle-regulating and DNA repair-related gene expression has been observed in the BL1 subtype[77]. Possible therapeutic drugs for the BL1 subtype include PARP inhibitors and genotoxic agents; BL1 patients are usually sensitive to cisplatin treatment. On the other hand, the BL2 subtype has abnormal activation of signaling pathways, such as the epidermal growth factor receptor (EGFR), mesenchymal epithelial transition factor (MET), nerve growth factor (NGF), Wnt/β-catenin, and insulin-like growth factor-1 receptor (IGF-1R) pathways, and the potential targeted therapeutic drugs include mammalian target of rapamycin (mTOR) inhibitors and growth factor inhibitors (lapatinib, gefitinib, and cetuximab)[64]. Meanwhile, the IM subtype has significantly enriched immune cell-associated genes and signal transduction pathways, such as the Th1/Th2, NK cell, B-cell receptor, dendritic cell (DC), T-cell receptor, interleukin (IL)-12, and IL-7 pathways[78]; thus, the IM subtype is highly similar to medullary carcinoma of the breast. PD1, PDL1, CTLA-4, and other immune checkpoint inhibitors are recommended for the treatment of patients with breast cancer of the IM subtype. The M subtype, on the other hand, has highly activated cell migration-related signaling

pathways (regulated by actin), extracellular matrix-receptor interaction pathways, and differentiation pathways (Wnt pathway, anaplastic lymphoma kinase pathway, and transforming growth factor [TGF]-β signaling). The M subtype has sarcoma-like or squamous epithelial cell-like tissue characteristics and is prone to developing resistance to chemotherapy drugs[79]. Patients with the M subtype may be treated with mTOR inhibitors or drugs that target epithelial-mesenchymal transition[15]. Compared with the M subtype, the MSL subtype shows a lower expression of cell proliferation-related genes but a higher expression of stem cell-related genes, *HOX* genes, and mesenchymal stem cell-specific markers. Presumably, patients with the MSL subtype can be treated with PI3K inhibitors, Src antagonists, and angiogenesis inhibitors[80]. Compared with other TNBC subtypes, the LAR subtype has a significantly different gene expression profile[81]. This subtype does not express ERs, but has highly activated hormone-related signaling pathways (e.g., steroid synthesis, porphyrin metabolism, and androgen/estrogen metabolism). Notably, androgen receptors (ARs) are highly expressed in breast cancers of the LAR subtype, with messenger ribonucleic acid (mRNA) levels nine times higher than in other TNBC subtypes. Immunohistochemistry has also shown that several metabolic markers of AR and its associated activators (24-dehydrocholesterol reductase [DHCR[24]], activated leukocyte cell adhesion molecule [ALCAM], fatty acid synthase [FASN], FK506-binding protein 5 [FKBP[5]], apolipoprotein D [APOD], prolactin-induced protein [PIP], sterile alpha motif pointed domain-containing ETS transcription factor [SPDEF], and claudin-8 [CLDN[8]]) are highly expressed in the LAR subtype. Therefore, anti-AR therapy is recommended for breast cancer patients with the LAR subtype.

Besides, biomarkers that predict the clinical benefit of immunotherapy in TNBC are also required. PD-L1 expression on immune cells and mismatch-repair deficiency are the only two validated biomarkers that are currently available[82,83]. The majority of patients with mTNBC are PD-L1-negative by the presently authorized SP142 test[83], despite the fact that mismatch repair failure is uncommon in breast cancer but more frequent in the early-stage illness[73]. The variability of PD-L1 expression over time and at metastatic sites[84], the discrepancy between PD-L1 assays, particularly when staining immune cells, the observation that some PD-L1-negative patients respond to ICIs[85], and the recent trials in early disease setting that show little to no correlation of PD-L1 expression with benefit specific to ICIs, such as the KEYNOTE522 and NeoTRIPaPDL1 trials, are additional factors that limit the utility of PD-L1[85,86].

Moreover, the IMpassion130 trial has shown a significant, modest improvement in progression-free survival (PFS) but a marked difference in OS[87]. The subgroup of patients with PDL1 > 1% (185/451 patients) benefited from atezolizumab; a trend toward a higher ORR was observed in patients with PD-L1-positive versus PD-L1-negative ICs in the overall population[69]. With the various outcomes from clinical trials, the focus of further research is on identifying more prognostic biomarkers to demonstrate the benefit for each patient receiving immunotherapy (Table 3).

4. Conclusion

TNBC, compared with other BC subtypes, has a poor prognosis and is still a complicated cancer for immunotherapy to be developed thus far. However, to improve the prognosis, immunotherapy techniques must be used. Research efforts should focus on using the ICB we have in relation to the molecular biology of TNBC to discover mono antibody therapies and other more effective drug combinations. For this highly diverse subtype of BC, personalized medicine appears to be of great importance. When deciding on a treatment plan, tumor molecular profiling should be carried out at the time of diagnosis, after each tumor recurrence or progression, and as needed. The functions of a cluster of biomarkers may be crucial to predicting an individual's response to future TNBC immunotherapy.

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Conflict of interest

The authors declare that they have no competing interests.

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