

# Role of Immune Checkpoints (PD-1, PDL1 and CTLA-4) In Triple-Negative Breast Cancer and Therapeutic Implications

## ABSTRACT

Triple-negative breast cancer (TNBC) is one of the most prominent types of breast cancers. It is a very aggressive subtype that is characterized by the absence of certain receptors which are expected on the surface of such cells. This paper reviews the role of immune checkpoints in TNBC. It gives a focus on the probable system of immune evasion by tumor cells and their prognostic implications. It also provides a simple overview of the current state of immune checkpoint inhibitors (ICIs) as monotherapies, including anti-PD-1/PD-L1 (e.g., pembrolizumab, atezolizumab) and anti-CTLA-4 (e.g., ipilimumab) therapies, as well as their limitations in breast cancer treatment. This review is based on an extensive analysis of relevant scientific literature obtained from reputable peer-reviewed journals, databases, and reports. It synthesizes current knowledge on the role of immune checkpoints in TNBC, including their mechanistic involvement in immune suppression and prognostic implications. Recent advances in cancer immunotherapy have highlighted the potential of targeting immune checkpoints, such as PD-1/PD-L1 and CTLA-4, to overcome immune evasion in TNBC. These immune checkpoints play pivotal roles in shaping the tumor microenvironment (TME) by suppressing T-cell activation and promoting tumor immune tolerance. Combination therapies involving ICIs with chemotherapy, radiotherapy, or other immunomodulatory approaches are also examined, highlighting their synergistic potential. Furthermore, emerging therapeutic strategies, including dual checkpoint blockade, modulation of the TME, and neoantigen-based immunotherapies, are proposed as innovative avenues for enhancing immune response and overcoming resistance to current treatments. By elucidating the intricate interplay between TNBC, its immunosuppressive TME, and immune checkpoints, this emphasizes the need for continued research to refine existing therapies and develop novel approaches that leverage immune modulation, ultimately aiming to improve clinical outcomes for triple-negative breast cancer patients.

## 1. INTRODUCTION

Breast cancer is a heterogeneous type of malignancy that develops in the epithelial cells of the mammary glands. Many studies classify it as one of the deadliest and most common cancers globally. Just like other types of cancers so far, the direct cause is still largely unknown (Gupta and Smith-Graziani, 2024). However, there are some risk factors for breast cancers that are recorded. They include: genetic mutations (e.g., BRCA1/2), hormonal influences, age, and some lifestyle factors (Almansour, 2022; Orrantia-Borunda et al., 2022). Clinically, breast cancer is often categorized into various subtypes based on molecular characteristics. One of such criteria is hormone receptor status and epidermal growth factor receptor 2 – expression pattern. So far, early detection has been made possible through mammography and tissue biopsy. There have also been advancements in targeted therapies and immunotherapy (Almansour, 2022; Gupta and Smith-Graziani, 2024). All these have significantly improved prognosis and survival rates which can help patients with the condition. Although there are still challenges in treatment and limitations that need to be addressed (Almansour, 2022; Orrantia-Borunda et al., 2022).

The prominence and aggressiveness of triple-negative breast cancer is well documented in relevant studies. It is characterized by the absence of some key hormone receptors like estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression on the surface of tumor cells (Howard and Olopade, 2021). To add to that, there is a distinct molecular profile in triple-negative tumor cells. Which may be responsible for undermining the effect of targeted therapies like hormone therapy or human epidermal growth factor receptor 2-directed agents. This makes it difficult for the disease to be treated, given that there is absence of receptors for implicative binding.

According to Almansour (2022), triple-negative breast cancer may account for approximately 15–20% of all breast cancer cases and can disproportionately affect younger women and women of African descent. Notably, affected women are commonly found with BRCA1 mutations (Almansour 2022; Gupta et al., 2024). Clinically, triple-negative breast cancer presents a unique set of challenges due to its rapid progression. In this condition there is early recurrence, and high tumour metastatic potential. Unlike other breast cancer subtypes, the lack of specific therapeutic targets forces reliance on majorly systemic chemotherapy, which often yields suboptimal outcomes. In terms of the survival rate, Obidiro et al., (2023) reported that patients with TNBC frequently experience a shorter disease-free survival period and worse overall survival compared to other breast cancer subtypes (Howard and Olopade, 2021; Obidiro et al., 2023). The heterogeneity within Triple-negative breast cancer which further complicates treatment strategies have been linked with the presence of multiple molecular subtypes, each with distinct biological behaviours. All these factors underscore the urgent need for novel therapeutic approaches that can address the unmet needs of this aggressive malignancy (Schmid et al., 2022; Obidiro et al., 2023).

Recent advances in cancer immunotherapy have revealed dynamic potential of harnessing the immune system to combat malignant tumours like breast cancer (Ajutor et al., 2024). Immune modulation, particularly through the inhibition of immune checkpoints, is a critical aspect seen in treatment paradigms for multiple tumour types (Howard and Olopade, 2021). Immune checkpoints are crucial in these mechanisms as they regulate pathways that maintain immune homeostasis. These molecules majorly promote the downregulation of immune response preventing excessive immune activation where needed. However, cancer cells exploit these pathways to evade immune detection and destruction. Among these immune checkpoints, programmed death-1 (PD-1), its ligand (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are the most studied. Implicatively, these checkpoints may be critical mediators of immune escape in triple-negative breast cancer (Cirqueira et al., 2021; Badve et al., 2022). The immune microenvironment of TNBC is characterized by a complex interplay between tumor-infiltrating lymphocytes (TILs), and myeloid-derived suppressor cells. Other immune components are also involved. Collectively, these factors make it a promising target for immunotherapy (Gupta et al., 2024).

Studying immune checkpoints in triple-negative breast cancer not only enhances our understanding of the tumor's biology but also it would pave the way for the development of innovative therapeutic strategies. Reports have shown a high expression of PD-L1 in 20–50% of TNBC cases and correlates with an inflamed immune microenvironment, suggesting that TNBC might be particularly amenable to immune checkpoint blockade (Carter et al., 2021). This further justifies our submission on the role of immune checkpoints in the development of tumours as emphasized earlier. Furthermore, immune checkpoint inhibitors (ICIs), such as anti-PD-1 and anti-PD-L1 antibodies, have already demonstrated clinical effectiveness in some cancer patients. This then highlights the translational significance of this research (Howard and Olopade, 2021).

This study on immune checkpoints in cancer is implicative for bridging existing knowledge gaps and exploring how immune checkpoint pathways are harnessed by tumour cells to evade immune reactions. And how immune checkpoint inhibitors may be exploited for therapeutic gain in the growing global burden of triple-negative breast cancer. Furthermore, continuous studies will shed more light on these pathways to help clinicians identify possible predictive biomarkers to improve patient stratification. It would also help to develop combination therapies that synergize with immune-based approaches. In light of the persistent challenges posed by TNBC and the promise of immunotherapy, this review aims to provide a comprehensive analysis of the role of PD-1, PD-L1, and CTLA-4 in TNBC and their therapeutic implications.

## **2. TRIPLE NEGATIVE BREAST CANCER (TNBC)**

Triple-negative breast cancer is a widely known tumour type that is significantly more challenging to treat compared to other breast cancer subtypes. As we have stated earlier TNBC accounts for a significant amount of breast cancer diagnoses globally, making it a critical area of focus in oncology research (Sung et al., 2021). Unlike hormone receptor-positive or HER2-positive breast cancers, TNBC may be classified as a "basal-like" subtype in the majority of cases. This is largely due to its molecular profiling. Huang et al. (2024) agreed with the classification of six distinct subtypes within the TNBC class. Basal-like 1, Basal-like 2, mesenchymal, mesenchymal stem-like, immunomodulatory, and luminal androgen receptor are the subtypes that have been identified. In the present, studies also suggest that each subtype can have varying biological behaviors and therapeutic responses. These classifications highlight the molecular heterogeneity of TNBC (Bando et al., 2021; Huang et al. 2024).

This may explain why the condition poses significant challenges for developing universal treatment strategies (Zagami and Carey, 2022).

TNBC has been distinguished by its aggressive clinical course and unique biological characteristics. It is more likely to occur in younger women, those with BRCA1 gene mutations, and certain ethnic or racial groups. In particular, women of African or Hispanic descent have reported more diagnosed cases. In addition to this, the aggressive nature of TNBC often results in early onset of metastasis, particularly to visceral organs such as the lungs and liver, as well as the central nervous system (Carter et al., 2021; Badve et al., 2022).

Another defining feature of TNBC is its immunogenicity. This may be seen by the frequent presence of tumor-infiltrating lymphocytes (TILs) in TNBC condition. Sukumar et al. (2021) and Bando et al. (2021) noted that TILs are not only a hallmark of the tumor microenvironment in TNBC but also a potential prognostic biomarker, with higher levels associated with better outcomes in early-stage disease. This characteristic positions TNBC as a promising candidate for immunotherapeutic approaches, despite its other challenges (Bando et al. 2021; Orrantia-Borunda et al., 2022).

Histologically TNBC is diagnosed by immunohistochemistry (IHC). However, triple-negative phenotype shows significant overlap with the basal-like molecular subtype of breast cancer (Sukumar et al., 2021; Orrantia-Borunda et al., 2022). Basal-like breast cancers are most commonly triple-negative, leading to a misconception that these two terms are synonymous. However, 70–80% of TNBC are basal-like, while about 70% of basal-like tumors are triple-negative. Recently, a TNBC subgroup lacking basal markers was identified (Zagami and Carey, 2022). These tumors are enriched for stem cell and epithelial–mesenchymal transition (EMT) markers and belong to the so-called claudin-low molecular subtype found in some studies. These findings highlight the heterogeneous nature of TNBC (Sukumar et al., 2021).

Globally, TNBC is a major contributor to breast cancer as well as general tumormorbidity and mortality. Reports from the GLOBOCAN 2020 database estimate that breast cancer is the most diagnosed malignancy worldwide, with TNBC representing a disproportionately high percentage of breast cancer-related deaths (Sung et al., 2021). This high mortality rate in this subtype of cancer may be attributed to its aggressive nature, rapid progression, and the lack of highly effective targeted therapies (Sung et al., 2021).

From study reports, there has been demonstrations that TNBC may be associated with poorer survival outcomes compared to other subtypes. A meta-analysis found that the five-year survival rate for TNBC may be up to 62%, significantly lower than the 85% survival rate observed in hormone receptor-positive breast cancers (Sukumar et al., 2021). Although these numbers depend on the stage at diagnosis. Additionally, the recurrence rate for TNBC peaks within the first three years following diagnosis, emphasizing the urgency for effective therapeutic interventions (Beaubrun-Renard et al., 2022).

The presence of metastases, and individual patient factors such as genetic predisposition and immune profile can also affect survival rate. Early-stage TNBC has a relatively favorable prognosis when treated with standard chemotherapy, with a complete pathological response (pCR) being a strong predictor of long-term survival. However, advanced-stage TNBC remains highly fatal, with median survival rates often not exceeding one year (He et al., 2021; Battogtokh et al., 2024).

A notable disparity in TNBC outcomes is observed across different populations. For instance, Black women in the United States have a 28% higher mortality rate from TNBC compared to White women, even after adjusting for socioeconomic and healthcare access factors. These findings underscore the need for equitable healthcare solutions and targeted research to address these disparities (He et al., 2021; Battogtokh et al., 2024).

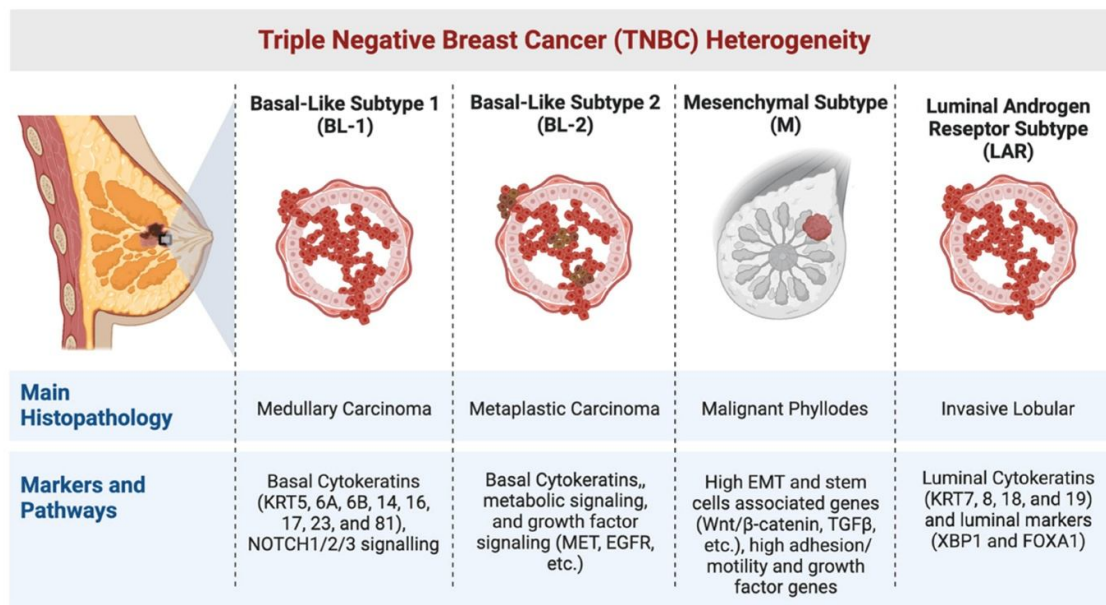


Figure 1: Triple-negative breast cancer heterogeneity, showing TNBC subtype's main histopathology, markers, and signalling pathways of some TNBC subtypes (Lehmann et al., 2021)

### 3. IMMUNE CHECKPOINTS IN TRIPLE-NEGATIVE BREAST CANCER

Immune checkpoints are certain regulatory molecules expressed on immune cells that play a critical role in maintaining immune homeostasis by preventing excessive immune activation. These checkpoints are essential for self-tolerance and they function to protect normal tissues from autoimmune damage (Chen et al., 2022). However, tumours exploit these pathways to evade immune surveillance, creating an immunosuppressive environment that is favourable for continuous oncogenesis and metastasis (Thomas et al., 2021).

The mechanism of this immune evasion is that tumours produce excess amount of immune checkpoint proteins which inhibit T-cell attacks (Chen et al., 2022). The most studied immune checkpoints in cancer are programmed death-1 (PD-1) together with its ligand PD-L1, as well as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). These pathways are central to immune regulation and have been effectively targeted in several cancers, including triple-negative breast cancer (TNBC). Immune checkpoint pathways have emerged as critical regulators of antitumor immunity, and their inhibition can unleash potent immune responses against tumors (Chen et al., 2022; Fang et al., 2025).

#### 3.1 PD-1 and PD-L1 Structure and Signaling Pathway

Programmed death-1 (PD-1) is an inhibitory receptor expressed primarily on immune cells. It has been found to be expressed on activated immune cells. T cells, B cells, and NK cells all have PD-1 on their surface. It is made up of 288 amino acids that are encoded by *Pdcd1* gene. It is a transmembrane protein with three components: an intracellular portion, a transmembrane region, and an extracellular portion that is represented by the IgV domain. It binds with two transmembrane glycoproteins, PD-L1 and PD-L2, have IgV and IgC domains that contain 40% amino acid similarity. Its primary ligand, PD-L1, is expressed on various cell types, including tumor cells, antigen-presenting cells (APCs), and some stromal cells (Chen et al., 2022). Structurally, PD-1 contains an immunoreceptor tyrosine-based inhibitory motif which is a sequential protein that regulates cell activation and an immunoreceptor tyrosine-based switch motif in its cytoplasmic tail, which are critical for signal transduction (Wu et al., 2021; Yin et al., 2025).

The binding of PD-L1 which is on surface of immune cells to PD-1, which is its ligand on receptor cells results in the recruitment of phosphatases such as SHP-2, which then dephosphorylate key signalling molecules that are involved in the T-cell receptor (TCR) and CD28 pathways. The result leads to reduced T-cell proliferation, reduced cytokine production, and inhibited cytotoxic function. As

described by Yang et al., (2025), the PD-1/PD-L1 pathway acts as a molecular brake on immune activation, ensuring that T-cell responses do not cause excessive tissue damage (Gosh et al., 2021, Yang et al., 2025).

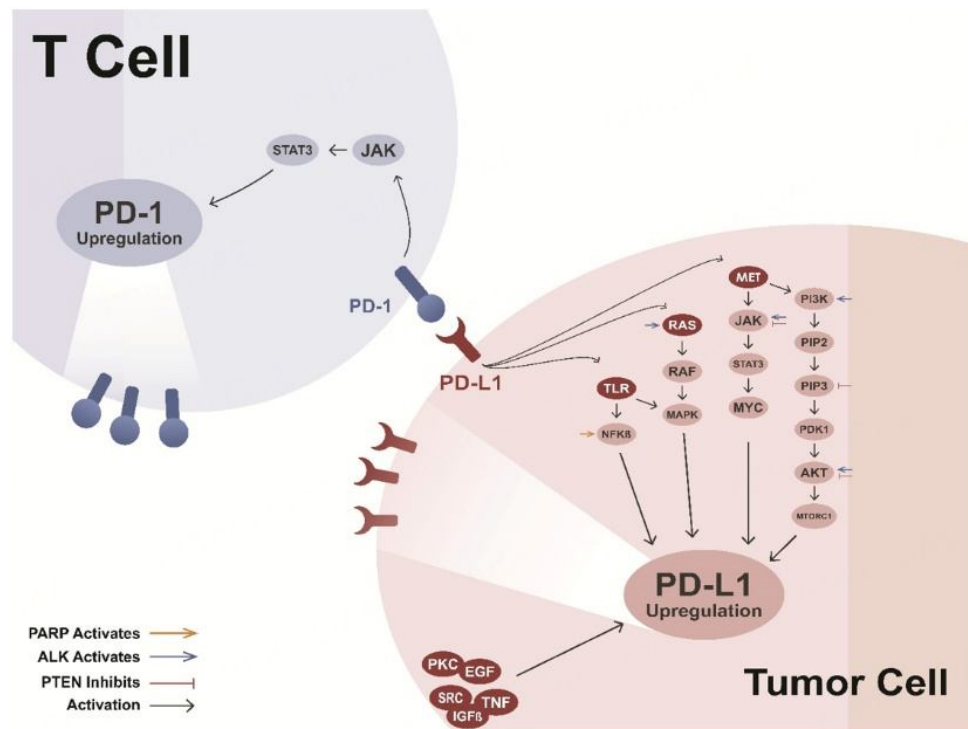


Figure 2: PD-1 and PD-L1 on immune cell (T-cell) and tumor cell respectively with pathway concerning other signalling mechanisms (Sabaghian et al., 2024).

### 3.1.1 Role in Immune Evasion in TNBC

In TNBC, PD-L1 is often overexpressed on tumor cells and tumor-associated immune cells. This may create an immunosuppressive microenvironment. This overexpression is driven by intrinsic oncogenic pathways such as the PI3K/AKT/mTOR and JAK/STAT pathways, as well as extrinsic factors like IFN- $\gamma$  secretion by immune cells. Yazdanpanah et al. (2021) reported that a higher amount (approximately 20–50%) of TNBC tumors exhibit high PD-L1 expression, which correlates with the suppression of cytotoxic T-cell activity. This may explain one of the reasons for the poor immune system activation against tumor cells (Chen et al., 2022; Parvez et al., 2023). The inference to this is that, the higher the PD-L1 ligand (as deceptively produced by cancer cells) the greater the immune suppression.

By engaging the PD-1 receptor on T cells, PD-L1 inhibits the ability of these immune cells to recognize and destroy tumor cells, facilitating immune evasion. This mechanism is particularly relevant in TNBC, where the immunogenic nature of the tumor would have elicited robust antitumor immunity (Zagami and Carey, 2022).

### 3.1.2 Role in cancer therapy

PD-L1 expression in TNBC has been shown to correlate with clinical outcomes, although we have found in reviews that the relationship is complex and context-dependent. Some studies suggest that high PD-L1 expression is associated with better prognosis due to its correlation with an inflamed tumour microenvironment and the presence of tumour-infiltrating lymphocytes (TILs). For instance, Adams et al. (2019) noted, that the presence of PD-L1-positive TILs is a marker of an active immune response and predicts improved survival in early-stage TNBC (Liu et al., 2022; Ye et al., 2024). Conversely, major studies have linked PD-L1 overexpression to worse outcomes, particularly in advanced or metastatic TNBC, where immune evasion is more pronounced. In these cases, PD-L1 expression may indicate a highly immunosuppressive tumour environment, which limits the effectiveness of innate antitumor immunity. Schmid et al. (2020) highlighted this duality, stating that

while PD-L1 expression is a marker of immune activation, it also signifies a mechanism of immune resistance that can be targeted therapeutically (Schmid et al. 2020; Zagami and Carey, 2022). The therapeutic relevance of the PD-1/PD-L1 axis in TNBC has been confirmed by clinical trials of immune checkpoint inhibitors (ICIs). For example, the IMpassion130 trial demonstrated that atezolizumab (anti-PD-L1) combined with nab-paclitaxel significantly improved progression-free survival in PD-L1-positive metastatic TNBC patients (Miles et al., 2021; Sabaghian et al., 2024).

### **3.2 CTLA-4 in Triple-Negative Breast Cancer (TNBC)**

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is an immune checkpoint receptor expressed primarily on activated T cells and regulatory T cells (Tregs). CTLA-4 competes with the costimulatory receptor CD28 for binding to B7 molecules (CD80/CD86) on antigen-presenting cells (APCs). But unlike CD28, which promotes T-cell activation, CTLA-4 transmits inhibitory signals that dampen T-cell responses (Navarrete-Bernal et al., 2020).

#### **3.2.1 Mechanism of inhibitory effect of CTLA-4**

The inhibitory effects of CTLA-4 occur at two levels. Firstly, it blocks T-cell Activation. CTLA-4 outcompetes CD28 for B7 binding sites on t-cells due to its higher affinity, which then prevents the costimulatory signaling required for T-cell activation.

We may term the second level as a further recruitment of immunosuppressive mechanisms. Here, CTLA-4 enhances the function of Tregs, which secrete immunosuppressive cytokines like TGF- $\beta$  and IL-10 which are inhibitory cytokines. These in turn inhibit the activity of effector T-cells in the tumor microenvironment, which may contribute to immune evasion.

CTLA-4's role in the immune system is pivotal for maintaining self-tolerance and preventing autoimmunity, but in cancer, this regulatory mechanism is exploited by tumors to evade immune detection and destruction (Kern and Panis, 2021).

#### **3.2.2 Potential Contributions to Immune Suppression in TNBC**

While CTLA-4's role in TNBC may be less well-studied than that of PD-1/PD-L1, its involvement in immune suppression is increasingly recognized. TNBC tumors are often enriched with Tregs, which are critical mediators of CTLA-4-dependent immunosuppression. Elevated Treg levels in the tumor microenvironment (TME) correlate with poor prognosis, because they may likely inhibit the activity of cytotoxic CD8+ T cells that are essential for antitumor immunity (Maurer et al., 2018).

CTLA-4 expression on Tregs in TNBC enhances their suppressive activity, further contributing to an immunosuppressive milieu. In addition, CTLA-4 may indirectly modulate the immune landscape by promoting the recruitment of tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), both of which contribute to immune evasion (Coffelt et al., 2015).

Anti-CTLA-4 therapies, such as ipilimumab, have shown promise in enhancing T-cell activation and reducing Treg-mediated suppression. While these therapies have been transformative in melanoma and other cancers, their efficacy in TNBC remains under investigation. Combination strategies that include CTLA-4 inhibitors alongside PD-1/PD-L1 blockade are being explored to enhance the immune response in TNBC.

### **3.3 Crosstalk Between PD-1/PD-L1, CTLA-4, and Other Pathways in TNBC**

The immune checkpoints PD-1/PD-L1 and CTLA-4 are not isolated in their function. Rather, they interact and converge with other signalling pathways to shape the immune landscape of TNBC (Kim et al., 2022). This crosstalk is critical for tumor immune evasion and has important therapeutic implications.

#### **3.3.1 Synergistic immune suppression**

PD-1 and CTLA-4 are understood to operate at different stages of T-cell regulation but have complementary roles. While CTLA-4 primarily acts in lymphoid tissues to inhibit the early stages of T-cell activation, PD-1 functions in the tumor microenvironment to suppress the effector phase of T-cell responses (Kim et al., 2022). Together, these pathways create a multi-layered barrier to effective antitumor immunity (Kumar et al., 2023).

In TNBC, simultaneous expression of PD-L1 and CTLA-4 on tumor cells and immune cells has been observed. We can then infer that these pathways may work synergistically to suppress T-cell activity. For example, tumors that are resistant to PD-1/PD-L1 blockade often exhibit high CTLA-4 expression to support immune evasion. This means opens the door to the need for combination therapies (Zappasodi et al., 2018; Kim et al., 2022).

#### **3.3.2 Interaction with Other Pathways**

In addition to their direct synergistic effects, PD-1/PD-L1 and CTLA-4 influence other immunosuppressive mechanisms in the TME. One of these is the TAM and MDSC Recruitment (Kim

et al., 2022). PD-L1 and CTLA-4 signalling can enhance the recruitment of TAMs and MDSCs, both of which further suppress T-cell activity through various mechanisms, including the production of immunosuppressive cytokines and metabolic reprogramming of the TME (Thomas et al., 2021).

Also, in cytokine networks, both pathways modulate cytokine signaling, with PD-1/PD-L1 reducing IFN- $\gamma$  production by T-cells and CTLA-4 enhances TGF- $\beta$  and IL-10 secretion by Tregs. These cytokines further contribute to immune suppression and tumor progression (Thomas et al., 2021; Liu et al., 2022).

Immune checkpoint pathways indirectly promote angiogenesis and hypoxia, which create physical and metabolic barriers to immune cell infiltration and function (Thomas et al., 2021; Liu et al., 2022).

#### **4. THERAPEUTIC IMPLICATIONS - IMMUNE CHECKPOINT INHIBITORS (ICIs)**

Immune checkpoint inhibitors (ICIs) are type of drugs that block immune checkpoint proteins. These synthetic compounds have revolutionized cancer treatment by strengthening the immune system's ability to target and destroy tumour cells (Mehdizadeh et al., 2021). In Triple-negative breast cancer where limited therapeutic options exist, checkpoint inhibitors offer a promising strategy to overcome immune evasion in cancer and improve patient outcomes. These therapies primarily target key immune checkpoints such as PD-1, PD-L1, and CTLA-4, which are usually found to be high and are exploited by TNBC (Masoumi et al., 2021; Fang et al., 2023).

##### **4.1 Anti-PD-1/PD-L1 Therapies in TNBC**

Anti-PD-1/PD-L1 therapies function by disrupting the interaction between PD-1, an inhibitory receptor on T cells, and its ligand, PD-L1, expressed on tumour and immune cells.

By blocking PD-1 or PD-L1, these therapies restore T-cell activity, enabling cytotoxic T-lymphocytes to recognize and kill Triple-negative breast cancer cells (Masoumi et al., 2021; Fang et al., 2025). This reactivation of the immune response not only enhances the direct antitumor effects but also promotes immunologic memory, potentially preventing recurrence (Mehdizadeh et al., 2021).

Anti-PD-1/PD-L1 therapies have demonstrated efficacy in subsets of some TNBC patients, particularly those with high PD-L1 expression. Pembrolizumab for example is an anti-PD-1 antibody which has been approved for use in PD-L1-positive metastatic TNBC and in combination with chemotherapy for early-stage TNBC in the neoadjuvant setting. Similarly, another drug, atezolizumab, an anti-PD-L1 antibody, has shown benefit when combined with nab-paclitaxel in metastatic TNBC (Sharma et al., 2021).

The effectiveness of these therapies depends on several factors, including PD-L1 expression levels, the presence of tumor-infiltrating lymphocytes (TILs), and the overall immunogenicity of the tumour. While response rates in TNBC are lower compared to highly immunogenic cancers like melanoma, patients who do respond often experience durable benefits. Challenges remain, however, as a significant proportion of patients exhibit primary or acquired resistance to these therapies (Park et al., 2022).

##### **4.2 Anti-CTLA-4 Therapies in TNBC**

Anti-CTLA-4 therapies, such as ipilimumab, target CTLA-4, an inhibitory receptor that suppress T-cell proliferation and cytokine production. By blocking CTLA-4, these therapies enhance the activation and proliferation of T cells, increasing the pool of effector T cells capable of targeting tumour cells. Additionally, anti-CTLA-4 therapies reduce the suppressive activity of regulatory T cells (Tregs), which are often abundant in the TNBC tumour microenvironment (TME) and contribute to immune evasion (Yi et al., 2021).

In terms of effectiveness, although anti-CTLA-4 therapies have shown remarkable success in melanoma, their application in TNBC has been more limited. TNBC's highly immunosuppressive TME and the lower overall mutational burden compared to melanoma may contribute to reduced efficacy (Park et al., 2022). However, preclinical and early clinical studies suggest that anti-CTLA-4 therapies could be effective when combined with other treatments, such as anti-PD-1/PD-L1 therapies, chemotherapy, or radiation (Yi et al., 2021; Farshbafnadi et al., 2021).

Combination approaches aim to leverage the complementary mechanisms of PD-1/PD-L1 and CTLA-4 blockade. While CTLA-4 inhibition primarily enhances the priming and activation of T cells in lymphoid tissues, PD-1/PD-L1 blockade reactivates exhausted T cells within the tumor. This dual approach can potentially overcome resistance mechanisms and produce synergistic effects (Sharma et al., 2021).

##### **4.3 Immune Checkpoint Inhibitors (ICIs) in Combination with Other Therapies**



immune checkpoint inhibitors (ICIs) are also sometime combined with other therapies which has emerged as a promising strategy to improve clinical outcomes in triple-negative breast cancer (TNBC). Chemotherapy is so far a standard treatment for TNBC which has been employed in synergy with ICIs by inducing immunogenic cell death, increasing tumor-associated antigen presentation, and depleting immunosuppressive cells in the tumor microenvironment (TME) (Masoumi et al., 2021). For instance, pembrolizumab combined with nab-paclitaxel demonstrated improved progression-free and overall survival in metastatic TNBC. In a similar manner, radiotherapy has also been used in combination with checkpoint inhibitors to enhance the immunogenicity of tumours (Masoumi et al., 2021). The mechanism is by promoting antigen release, increasing T-cell infiltration, and upregulating PD-L1 expression, making tumours more responsive to PD-1/PD-L1 blockade. This approach is particularly effective in converting what is called “cold” tumours into “hot” ones (Sharma et al., 2021; Fang et al., 2023). These synergistic strategies leverage the complementary mechanisms of ICIs with chemotherapy or radiotherapy, addressing immune resistance and creating a more favourable tumour microenvironment. Continued exploration of these combinations could transform the therapeutic landscape for TNBC, providing hope for improved survival outcomes (Sharma et al., 2021; Fang et al., 2023).

## CONCLUSION

Triple-negative breast cancer (TNBC) is a highly aggressive subtype with limited treatment options and poor prognosis. Immune checkpoints, including PD-1, PD-L1, and CTLA-4, play key roles in immune evasion, making them critical therapeutic targets. Immune checkpoint inhibitors (ICIs) have shown promise, particularly in TNBC patients with high PD-L1 expression, but their efficacy is often limited by resistance mechanisms and the immunosuppressive tumor microenvironment (TME). Combination strategies, such as ICIs with chemotherapy, radiotherapy, or other immunotherapies, have demonstrated synergistic effects by enhancing tumor immunogenicity and overcoming immune suppression. Emerging approaches, including dual checkpoint blockade and TME modulation, offer additional avenues for improving outcomes. Ongoing research into predictive biomarkers and novel therapeutic combinations is essential to maximize the potential of immunotherapy in TNBC. These efforts hold promise to revolutionize TNBC treatment, offering hope for more durable responses and improved survival in this challenging cancer subtype.

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