Immune Checkpoint Inhibitors for Triple-Negative Breast Cancer

Yaqi Zhu

Department of Thyroid and Breast Surgery, Peking University First Hospital, Beijing, China

zhuyaqi@pku.org.cn

Abstract. Triple negative breast cancer (TNBC) is still the most serious subtype of breast cancer because of the least favorable prognosis due to the greatest recurrence and mortality rates. In the past decade, with an deeper understanding of tumor biology, it became possible to identify subgroups of patients with molecular characteristics and apply numerous novel targeted therapies. In this aspect, immune checkpoint inhibitors (ICIs) have developed as a promising therapy method for TNBC patients to improve pathologic complete response rate and the outcomes of patients. Nowadays, PD-1/PD-L1 inhibitors are used in the clinic applying for TNBC alone or with other types of therapies. Despite the advances, there are many challenges including optimizing patient selection, reducing resistance and enhancing control of immune-related adverse events. This review includes an overview of current clinical treatment for TNBC and pathways of PD-L1. The ongoing clinical trials, current challenges, and future perspectives about ICI, particularly anti-PD-1/PD-L1 therapy, are briefly discussed to portray their promising prospects.

Keywords: TNBC, ICI, PD-1/PD-L1.

1. Introduction

TNBC is heterogeneous both biologically and clinically. Because of its aggressive behavior and bad prognosis TNBC has long been seen as a key unmet need. Decades of research have resulted in the development of new therapy alternatives, including ICIs. The most common ones are anti-PD-1/PD-L1 agents which are used alone or take advantage with the combination therapy.

The field of immune checkpoint therapy was opened in 2011 when the first ICI, ipilimumab (anti-CTLA4) was approved by the FDA. Subsequently, in 2014 the first PD-1 inhibitors have licensed to treat melanoma. Nowadays, the PD-1/PD-L1 inhibitors are approved for treatment in several tumor types, including TNBC. ICIs have enabled a leap forward in the treatment within the past decade.

Herein, characteristics of TNBC, including epidemiology and different subtype classification, and a comprehensive overview of the current therapeutic strategies is provided. As for ICIs, the downstream of PD-1/PD-L1 and related regulatory mechanism of PD-L1 in TNBC cells are also discussed. Although PD-1/PD-L1 targeting drugs showed potential clinical appliance, most patients with TNBC are not responsive, some patients become resistant to the treatment after initial response and a few patients suffer from immune-related adverse events (irAE). Therefore, further development of ICIs is still necessary for expanding the application. Herein, major challenges, related researches and ongoing clinical trials are also described.

2. Brief Introduction of TNBC

2.1. Epidemiology

Breast cancer (BC) shows a high occurrence worldwide, furthermore, also a great reason of mortality related to cancer, despite numerous advances in early identification and treatment [1]. BC is typically classified according to molecular markers, consisting of ER, PR, and HER2. There are HR+ subtype, HER2+ subtype, and TNBC. TNBC accounts for between 15% and 20% of all BCs [1]. TNBC has a higher risk of early metastatic recurrence and a worse prognosis than other types of BC. More over half of individuals relapse within the first 3 to 5 years of being diagnosed [1]. In

patients with metastasis, the median overall survival (OS) is less than 2 years despite recent breakthroughs in systemic therapy [1].

2.2. Classification

TNBC is a heterogeneous disease biologically and clinically with a poorly understood biology due to a definition according to the absence of molecular features instead of characteristics causing tumor growth. TNBC can be regarded as an umbrella term including multiple subtypes of BC. It is necessary to identify the complex subtypes and biomarkers. Because these features are linked with effective therapeutic strategies and clinical outcomes.

TNBC has been classified into distinct molecular subtypes for over a decade, initially with Lehmann's six subtypes, including two basal-like, a mesenchymal stem-like, an immunomodulatory (IM), a LAR and a MES subtype [1]. Burstein's four subtypes followed, including BLIA, BLIS, MES and LAR [1]. The four-subtype classification was revised to incorporate messenger and long noncoding RNA profiling to describe the IM, MES, LAR, and BLIS subtypes [1]. The IM-subtype was enriched with immune-related signatures including immune cell signaling and tumor-infiltrating lymphocytes (TILs) [1]. In addition, TNBC was clustered into three subtypes by immune metagene information: C1 (LAR), C2 (basal-like with low immune response) and C3 (basal-enriched with high immune response) which shows that immune therapy will probably become an important component of some subtypes combined therapies [1].

2.3. Current treatment

Nonspecific chemotherapy and local-regional therapy, including surgery and radiation, remain important parts of therapy strategies. Due to HR and HER2 negative, endocrine or HER2-targeted drugs are not beneficial for patients with TNBC like other types of BC. However, decades of research have resulted in the development of novel treatment options in the past few years, including ICIs, ADCs, PARP inhibitors and the combination therapies with other agents. According to different stages of tumor, therapy strategies change.

2.3.1 Early triple-negative breast cancer

Regarding neoadjuvant therapy, patients with clinically node-positive and/or tumor greater than 1cm in greatest dimension should be given a taxane- and anthracycline-containing regimen [2]. To increase pathologic complete response (pCR) carboplatin may be offered [2]. For patients with stage II or III TNBC, it was recommended use of pembrolizumab (anti-PD-1) in conjunction with neoadjuvant chemotherapy and adjuvant pembrolizumab administered after surgery [2].

Surgery is an essential part of local-regional therapy including mastectomy, breast-conserving surgery and axillary dissection. For patients with a clinically negative axilla, the standard approach is sentinel node biopsy (SNB) [2]. Axillary lymph node dissection (ALND) should not be performed on patients without sentinel lymph node (SLN) metastases [2]. ALND should be provided to patients with more than two metastatic SLNs or those undergoing mastectomy who have one or two SLN metastases [2]. Patients with residual nodal metastasis after neoadjuvant therapy on SNB generally warrant ALND [2].

Another local-regional therapy is radiation. Whole breast irradiation after breast conserving surgery is still the recommended therapy for best outcomes [2]. Also, the patients suffering triple-negative positive nodes are suggested receiving postmastectomy radiotherapy (PMRT) to the chest wall and regional lymph nodes [2]. Additionally, patients with axillary nodal involvement after neoadjuvant therapy should receive PMRT [2].

Regarding adjuvant treatment, alkylator-, taxane- and anthracycline-based chemotherapy is considered the optimal strategy for many patients [2]. Patients with residual invasive cancer after standard neoadjuvant therapy should be offered adjuvant capecitabine [2].

2.3.2 Advanced triple-negative breast cancer

Advanced breast cancer (ABC) includes both unresectable locally advanced BC and metastatic BC. For most patients with ABC systemic treatment is dominating. Either combination or sequential, single-agent chemotherapies are reasonable alternatives [3]. First-line chemotherapy for TNBC is typically taxane- or anthracycline-based regimens, preferably as single drugs [3]. In patients with previous anthracycline treatment, carboplatin is an important treatment option [3]. Atezolizumab and nab-paclitaxel combination is a first-line treatment option for PD-L1-positive TNBC [3]. As for the patients suffering TNBC with BRCA mutation, a preferred therapy choice is a PARP inhibitor [3].

3. Immune checkpoint inhibitors

Immune checkpoints are cell-surface proteins that regulate the onset, duration, and degree of immune responses [4]. An important aspect is in the maintenance of self-tolerance which is required during immune responses to protect normal tissues [4]. However, tumors can elude the immune system by subverting immune checkpoints, which is one of traits required for cancer process [4]. ICI, mainly antibodies against these checkpoints, can inhibit this suppressive immune environment of tumors to activate the immune cells allowing the T cells or NK cells to kill cancer cells. CTLA4 and PD-1 are two most clinically relevant checkpoints and LAG-3 is the latest one approved by FDA to be targeted in the clinic. In addition, many immune checkpoints are under investigation, such as TIM-3 and B7-H3.

3.1. Mechanism

Different ICIs have distinct functional mechanisms. PD-1/PD-L1 inhibitors are the most common ICIs used for patients with TNBC. Within the context of cancer cells, the interaction between PD-L1 and PD-1 reduces T-cell repertoire expansion, suppresses cytokine production, as well as activates cell intrinsic tolerogenic signals in order to avoid immune response and provide a means of escape [5].

Particularly, PD-L1 on tumor cells binding to PD-1 on activated B and T cells inhibits immune response. Firstly, immune cells enter solid tumors, where antigen presenting cells (APCs) phagocytose tumor-specific antigens. Then these APCs activate tumor-specific cytotoxic T cells (CTLs) which undergo proliferation and PD-1 upregulation in lymph nodes. Next, after CTLs migrating and infiltrating the tumor microenvironment (TME), antigen-specific tumor cells are targeted and CTLs release interferon-gamma (IFN-γ), perforins and granzymes to kill tumor cells. However, tumor-derived PD-L1 engages PD-1 on CTLs via the cell surface and exosomes to inhibit T-cell activity, activate T-cell death, suppress production of pro-inflammatory cytokine, cause antigen tolerance and promote the anti-apoptotic gene expression in tumor cells [5]. Therefore, ICIs could reduce the immune escaping by impeding the PD-1/PD-L1 axis.

The major PD-L1 cascade regulating in TNBC cells are showed in Fig.1. IFN-I and IFN-II signaling pathways are important in regulation of PD-L1 expression. Interferons signal leading to STAT transcription factors recruited and phosphorylated through JAK1 and JAK2 membrane associated kinases. IRF1 expression regulating PD-L1 gene is induced by phosphorylated STAT dimers translocating to the nucleus [5]. For example, exposure to IFN-γ induces an increasing level of PD-L1.

Moreover, PD-L1 upregulation shows a complicated signal conducting cascade. In a part of basal phenotype TNBCs, PD-L1 gene on chromosome 9p24.1 amplified and the amplicon usually covers JAK2 genes, which enhance dynamic PD-L1 expression [5]. Additionally, PTEN loss increases levels of PI3K/AKT activity which upregulates PD-L1 expression and this regulation is transcriptional [5]. Syntenin1, a key oncogene in melanoma, also induces PD-L1 expression through STAT3 activation in TNBC cells, which significantly increased phosphorylated STAT3 [5].

In addition, various proteins also impact PD-L1 expression. There is a positive association between Epidermal growth factor receptor (EGFR) and PD-L1 through AKT and STAT3 downstream

signaling pathways [5]. Nucleophosmin, commonly called NPM1, is a protein that is essential for many cellular processes and can bind to the PD-L1 promoter increasing PD-L1 expression [7]. RBMS1 is a RNA binding protein frequently existing in immune-cold TNBC, which controls B4GALT1 mRNA stability to mediate PD-L1 glycosylation for reducing PD-L1 protein degradation [7]. MUC1, a transmembrane mucin, drives PD-L1 transcription through MYC and NF-κB p65 occupying the PD-L1 promoter in basal B TNBC cells [5].

In TNBC cells with stem cell characteristics, Wnt signaling pathway, an important signaling pathway involved in multiple cellular functions, upregulated PD-L1 expression [5]. Additionally, CD44, a membrane receptor and cancer stem cell marker, undergoes cleavage releasing an intracellular domain which translocates into nucleus and functions by binding to the DNA sequence to activate PD-L1 expression [8].

Furthermore, the depletion of ALIX which is necessary for transport component, causes decreased exosomal and raised surface PD-L1 expression through the multivesicular body (MVB) [5]. In basal-like breast cancer cells ALIX is also an EGFR inhibitor which regulate PD-L1 expression [5]. All of these pathways modulate immunosuppression by regulating PD-L1 expression.

Finally, some drugs upregulate PD-L1 expression as well. For instance, PARP inhibitors inactivate GSK3β which binds to, phosphorylates and destabilizes PD-L1 [5]. PARP inhibitors also promote PD-L1 expression by decreasing NPM1 and PARP1 connection to enhance NPM1-PD-L1 promoter association in human TNBC cells [6].

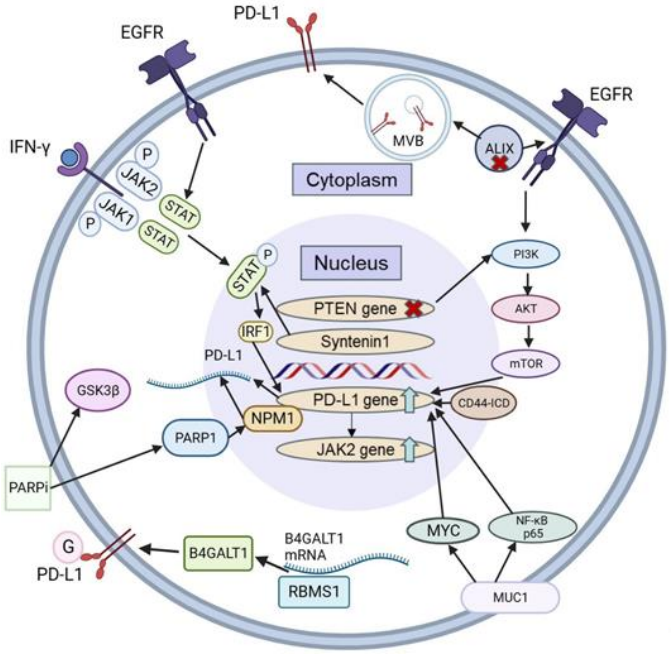

Figure 1. The regulatory pathway of PD-L1 expression in TNBC cells

4. The interaction between TNBC and ICI

Since the 1980s breast cancer has historically been regarded as an “immune cold” or “immune inert” type with fewer neoantigens and infiltrating immune cells than other solid tumors. However, breast cancer subtypes are immensely heterogeneous, which has been proven by decades of research. Because TNBC is more immunogenic than other subtypes, patients have derived most benefits from immunotherapy [9]. Thus, the immune infiltration and immunotherapy of TNBC have received a lot of attention in the last decade. Within TNBC, tumors with high TIL concentrations are considered “immune hot” or “immune enriched” [9]. The level of TILs acts as a marker for tumor endogenous immune response. Therefore, parts of patients with potentially immunologically active tumors and therapies targeting at activating or reinvigorating immune cells are beneficial, such as ICIs.

4.1. Clinical trials

ICIs targeting PD-1 and PD-L1 have been applied in clinic for breast cancer, especially TNBC, such as Atezolizumab and Pembrolizumab. Meanwhile, a vast number of clinical studies have been ongoing [10]. There are greater than 100 registered studies focused on anti-PD-1/PD-L1 related therapies for TNBC. Some of them are summarized in Table 1 and 2.

Table 1. An overview of ongoing clinical trials focused on anti-PD-1

Drug	Trial	Phase	Type of Tumer	Comments
Balstilimab	NCT05318469	I/II	PD-L1 negative metastatic TNBC	with ivermectin
Camrelizumab	NeoCAT	II	Early-stage TNBC with a high proportion of TILs	with Apatinib (a VEGFR2 TKI)
Camrelizumab	NCT05088057	II	Stage II or III TNBC	with chemotherapy
Carilizumab	NCT04537286	II	Metastatic TNBC	with nab-paclitaxel and cisplatin
Cemiplimab	NCT04243616	II	High risk or locally advanced TNBC	with chemotherapy
Cemiplimab	NCT04916002	II	Advanced TNBC	with intratumoral Vidutolimod (CMP-001)
HLX10	NCT04301739	III	Resectable TNBC	with chemotherapy
JS001	NCT03251313	I	Advanced TNBC	with gemcitabine and cisplatin
Nivolumab	NCT03414684	II	Metastatic TNBC	with carboplatin
Pembrolizumab	NCT03012230	I	Advanced TNBC	with JAK2 inhibition
Pembrolizumab	LEAP-005	II	Previously treated TNBC	with lenvatinib
Pembrolizumab	NCT02411656	II	Metastatic or recurrent TNBC which has achieved stable disease or clinical response to prior chemotherapy	Alone
Pembrolizumab	Saci-IO TNBC	II	PD-L1-negative metastatic TNBC	with sacituzumab govitecan
Pembrolizumab	NCT05539365	II	Advanced TNBC	with dendritic cell-based treatment
Pembrolizumab	KEYNOTE-355	III	Advanced TNBC	with chemotherapy
Pembrolizumab	KEYNOTE-522	III	Locally advanced non-metastatic TNBC	Alone or with chemotherapy
Sintilimab	NeoPD1TNBC	II	Stage I-III TNBC	with chemotherapy
Tislelizumab and Spartalizumab	ACROPOLI	II	PD1-high mRNA expressing TNBC	Alone
Tislelizumab	AdvanTIG-211	II	Advanced TNBC	with Ociperlimab (anti-TIGIT) and chemotherapy

Table 2. An overview of ongoing clinical trials focused on anti-PD-L1

Drug	Trial	Phase	Type of Tumer	Comments
Atezolizumab	NCT02530489	II	Early-stage TNBC	with nab-paclitaxel
Atezolizumab	ALICE	II	Metastatic TNBC	with immunogenic chemotherapy
Atezolizumab	NCT03206203	II	Advanced TNBC	with carboplatin
Atezolizumab	IMpassion030	III	Resectable TNBC	with adjuvant anthracycline/ taxane-based chemotherapy
Atezolizumab	NeoTRIPaPDL1	III	Early-stage high-risk and locally advanced TNBC	with carboplatin and nab-paclitaxel
Atezolizumab	NSABP B-59	III	High risk TNBC	with chemotherapy
Avelumab	PAveMenT	I	Androgen receptor positive metastatic TNBC	with Palbociclib
Avelumab	A-Brave	III	High-risk TNBC	Alone
Bintrafusp Alfa	NCT04789668	I/II	Brain Metastases	with pimasertib, Bintrafusp Alfa (anti-PD-L1 and TGF-beta)
Durvalumab	NCT02826434	I	Stage II or III TNBC	with PVX-410 Vaccine
Durvalumab	B-IMMUNE	I/II	Locally advanced TNBC	with a dose-dense EC regimen
FAZ053	NCT02936102	I	Advanced TNBC	Alone or with PDR001 (Anti-PD-1)
NM21-1480	NCT04442126	I/II	Advanced TNBC	NM21-1480 (anti-PDL-1/anti-4-1BB/anti-HSA tri-specific antibody)

Because the majority of TNBC patients have resistance to anti-PD-1/PD-L1 monotherapy. Except several trials, the majority is focused on the combination of ICI and other drugs. Conventional chemotherapeutic drugs, including taxane, cyclophosphamide, and cisplatin are used frequently, which can promote tumor antigen release, provide a favorable tumor immune microenvironment and improve antitumor response [11]. It was also revealed that PARP inhibitors boosted PD-L1 expression, whereas PD-L1 blockade sensitized cells to PARP inhibitors, indicating that PD-L1 blockage in combination with PARP inhibitor increased therapeutic efficacy [11]. There are several trials testing the addition of niraparib, olaparib or talazoparib to PD-1/PD-L1 inhibitors in TNBC patients. Aside from the combination of PARP inhibitors with immunotherapy, a number of trials of ICI combined with other novel medicines have entered clinical studies. Sacituzumab govitecan, for instance, is the ADC for relapsed refractory metastatic TNBC patients who have been treated at least twice, and a clinical trial (Saci-IO TNBC) evaluating its combination with pembrolizumab is ongoing.

In conclusion, there are many different clinical studies focused on various therapies combined with ICIs, including molecular target therapies (such as multi-TKIs, the CDK4/6 inhibitor, the MAP kinase 1/2 inhibitor and the JAK2 inhibitor), immunotherapies (such as oncolytic virus, immune cell-based treatment and tumor-associated vaccines), anti-angiogenic agents (such as Apatinib), radiotherapy and even the antiparasitic agent with demonstrated antiviral activity.

Although pembrolizumab and atezolizumab are the two most commonly used ICIs for TNBC patients, alternative PD-1/PD-L1 inhibitors have also been explored. For instance, camrelizumab, HLX10, JS001 and avelumab have already been tested in phase III trials, and nivolumab and spartalizumab in phase II trials. Because of the current insufficient immune response to PD-1/PD-L1 targeting, other targets have been explored, even double targets for ICB, such as Ociperlimab (anti-TIGIT) plus Tislelizumab (anti-PD-1).

The research on bispecific antibodies (BsAb), engineered recombinant proteins targeting two specific antigens, has progressed enormously. Bintrafusp alfa, a bifunctional fusion protein, captures TGF-β and blocks PD-L1. More related clinical studies are ongoing. Additionally, several BsAbs targeting PD-L1 and CTLA4 were developed for TNBC treatment, including KN046, XmAb20717, and SI-B003. The BsAbs MGD013 and GEN1046 both targeting PD-L1 and LAG-3 are also being explored in the clinic. Furthermore, a phase I trial of NM21-1480, a tri-specific antibody consisting of anti-PDL-1, anti-4-1BB and anti-HAS, is ongoing as well.

4.2. Limitations and future perspectives

Although ICIs offer the possibility of improving outcomes, there are still some limitations of ICI about predictive biomarkers, resistance and immune-related adverse events (irAEs). Firstly, one of the major challenges is lacking suitable predictive biomarkers for selecting patients. Biomarkers have traditionally concentrated on tumor features or single markers. With increasing researches on antitumor immunity, it has been realized that single biomarkers are inadequate and strategies capturing features of the host and tumor immune ecosystem are required [12]. PD-L1 expression evaluated by IHC is commonly used to select patients applying anti–PD-1/PD-L1 therapy. However, in some cases, patients who have tumors with high PD-L1 expression do not respond to ICIs and patients benefit from ICIs with negative or low PD-L1 expression tumor, that emphasizes the challenge in utilizing PD-L1 as a single biomarker [12]. There are also other predictive biomarkers such as Tumor mutational burden (TMB) and the proportion or abundance of TILs. However, none of these biomarkers are accurate enough to be implemented in the clinic and novel ones are still necessary. It was recently demonstrated that ARID1A mutations in tumor tissues and chemokine CXCL13 expression associate with response to anti-PD-1/PD-L1 drugs, with increased ability to predict compared to either biomarker alone [12].

Secondly, ICIs continue to be restricted to specific tumor types and disease situations. Within TNBC, long-lasting and potent responses have been confined to a subset of individuals, with several patients showing primary resistance. Furthermore, patients who initially respond well to ICIs may develop resistance with time. Thus, it is important to improve clinical benefit for a greater number of patients. New drugs and sensible combination therapies are required, based on an accurate understanding of each drug's mechanism and effects on immune responses. TME is one of factors which are critical to response and resistance to ICIs. A study created a platform delivering TLR-7 and TLR-3 agonists at the same time to take advantage of the distinct signaling pathways, transforming the TME of TNBC to a "hot" state and synergistic antitumor efficacy was obtained in combination with anti-PD1 antibody therapy [13]. In addition, innate immune responses in enhancing overall antitumor immunity gain growing interest. The agonism of STING is one of systemic methods to stimulate innate immunity [12]. In BRCA1-deficient TNBC immunocompetent models, inhibitors of polymerase theta (POLθ) led to increased micronuclei, activation of cGAS/STING pathway, IFN-I gene expression, the infiltration and activation of CD8 T cell and PD-L1 expression to augment antitumor effects with anti-PD-1 therapy [14]. Collectively, these researches are helpful for designing clinical trials of which the results may guide rational combinatorial strategies in the future.

Finally, limitations are about irAEs, toxicities resulting from disruption of immune-checkpoint signaling, which differ from the predicted adverse effects of traditional cancer therapies. As combination strategies are pursued, the risk of development of irAEs is increasing. IrAEs can range in severity from mild to deadly and any organ can be affected, most frequently skin, gastrointestinal tract, and endocrine system. To avoid severe events, it is vital to recognize and treat irAEs early. Many biomarkers for earlier predictions of irAEs need to be developed, including blood-based biomarkers and technology-based approaches with patient symptom reporting [12]. The treatment of irAEs such as using immunosuppressive drugs will be critical for patients to continue on ICI therapy. The gut microbiome is one of factors which can influence whether irAEs are likely to accompany ICI treatment. Manipulation of the gut microbiome remains in early stage of exploration, including

antibiotic treatment, microbiota transplantation, or diet, which may be used as an additional method to reduce irAEs as well as enhance responses to ICIs [12].

5. Summary

TNBC is still the most challenging subtype of breast cancer with poorer outcomes than HR and/or HER2 positive BC. Because it has aggressive behavior and no benefit from endocrine or HER2-targeted therapy. However, in the past few years, important advances in understanding its biology and in therapy development have achieved the adoption of various therapeutics. ICIs, especially anti-PD-1/PD-L1 agents, are changing the therapeutic protocol in both early and advanced stage settings. Nevertheless, challenges and opportunities remain including providing optimal predictive biomarkers, increasing response and reducing irAEs. The researches on limitations of ICI are rapidly evolving which are discussed in this review and this study area requires further development to optimize the therapeutic benefits. With discovering novel predictive biomarkers and reasonable combinations it will be more accurate to apply effective therapies and predict prognosis of patients. More and more patients with TNBC will benefit from PD-1/PD-L1 inhibitors by combination with new therapies which can address primary and adaptive resistance issues. If the problem of irAEs is solved by more developments, ICIs will not be withheld in patients with severe side effects. It is conceivable that the future of immune checkpoint therapy is promising and ICIs with other drugs specific for each TNBC subtype will be significant for personalizing treatments in order to maximize therapeutic benefit.

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