

# Triple-Negative Breast Cancer and Immunotherapy: A Systematic Analysis of Immune Checkpoint Inhibitors

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## ABSTRACT

**Background:** Immune checkpoint inhibitors (ICIs) have changed neoplastic therapy by empowering the human defense system to better recognize and eradicate neoplastic cells, in contrast to traditional treatments. They have shown notable efficacy in triple-negative breast cancer (TNBC), primarily as they target the noted proteins like PD-1, CTLA-4 and PD-L1. However, due to challenges such as immune-related treatment-related toxicities and restricted therapeutic responses, combination approaches are increasingly being investigated to increase treatment outcomes. **Methods:** A prior search was performed using Embase from January 1, 2020, to August 12, 2025, using the keyword “immune checkpoint inhibitors in triple-negative breast cancer”. 1612 articles were identified with relevant information. These articles were analyzed to support the objective of our study, which focuses on evaluating the risk-to-benefit profile of ICIs in TNBC. **Results:** Based on the efficacy and side effects caused by ICIs in TNBC, it is determined that as a single-agent therapy or alongside other chemotherapeutic agents, ICIs have shown a better prognosis in TNBC with minimal side effects. However, this prognosis is impacted by the vivid heterogenic nature of TNBC. **Conclusion:** ICIs can be promising in TNBC treatment field as they have shown better prognosis with limited side effects.

**Keywords:** Immune checkpoint inhibitors (ICIs), Triple-negative breast cancer (TNBC), Risk vs Benefit profile, Immune-related side effects.

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## INTRODUCTION

TNBC represents for most of the breast cancer occurrences with a bad disease outcome, and therapeutic effects are contrasted due to neoplastic heterogeneity<sup>1</sup>. TNBC is characterized by the absence of estrogen and progesterone receptors (ER/PR) with the lack of overexpression or increase of “human epidermal growth factor receptor 2” (HER2)<sup>2</sup>. TNBC shows poor prognosis and treatment outcomes because of its marked cellular and microenvironmental diversity and absence of reliably targetable oncogenic drivers<sup>1</sup>. The most frequently used chemotherapy regimen for early-stage TNBC consists of a combination of anthracyclines (A) and cyclophosphamide (C), followed by taxanes (T), termed as AC-T3<sup>4,5</sup>, which obtains “pathological complete response” (pCR) rates of 25–50%<sup>6,7,8,9,10</sup>. Given the limited efficacy and significant cytotoxic adverse effects associated with traditional therapies, there is a pressing need to explore alternative treatment methods for TNBC. ICIs are promising in advanced TNBC. When administered in combination with chemotherapy, these agents have demonstrated enhanced therapeutic potential, especially in high-risk patients profiles or those recognized at an initial stage.

### ACTION OF ICIS IN TNBC:

The ICIs “programmed death receptor-1” (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) serve as key negative regulators of T cell-mediated immune responses. PD-1 is expressed on activated T cells. The two ligands PD-L2 and PD-L1 bind to PD-1 on tumor cells and antigen-presenting cells (APCs). This binding suppresses T cell proliferation and cytokine

generation, including interferon-gamma (IFN- $\gamma$ ) and tumor necrosis factor-alpha (TNF- $\alpha$ ), thereby weakening T cell survival and cytotoxic function, resulting in tumor immune evasion<sup>12</sup>. CTLA-4 downregulates immunity by inhibiting T cells and APCs, thereby diminishing the capability of the immune cells to recognize neoplastic cells. ICIs bind to T cells with a higher affinity than that of CD28, an antigen required for co-stimulatory action on T cell activation and survival, without delivering essential co-stimulatory signals. Blocking CTLA-4 and other immune checkpoints increases the immune system's ability to identify and remove neoplastic cells, a key objective in immunoncology. Beyond monotherapy, ICIs have been given in combination with other chemotherapies. These combination strategies aim to synergistically amplify immunogenic mechanisms across different pathways, thereby improving therapeutic outcomes. ChT, an immunomodulator, induces cell death of neoplastic cells, which causes the liberation of tumor antigens in the bloodstream and is cleared up by the immune system<sup>15</sup>.

### EFFICACY OF ICIS IN TNBC:

Tumours show diversity in the mechanisms by which they cannot be detected or eradicated through body's defense system. The ICIs act as stimulating the inhibitory pathway and the eradication of cancer cells by the mechanism of action as described above. TNBC with fewer mutations and heterogeneity has been found to have an improved prognosis with ICIs. Therapeutic reaction to ICIs differs with only a limited number, hence most of patients have a

greater survival rate<sup>21,22</sup>. To date, anti-PD1 antibodies cemiplimab, nivolumab, and pembrolizumab; and anti-PD-L1 antibodies avelumab, atezolizumab, and anti-CTLA-4 antibody ipilimumab; and durvalumab have been approved by the FDA<sup>23,24</sup>. Currently, Most breast cancer studies concentrate on the Suppressio of the PD1/PD-L1 pathway. The efficacy of ICIs, especially those aimed at PD-L1 and PD-1, has been showed in both metastatic and early-stage TNBC, with great enhancements in overall survival (OS), PFS, and pCR rates when merged with chemotherapy<sup>29,30,31</sup>. Pembrolizumab, for instance, has gained FDA acceptance for use in both contexts, showing significant survival benefits in PD-L1 patients in studies like KEYNOTE-355 and KEYNOTE-52229. However, prognostic significance of PD-L1 expression remains inconsistent throughout studies, with some trials indicating benefit regardless of PD-L1 status<sup>29</sup>. Some biological markers are being explored to enhance patient stratification and enhance clinical results like TMC, sTILs, and CD8+ T-cells<sup>29,30</sup>. Despite promising results, challenges persist in optimizing treatment timing, managing toxicity, and overcoming resistance. Emerging strategies, including combined therapies with PARP inhibitors, anti-drug conjugates, and dual ICIs, aim to broaden the efficacy of immunotherapy in TNBC. Continued research into biomarker-driven approaches and novel immunomodulatory combinations is crucial to fully harness the possible of ICIs in this difficult-to-treat breast cancer subtype. A single-arm pilot study revealed that PD-L1 ligand CTLA-4 checkpoint inhibition showed an objective responsive rate (ORR) of 43 percent in prognosis patients with advanced TNBC, but no response being noted in cases with HER2+ cancer<sup>27</sup>.

Hence, efficacy in TNBC is highlighted in overall studies that emphasize the use of ICIs in monotherapy or with other chemotherapy for better prognosis.

#### SIDE EFFECTS OF ICIs

ICIs have exhibited promising effectiveness in treating TNBC, Its use is accompanied by a spectrum of immunity-related adverse reactions that necessitate vigilant assessment of need. Common side effects include diarrhea, fatigue, rash, adrenal insufficiency and hypothyroidism, and are generally manageable with supportive care or corticosteroids<sup>32</sup>. However, severe toxicities have also been reported, including pneumonitis, hepatitis, and serious conditions like acute respiratory distress syndrome, particularly in early-stage TNBC patients receiving neoadjuvant ICI-based regimens<sup>32</sup>. The incidence and severity of irAEs correlate with the intensity and duration of immune activation, necessitating vigilant monitoring and prompt intervention. Moreover, the safety profile of ICIs varies with their combination

partners in chemotherapy, as certain regimens are associated with increased hematologic and gastrointestinal toxicities.<sup>33</sup> Despite these risks, ICIs are generally well tolerated in selected patients, especially those with greatest PD-L1

presence, and have a safe profile than other chemotherapies in several trials<sup>35</sup>. Integration of cross-disciplinary care and biomarker-guided patient selection is important to optimize therapeutic benefit while minimizing harm.

#### ICIS AS A THERAPEUTIC WEAPON IN TNBC:

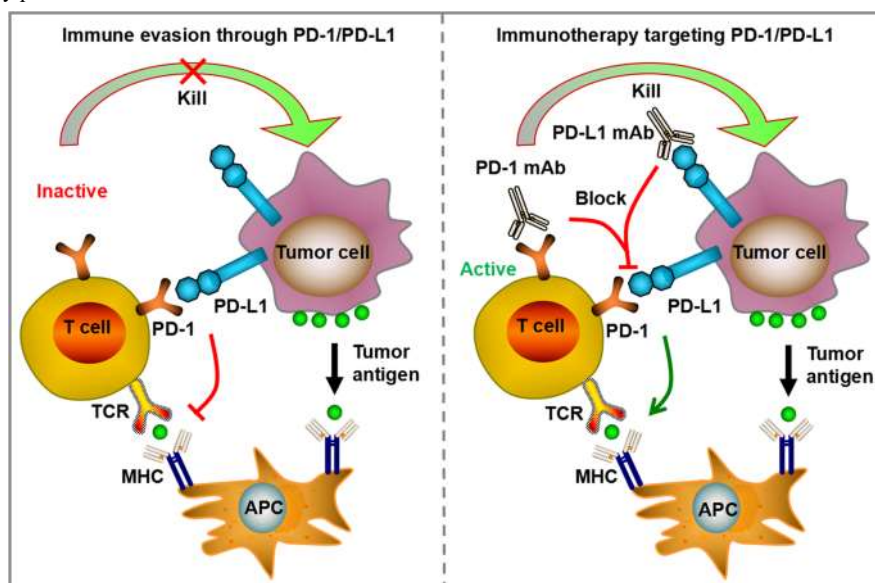
##### PD-(L)1 INHIBITORS AS MONOTHERAPY:

PD-(L)1 protein is found in most of the TNBC cases. They are expressed on various cells, among which activated T-cells dominate. PD-L2 and PD-L1 are the a pair of ligands of PD-1. PD-L1 is overexpressed in neoplastic cells, and they bind to the PD-1 sites to promote apoptosis of lymphocytes, causing abnormal cytokine secretion that escapes the immune responsiveness method to detect the abnormal cells of tumour, and no clearance occurs. PD-L2 suppresses and activates T-cells. Hence, PD-(L)1 inhibitors act by blocking the PD-1/PDL-1 signalling pathway, causing T-cells immune responsive function to function properly and kill neoplastic cells as shown in Figure 1.

In KEYNOTE-012 1b Phase study, pembrolizumab demonstrated acceptable tolerability and tumor clearance when used as a standalone therapy in PD-L1 +ive TNBC<sup>35</sup>. The “KEYNOTE-086” II Phase study provided a treatment response rate of 21.4% with pembrolizumab used as first- or second-line therapy<sup>36,37</sup>. In III Phase randomized KEYNOTE-119 experiment, the ORR was not satisfactory, as no meaningful improvement was detected. Nevertheless, patients who have higher PD-L1 expression showed the greatest therapeutic benefit from pembrolizumab<sup>38</sup>.

##### PD-(L)1 INHIBITORS WITH OTHER CHEMOTHERAPIES:

Preclinical studies have demonstrated toxicity toward tumor cells, and clinical trials have shown consistent findings supporting these results. Chemotherapies target the tumours via immunological pathways by enhancing activation of T-cells and killing of tumour cells<sup>39</sup>. Chemotherapeutic agents act through multiple mechanisms, either by directly inhibiting tumor-cell division or by promoting their elimination through immune-mediated pathways. They can enhance MHC expression or trigger the cytokine and chemokine release, thereby increasing the recruitment and activation of immune cells effector cells to eradicate neoplastic cells<sup>40</sup>.



**<sup>42</sup>Figure PD-1/PD-L1 pathway contributes to tumor immune escape, enabling tumors resistant to immune response**

**ADVANCED TNBC:**

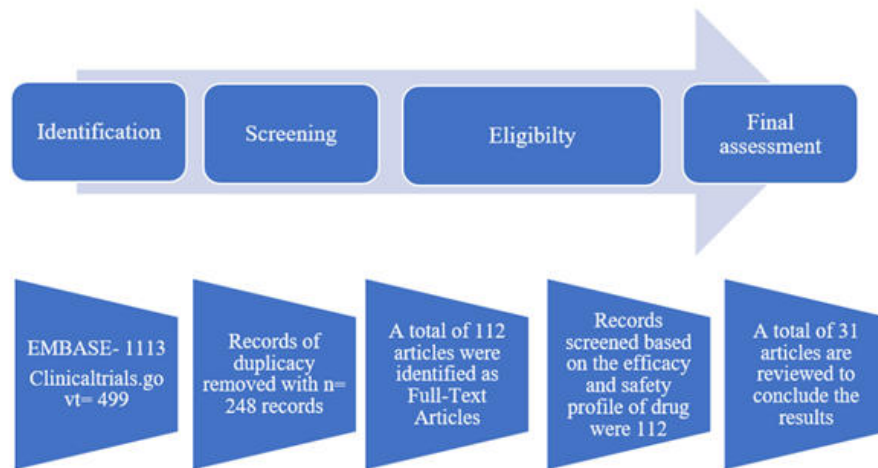
III Phase RCT “KEYNOTE-355” has described the safe and effectiveness of pembrolizumab with placebo vs other chemotherapy as the first choice of drugs in TNBC. This study concluded that pembrolizumab in alongside other chemotherapies exhibited substantial improvement as contrasted to monotherapy with pembrolizumab, with minimal side effects<sup>41</sup>.

**MATERIAL & METHODS:**

An advanced search was conducted in Embase literature search and clinicaltrials.gov from the time period of 01-Jan-2020 to 12-Aug-2025 with the keyword “immune checkpoint inhibitors in

triple-negative breast cancer”. 1612 articles were pulled with relevant information. These articles were analyzed to support the objective of our study, which focuses on evaluating the risk-benefit profile of checkpoint inhibitor therapy in TNBC. The identified articles were evaluated for efficacy and side effects associated with ICIs, and their results will conclude the objective of this article.

As of 12 Aug. 2025, more than 245 research articles were found in Embase among 1612 articles pulled. These articles were used to explore the therapeutic response of ICIs as a monotherapy or with other chemotherapy, along with the side effects associated with ICIs, as shown in a schematic presentation in Figure 2.



**Figure 2: Schematic representation of the study**

**STATISTICAL METHOD:**

**CONFOUNDERS WERE FOLLOWING:**

Side effects from other chemotherapy in adjuvant use  
 Concurrent conditions (existing cancers).  
 The efficacy of adjuvant chemotherapeutics in a regimen

Table 1 explains results and efficacy along with the confounders impacting the safety and effectiveness of ICIs used as monotherapy or as adjuvant chemotherapeutics. P-values were derived by applying the T-test for mean values using SPSS as directed earlier for both efficacy and safety. These values were then analysed for confounding, as listed below, to study the impact on efficacy and the contribution of the adjuvant to side effects.

**RESULTS OF ANALYSIS:**

**Table 1. Significance calculated from the articles' results and discussion to determine safety and efficacy**

Regimen	P-value (Efficacy)	P-Value(Safety)	Confounders
ICIs in monotherapy	0.0037	0.097	No impact due to side effects (0.6062)
ICIs in adjuvant with chemotherapy	0.0012	0.086	Mild impact seen (0.0168) due to underlying conditions
ICIs in advanced TNBC as monotherapy	0.0031	0.009	No significant impact of confounders on efficacy
ICIs in advanced TNBC with adjuvant chemotherapy	0.003	0.023	No impact on efficacy due to adjuvant (0.7102)

\*The significance level of p-value (α) is set at 0.05

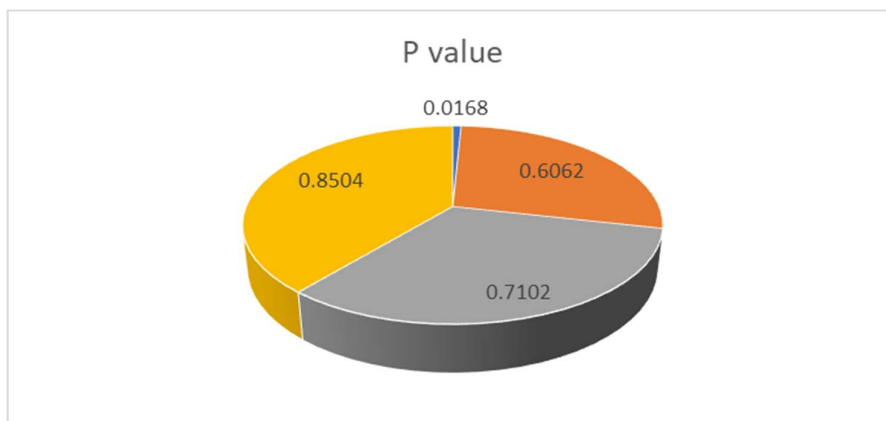
Table 2 and Figure 3 document the analysis of predisposing factors of patients towards the increased side effects or adjuvant therapies promoting efficacy. The concurrent diseases in patients have an impact on the ICIs, with of 3.413 odds ratio in contribution

towards efficacy/side effects. Adjuvants have an impact of 1.261 odds ratio in both the safety/efficacy profile of ICIs. Population age has a 1.308 odds ratio impact on ICI's safety/efficacy profile.

**Table 2. Analysis of factors predisposing patients to increased side effects or efficacy due to below factors:**

Factors	Odds ratio	95% confidence interval	P value
Concurrent diseases	3.413	1.203-9.728	0.0168
Efficacy of adjuvants	1.261	0.5439-2.898	0.6062
Side effects from adjuvants	0.8649	0.4092-1.852	0.7102
Age of the population (removal of Pediatric/geriatric population)	1.308	0.0676-25.17	0.8504

\*Odds Ratio 1.000: no odds of the impact due to ICI exposure, >1.000 increased risk of impact on ICI, and <1.000 reduced impact on the outcome of ICIs



**Figure 3: Predisposing patients to increased side effects**

Table 3 explains the safety profile of ICIs as adjuvant or as a monotherapy. As pf p-value less than 0.5 shows the impact of the chemotherapy. ICIs as monotherapy contribute to about 0.008 percentile in side effects, as per Student's T-test. The ICIs in

Adjuvant to other chemotherapies have a 0.002 percentile of safety profile analysis, whereas other chemotherapies have less impact on the safety profile of ICIs.

**Table 3. Raising concerns due to side effects with the use of ICIs**

Regimen	P-value (Side effects)	Side effects
ICIs in monotherapy	0.008	fatigue, rash, diarrhoea, alopecia, hypothyroidism, and adrenal insufficiency
ICIs in adjuvant with chemotherapy	0.002	Pneumonitis, hepatitis, and acute respiratory distress syndrome
ICIs in advanced TNBC as monotherapy	0.020	Haematological toxicities (anemia, neutropenia, leukopenia, multi-organ failure, allergic reactions
ICIs in advanced TNBC with adjuvant of chemotherapy	0.022	Gastrointestinal toxicities, End-organ damage, pneumonitis (mainly with use of platins)

The results from Table 1 show a significant impact of ICIs in TNBC and much lower side effects compared to conventional therapies for TNBC.

The confounders were analysed through odds ratios, and the p-value was not impacted by the underlying conditions. However, the side effects with adjuvant therapies have been seen predominantly in adult populations along with the use of ICIs, raising safety concerns.

**DISCUSSION:**

Immune-based therapy has developed into a strong medicated option for TNBC, with promising therapeutic responses. Nevertheless, there are instances where ICIs have not shown notable response due to drug resistance. Pharmacogenomics has played a vital role in understanding the therapeutic outcome with use of ICIs.

ICIs have contributed to the understanding of the mechanisms associated with cancer progression and its complex mechanisms.

Currently, TNBC and ICIs are linked with the targeted protein and its ligand, PD-1/CTLA-4 and PDL-1. The inhibition of this ligand and the repair of the impaired defense system have contributed to the clearance cells of cancer from the body and a better prognosis of TNBC.

ICIs have shown significant improvement in TNBC, both in monotherapy and in combination. In monotherapy, ICIs have shown significant prognosis, but minimal side effects, particularly noted as gastrointestinal reactions. In combination, the remission period has been achieved in a shorter span; however, the associated side effects have had a greater impact in the overall health of the patient, thus showing limitations in use of ICIs.

ICIs have shown enhanced efficacy in anti-tumour activity via both immunological and non-immunological pathways. TNBC with less heterogeneity has been found to have a better prognosis with ICIs. ICIs act by stimulation of the inhibitory pathway and eradication of cancer cells (the mechanism of action has been described above).

ICIs' impact on PD-1 and CTLA-4 act as key negative regulators of T cell-mediated immune responses. PD-L1, along with PD-L2, is the binder where PD-1 binds to APCs and neoplastic cells. This suppresses T cell proliferation, reduces critical cytokines production including TNF- $\alpha$  and IFN- $\gamma$ , and impairs T cell survival and cytotoxic function, thereby enabling tumor immune evasion [12].

ICIs have shown better efficacy in TNBC, yet their use has a wider range of irAEs that require careful management. Common irAEs—such as fatigue, rash, diarrhea, and endocrinopathies like hypothyroidism and adrenal insufficiency—are typically manageable with supportive care or corticosteroids. However, severe toxicities, including pneumonitis, hepatitis, and ARDS, have been documented, particularly in early-detected TNBC patients with chemoadjuvant ICI-based therapies. The frequency with severity of irAEs appear to correlate with the extent and duration of immune activation, underscoring the need for vigilant monitoring and timely intervention. Additionally, the safety profile of ICIs varies with chemotherapy combinations, with certain regimens linked to increased hematologic and gastrointestinal toxicities. The review of the articles and their results has helped us to understand the probability of remission versus the probability of side effects that can occur with ICIs.

The findings have revealed that there is a significant impact of ICIs in TNBC with much lesser side effects as compared to the conventional therapies in TNBC. The confounders are also analysed to ensure the true values are not impacted by the underlying conditions in patients. The side effects of adjuvant therapies have been seen predominantly in adult populations, with the use of ICIs raising safety concerns. However, the higher rate of efficacy is also seen in the adult population due to lower heterogeneity and targeted ICIs therapy in TNBC.

#### CONCLUSION:

This systematic findings has revealed valuable insights into the balance between effectiveness and safety of ICIs in the treatment of TNBC. While ICIs have showed improved prognosis in TNBC cases, their use is also linked to notable negative effects, raising

concerns about their broader applicability in this population. These safety issues underscore the need for cautious subject selection and monitoring. Further investigations are to be explored for advancements in ICI-based therapies, aiming to enhance therapeutic outcomes while minimizing toxicity.

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#### AUTHORS' CONTRIBUTIONS

Rishi Kant Pandey conceived the research, performed the prior search and data analysis, and manuscript drafted. Dr. Mamta Bishnoi and Dr. Mohd Mazhar supervised the project, guided the paper design and result's interpretation, and critically revised the research. Dr. Ajay Pal Singh provided overall academic leadership, methodological guidance, and critical oversight throughout the study. All authors checked and approved the final study.

#### CONSENT TO PARTICIPATE AND ETHICS

##### APPROVAL: NOT APPLICABLE

##### PUBLICATION CONSENT: NOT APPLICABLE

##### DECLARATION OF INTERESTS

The authors declare there is no conflict of interests.

##### AI USE STATEMENT- NO AI-ASSISTED TOOLS WERE USED IN THE RESEARCH PREPARATION, CREATION OF FIGURES AND DATA ANALYSIS, FOR THIS MANUSCRIPT.

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Not Applicable

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