

## Immune Checkpoint Inhibitors in Triple Negative Breast Cancer: What is the Evidence?

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### Abstract

Breast cancer is the most prevalent breast cancer in women. Despite our deeper understanding of mammary oncogenesis, 20% of breast cancer patients develop metastasis and die. There is a dire need for novel therapies especially for more aggressive subtypes like triple negative (TNBC) and HER2 positive breast cancers. For long, breast cancer was thought to be less immunogenic in nature compared to other solid malignancies like melanoma and non-small cell lung cancer, both later cancers yielding great results with immunotherapy. As we learn more about the role of tumor microenvironment in tumor occurrence, progression and response to therapy, there is growing evidence that TNBC is more immunogenic in nature compared to other breast cancers, which encouraged researchers to investigate its response to immune check point inhibitors. TNBC is characterized by a high level of immune cell infiltration including tumor infiltrating lymphocytes (TILs) which have been associated with better outcomes. The prognostic values of TILs and PD-L1 expression on tumor cells have been an area of interest and remain uncertain to date. The hope is that future trials will unravel more answers about the complex interaction between TILs and tumor cells in TNBC and help develop biomarkers to identify responders to checkpoint inhibitors. In this review, we discuss the immunogenic nature of TNBC, the clinical relevance of TILs and PD-L1 expression and the promising results of early phase trials of checkpoint blockade.

**Keywords:** Immune checkpoints; PD1; PD-L1; CTLA-4; Triple negative breast cancer; TILs

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**Abbreviations:** TME: Tumor Microenvironment; TNBC: Triple Negative Breast Cancer; PD-L1; Programmed Cell Death Ligand 1; PD-1: Programmed Cell Death 1 Receptor; CTLA-1: Cytotoxic T Lymphocyte-Associated Antigen 4

### Introduction

Breast cancer is the most prevalent cancer in women and statistically the second leading cause of death. Despite considerable progress in hormonal, targeted and systemic therapy and a deeper understanding of mammary oncogenesis, around 20% develop metastasis and have fatal outcomes. There are several risk factors for breast cancer including exposure to hormonal therapy, age, obesity, alcohol, radiation, benign breast disease, among others [1]. Genetic aberrations play a major role in sporadic and familial breast cancer occurrence, recurrence, response to treatment and progression. In light of the recent

genomic and proteomic revolutions, breast cancer has been re-classified into several subtypes: ER positive that is further classified into luminal A which is HER2 negative (HER2-) with low Ki67 and high progesterone receptor (PgR+) content, and luminal B which is HER2- and has either high Ki67 or low PgR. The second type is HER2 positive breast cancer. The third type is triple negative breast cancer (TNBC) which has all 3 biomarkers absent, HER2-, ER-, PgR- [2-4]. Another type of triple negative breast cancer, claudin low, expressing low cell-cell junction proteins has been described in the literature [5].

Breast cancer is a complex and heterogeneous disease. Cancer mutagenesis is constant and often results in temporary response to treatment until novel gene mutations and subsequent therapy resistance arise. At the same primary site, cancer cells may acquire distinct molecular and histologic characteristics within a single type of cancer resulting in inter-tumoral heterogeneity. New

gene mutations arise with disease progression and chemotherapy induced DNA breakages contributing to a temporal intra-tumoral heterogeneity. New genetic aberrations can also arise in distant metastasis compared to the primary tumor resulting in spatial intra-tumoral heterogeneity [6]. Analyzing the primary tumor might not necessary lead to the expected treatment response due to novel mutations acquired by metastases. A whole genome sequencing done by Shah et al. [7] showed 19 mutations present in the metastasis that were not present in the primary tumor. Among the most heterogeneous breast cancer types is the triple negative phenotype that occurs in about 20% of breast cancers. TNBC is associated with younger age of onset, increased risk of distant metastasis, advanced disease at diagnosis, worse overall outcomes and limited treatment options because it lacks targetable mutations [8]. Several subtypes of TNBC have been identified by genome wide approaches: basal like (BL1 and BL2), immunomodulatory, mesenchymal, mesenchymal stem-like 1, luminal androgen receptor and unstable [9,10]. Treatment options for TNBC patients are limited. The standard of care has been neoadjuvant and adjuvant chemotherapy. There is a dire need for new more effective and less toxic therapies for TNBC patients.

Immune check point inhibitors have been approved by the US Food and Drug Administration (FDA) for more immunogenic solid tumors like melanoma, non-small cell lung cancer, renal cell carcinoma and head and neck cancers over the past seven years. These drugs aim to overcome the tumor's immune escape mechanisms and strengthen anti-cancer immune defenses. Immune check point inhibitors are among the most exciting drugs in cancer immunotherapy due to the remarkable results achieved in cancers refractory to conventional therapies. Initially, they showed little success with breast cancer, thought to be less immunogenic in nature compared to other solid malignancies. However, there is growing evidence that breast cancer subtypes have variable immunogenic activities. TNBC and HER2+ breast cancers are more immunogenic in nature compared to the rest of breast cancer types which makes immunotherapy a potential treatment option. In this review, we explore the immunogenic nature of TNBC and highlight important clinical trials that investigated or are currently investigating the role of immune check point inhibitors in TNBC.

## Literature Review

### The immunogenic nature of triple negative breast cancer

TNBC subtypes are characterized by genomic instability and a myriad of mutations in genes involved in immunity that outweigh the number of mutations in any other breast cancer subtype [11]. Several studies showed a positive correlation between tumor mutational load and response to check point inhibitors including cytotoxic T lymphocyte-associated antigen 4 inhibitors (anti-CTLA-4), programmed cell death receptor (anti-PD1) inhibitors and programmed cell death ligand (anti-PD-L1) inhibitors [12-15]. Le et al. [16] demonstrated that high mismatch repair deficiency correlate with response to checkpoint inhibitors.

A comparative study between TNBC and non-TNBC showed that TNBC is characterized by higher expression levels of functional gene sets associated with 15 types of immune cells including B cells, CD4+ regulatory T cells, CD8+ T cells, macrophages, dendritic cells, natural killer cells, neutrophils among others, and higher expression levels of Cancer-Testis antigen genes which code for immunogenic proteins normally found in human germ line cells, tumor immune suppressive genes including immune check point genes that play a role in tumor immunosuppression: CTLA-4, PD-L1, PD-L2, PD-1, LAG3, TIGIT. Cytokine, cytokine receptor, pro-inflammatory and metastasis promoting genes are also more highly expressed in TNBC [17]. Smyth et al. described 26 target genes for immunotherapy, 22 of which are up-regulated in TNBC [18]. Despite these findings, there are no proposed genomic biomarkers to predict response to immunotherapy.

Previously, almost all cancer therapies aimed at targeting the cancerous cells themselves. We now understand that the tumor microenvironment plays a pivotal role in carcinogenesis, cancer progression, metastasis and response to therapy. This drove scientists to explore tumor microenvironments (TME) and develop therapies that target TMEs rather than tumors themselves. TNBC has higher proportions of surrounding inflammation inducing macrophages, activated dendritic cells, B cells, activated T cells, CD4+ memory cells than non TNBC tumors [19,20]. Immune cell infiltrates increase with higher tumor mutational burden [17]. These cells have variable roles and activities and depending on the proportion of each type, the outcome might be in favor of immune activation and stronger anti-tumor defenses or immune inhibition and disease progression [8,21,22]. The tumor infiltrating lymphocytes also known as TILs have gained special attention in breast cancer. TILs migrate from the blood to the tumor microenvironment and are present at higher levels in TNBC compared to non-TNBC [17]. TILs represent the strength of anti-tumor immune defenses. Higher levels have been associated with better outcomes. In a prospective-retrospective phase III randomized trial with 1010 early stage breast cancer patients, increase in TILs was significantly associated with decreased distant recurrence in TNBC [23]. A recent meta-analysis by Ibrahim et al. [24] with 2987 patients with TNBC from 8 different studies showed that TILs are significantly associated with 30% reduction in disease recurrence, 22% reduction in distant recurrence, 34% reduction in death, and a better overall survival outcome in rich TILs TNBC irrespective of the location of the lymphocytes (intratumoral or stromal). TNBC with high TILs have also been associated with better response to chemotherapy. The overall survival (OS) of TNBC with rich TILs compared to TNBC with low TILs following adjuvant anthracycline was 89% and 68%, respectively [25]. Some studies did not demonstrate a positive correlation between the presence of TILs and favorable prognoses [26-28]. One explanation for this contradiction could be a temporal evolution of TILs, initially involved in rigorous tumor attack and later in the process expire and fatigue. Overall, TNBC is characterized by more inflammation and stronger immune activities and immunogenicity compared to non TNBC which makes immunotherapy an attractive treatment option to consider in this breast cancer phenotype.

## PD-1 and PD-1 ligand expression in TNBC

PD-1/PD-L1 is an important immune checkpoint that plays a role in the pathogenesis of many solid tumors for which anti-PD-1 and anti-PD-L1 drugs are now approved for clinical use. In many tumors, PD-1 and PD-L1 expression was found to correlate with clinical response. Now we know that the degree of expression of these biomarkers doesn't not necessarily correlate with response; in some tumors, immune checkpoint inhibitors still have therapeutic benefit despite low levels of PD-L1 like in melanoma and renal cell carcinoma. Checkpoint inhibitors are not yet approved for use in breast cancer and this is an area of rigorous research. In breast cancer, PD-1 is expressed on activated lymphocytes including TILs and PD-L1 is expressed on cancer cells and immune cells [29]. PD-L1 expression has been found in 50% of all breast cancer subtypes [30]. The first study that looked at PD-L1 expression in breast cancer demonstrated higher PD-L1 expression in TNBC compared to non TNBC and an association between PD-L1 expression and the degree of TILs [31]. Other studies have also identified associations between PD-L1 expression and extent of TILs infiltration [32]. PD-L1 expression in breast cancer has been associated across different studies with: heterogeneity across different types of breast cancers, positive association with the presence of TILs, high histologic grades, young age, negative hormone receptors, high proliferative rate and aggressive subtypes [21].

## Discussion

The prognostic value of PD-L1 expression and PD-1/PD-L1 interaction between tumor cells and TILs has been an area of interest, yielding conflicting results across studies. Some studies reporting no correlation of PD-L1 expression with survival [30,33-39], others reporting worse survival [40,41], and some reporting better survival outcomes [36,37]. The association of PD-L1 expression with better overall survival seems counter-intuitive because PD-L1 on tumor cells interact with T cells leading to T cell inactivation and suppression of immunity; perhaps, higher PD-L1

expression is associated with higher levels of TILs, rendering high levels of PD-L1 a favorable marker reflecting the strength of the anti-tumor immune response [22,38]. These divergent results in survival outcomes might not necessarily be contradictory but rather highlight different stages of a complex and intricate process. PD-L1 and PD-1 expression might be a dynamic process affected by the surrounding microenvironment involving different signaling pathways, transcriptional factors, microRNAs and epigenetic factors [42,43]. Interestingly Brackhoff et al. [42] demonstrated that in TNBC, PD-L1 gene copies may be amplified, fall in the normal range or even below the average copy numbers in normal breast tissue, and PD-L1 gene expression did not correlate with PD-L1 protein expression. The study also demonstrated a direct correlation between PD-1 expression on TILs and PD-L1 expression on tumor cells; PD-1 expression on TILs was found to be the strongest prognostic factor of a favorable survival outcome [42].

## Clinical trials in TNBC

Immunotherapy is still investigational in breast cancer, especially in TNBC. The first data in TNBC came from KEYNOTE-012 trial where 27 heavily pretreated TNBC patients with PD-L1 expression in  $\geq 1\%$  of tumor cells received the anti-PD1 checkpoint inhibitor pembrolizumab (Keytruda, Merck & Co., Inc.), a humanized IgG4. The overall response rate was 18.5% with a median progression free survival of 1.9 months and a median overall survival of 10.2 months. One patient achieved complete response, four patients achieved partial responses and seven patients had stable disease. The most common side effects were arthralgia, fatigue, myalgia, nausea and diarrhea [32]. Other clinical trials with PD-1 and PD-L1 inhibitors followed, as frontline therapy or in pretreated patients, as monotherapy or in combination with conventional chemotherapy, in metastatic, locally advanced or early stage TNBC, in the neoadjuvant or adjuvant setting. **Table 1** highlights the important clinical trials exploring the role of checkpoint inhibitors in TNBC.

**Table 1** Clinical trials with checkpoint inhibitors as monotherapy or in combination with chemotherapy in different stages of TNBC

Trial	Checkpoint Inhibitor	Inclusion Criteria/Study Design	Result	Comments
KEYNOTE-012 (NCT01848834)	Pembrolizumab	Pretreated metastatic TNBC	ORR 18.5%, median PFS 1.9 months, median OS 10.2 months, CR 1, PR 4, SD 7	Analyzed patients with PD-L1 in $\geq 1\%$ of tumor cells
KEYNOTE-086 (NCT02447003)	Pembrolizumab	Part I: treatment naïve (frontl line) vs pretreated metastatic TNBC Part II expansion on pretreated cohort with strong PD-L1 expression	NA, still on going	Pretreated defined as at least one systemic treatment with anthracycline and a taxane in neoadjuvant, adjuvant or metastatic setting
KEYNOTE-119 (NCT02555657)	Pembrolizumab	Pretreated metastatic TNBC	NA, still on going	Pretreated defined as one or two systemic treatment with anthracycline and a taxane in neoadjuvant, adjuvant or metastatic setting

KEYNOTE-355 (NCT02819518)	Pembrolizumab	Frontline combination therapy with nab-paclitaxel or paclitaxel or gemcitabine in locally recurrent or metastatic TNBC	NA, still on going	
NCT01375842	Atezolizumab	Heavily pretreated metastatic TNBC	ORR 24%, 24 week PFS 33%, 3 pseudoprogressions; Among PD-L1 positive group, CR 2, PR 3	Included both PD-L1 negative and PD-L1 positive patients; PD-L1 positive defined as PD-L1 on 5% or more of immune cells infiltrating the tumor
NCT01633970	Atezolizumab	Combination of atezilizumab+nab-palitaxel in pretreated metastatic or locally advanced unresectable TNBC	ORR 41.7%, 3 pseudoprogressions	Included both PD-L1 negative and PD-L1 positive patients; PD-L1 negative tumors responded but response was higher with PD-L1 positivity
IMpassion (NCT02425891)	Atezolizumab	Frontline atezolizumab+nab-paclitaxel in treatment naïve metastatic TNBC	NA, still on going	
KEYNOTE-522	Pembrolizumab	Frontline neoadjuvant pembrolizumab or placebo combined with paclitaxel+carboplatin followed by pembrolizumab or placebo combined with doxorubicin+cyclophosphamide followed by adjuvant pembrolizumab or placebo, in locally advanced TNBC	NA, still on going	
THE NeoTRIPaPDL1 (NCT02620280)	Atezolizumab	Frontline neoadjuvant nab-paclitaxel+ carboplatin with or without atezolizumab in locally advanced TNBC	NA, still on going	
NCT02489448	Durvalumab	Frontline neoadjuvant nab-paclitaxel followed by doxorubicin+cyclophosphamide+ durvalumab in locally advanced TNBC	NA, still on going	
NCT02685059	Durvalumab	Frontline neoadjuvant durvalumab or placebo followed by nab-paclitaxel with or without durvalumab followed by epirubicin+cyclophosphamide with or without durvalumab in locally advanced TNBC	NA, still on going	
SWOG-21418 (NCT02954874)	Pembrolizumab	Adjuvant pembrolizumab with residual disease following neoadjuvant therapy and surgery in early stage TNBC	NA, still on going	
A-BRAVE (NCT02926196)	Avelumab	Part I Adjuvant pembrolizumab with residual disease following neoadjuvant therapy and surgery in early stage TNBC Part II Avelumab after surgery and adjuvant anthracycline+taxabe in early TNBC	NA, still on going	
JAVELIN (NCT01772004)	Avelumab	Avelumab in pretreated locally advanced or metastatic TNBC of any PD-L1 status	ORR lower than in atezolizumab and pembrolizumab studies in PD-L1 positive patients, but in PD-L1 positive TNBC was much higher 44%	Study didn't select for PD-L1 positivity initially
NCT02826434	Durvalumab	Avelumab in pretreated locally advanced or metastatic TNBC of any PD-L1 status	NA, still on going	

NA: Not Available; ORR: Objective Response Rate; PFS: Progression Free Survival; OS: Overall Survival; PD-L1: Programmed Cell Death Ligand 1; CR: Complete Response; PR: Partial Response; SD: Stable Disease; TNBC: Triple Negative Breast Cancer

## Conclusion

Studies have shown that immune dysregulation is implicated in the pathogenesis of breast cancer, more so in TNBC which is very heterogeneous and aggressive subtype associated with worse overall survival [44]. Immune checkpoint inhibitors are rigorously being studied as potential treatment options in TNBC which is more immunogenic compared to other breast cancers, with some promising results demonstrated so far. The prognostic value of TILs and PD-L1/PD-1 expression in TNBC remains uncertain and needs more longitudinal investigations. The hope is that future

trials will unravel more answers about the complex PD-1 /PD-L1 interaction between TILs and tumor cells. This is essential to help develop biomarkers to identify responders and increase therapeutic options for TNBC.

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## Competing Interests

The authors declare that they have no competing interests.

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