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# Neoadjuvant Immunotherapy in Triple-Negative Breast Cancer: The Clinical Impact of Immune Checkpoint Inhibitors—A Systematic Review

**Meharun Nesa Ripa[1*], Nazmus Sakib[2], Ashraful Hussain[1], Sultan M. Ajwad Quayyum[1], Ali Akbar[3], Muhammad Abdul Wadud[1], Monoranjon Sarker[1], A. K. M. Daud[1]**

[1]Department of Surgery, Jalalabad Ragib-Rabeya Medical College Hospital, Sylhet, Bangladesh
[2]Department of Surgery, Thaa Atoll Hospital, Veymandoo, Maldives
[3]Department of Surgery, Shahid Syed Nazrul Islam College, Mymensingh, Bangladesh
Email: *drmeherripa10@gmail.com

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## Abstract

Background: Neoadjuvant immunotherapy, particularly immune checkpoint inhibitors (ICIs), has emerged as a promising therapeutic strategy in the treatment of Triple-Negative breast cancer (TNBC). This systematic review evaluates the clinical impact of ICIs in combination with neoadjuvant chemotherapy, focusing on their improving pathological complete response (pCR) rates and outcomes. This review was conducted using PRISMA guidelines. A comprehensive literature search was conducted across multiple databases, including PubMed, Google Scholar, and EMBASE, for studies evaluating the use of ICIs in neoadjuvant therapy regimens for early-stage TNBC. Overall, while neoadjuvant ICIs represent a potential breakthrough in TNBC treatment, further clinical trials and long-term data are necessary to better define their role in improving patient outcomes.

## Keywords

Neoadjuvant Immunotherapy, Checkpoint Inhibitors, Triple Negative Breast Cancer (TNBC)

## 1. Introduction

Triple-Negative breast cancer (TNBC) is a distinct subtype of breast cancer characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression. It accounts

for approximately 10% - 20% of all breast cancer cases [1]. The defining features of TNBC include its aggressive nature, early metastatic potential, visceral organ involvement, and poorer prognosis compared to other breast cancer subtypes. Due to the lack of hormone and HER2 receptor expression, TNBC does not respond to endocrine therapies that target these pathways [2].

Immunotherapy has emerged as a crucial first-line treatment in advanced TNBC cases that test positive for PD-L1 using immunohistochemical (IHC) assays [3]-[5]. Additionally, there is growing evidence supporting the use of immunotherapy in early-stage TNBC [6]-[11]. Traditionally, platinum-based chemotherapy has been the cornerstone of TNBC treatment. However, advances in molecular classification and genome sequencing have led to the identification of new molecular targets, paving the way for novel treatment strategies [2]. Some of the promising therapeutic approaches being explored include immune checkpoint inhibitors (ICIs), poly (ADP-ribose) polymerase (PARP) inhibitors, antibody-drug conjugates, cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, and multikinase inhibitors [12]. The use of immunotherapy in early-stage TNBC is particularly promising. Strong biological evidence supports the potential benefit of immune checkpoint inhibitors in this setting. While breast cancer has historically not been considered highly immunogenic, early-stage TNBC exhibits significant immune cell infiltration, making it a viable candidate for immunotherapy [13] [14].

Immune checkpoints are regulatory molecules found on immune cells that interact with specific ligands on target cells to prevent excessive immune responses, thus protecting normal tissues from immune attack and reducing the risk of autoimmunity. Key immune checkpoints on T cells include programmed death-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) [15]. Many solid tumors, including melanoma, lung, breast, bladder, colon, liver, head, and neck cancers, evade immune destruction by expressing checkpoint ligands such as programmed death-ligand 1 (PD-L1). This immune escape mechanism has led to the development of checkpoint inhibitors—therapies designed to block these pathways and restore the immune system's ability to attack cancer cells [16]-[19].

In TNBC, the PD-1/PD-L1 pathway plays a crucial role in immune evasion. Research suggests that 20% - 30% of TNBC cases express PD-L1, often in association with tumor-infiltrating lymphocytes (TILs) [20], supporting the potential role of PD-1/PD-L1 inhibitors in this cancer type. By blocking PD-1/PD-L1 interactions, ICIs restore T-cell function, enhancing anti-tumor immunity and improving clinical outcomes. Compared to chemotherapy, which remains the standard treatment for TNBC, ICIs offer the advantage of longer-lasting responses, particularly in patients with high PD-L1 expression. Clinical trials, such as KEYNOTE-355 and IMpassion130, have demonstrated that combining ICIs with chemotherapy significantly improves progression-free survival (PFS) and overall survival (OS) in metastatic TNBC [3] [21].

Several immune checkpoint inhibitors have been investigated for their potential in TNBC treatment. PD-1 inhibitors (such as pembrolizumab, nivolumab, and

cemiplimab), PD-L1 inhibitors (including atezolizumab, avelumab, and durvalumab), and CTLA-4 inhibitors (such as ipilimumab and tremelimumab) have been studied in various clinical settings [18] [19]. A significant milestone in TNBC treatment was the IMpassion130 trial [3], which demonstrated positive outcomes with atezolizumab (a PD-L1 inhibitor) in combination with nab-paclitaxel for locally advanced or metastatic TNBC. Based on these findings, the U.S. Food and Drug Administration (USFDA) granted accelerated approval for this combination therapy on March 8, 2019 [21].

Despite these advancements, no targeted therapy has received full approval for early-stage TNBC (stages I-III), where neoadjuvant and adjuvant chemotherapy remain the standard of care. However, chemotherapy alone does not provide a substantial survival benefit, as evidenced by a five-year metastasis-free survival rate of 70% and a 30% - 40% incidence of distant metastasis and cancer-related mortality [1] [22]. In response, several clinical trials are investigating the clinical impact of combining checkpoint inhibitors with neoadjuvant chemotherapy (NACT) in early-stage TNBC. The aim of this systematic review was to investigate the clinical impact of combining checkpoint inhibitors with neoadjuvant chemotherapy (NACT) in early-stage TNBC.

## 2. Methodology & Materials

### 2.1. Selection Criteria

**1) Inclusion Criteria:**

a) Randomized controlled trials (RCTs), clinical trials, cohort studies, and meta-analyses.

b) Patients diagnosed with early-stage TNBC (Stage I - III).

c) Neoadjuvant immune checkpoint inhibitors (PD-1/PD-L1 inhibitors) ± chemotherapy.

**2) Exclusion Criteria:**

Non-clinical studies, no immune checkpoint inhibitors in neoadjuvant settings and no expert opinion were excluded.

### 2.2. Study Design

This review was conducted using PRISMA guidelines. The review consisted of 5 steps: 1) Problem identification; 2) Literature searching; 3) Data review and evaluation; 4) Data synthesis and analysis; 5) Data presentation.

### 2.3. Search Method

A comprehensive search was performed in electronic databases PubMed, Google Scholar, and Embase to identify relevant studies on neoadjuvant immunotherapy in TNBC. The following search terms were used:

- Triple-negative breast cancer.
- Neoadjuvant therapy.
- Immune checkpoint inhibitors.

- PD-1 inhibitors (e.g., pembrolizumab, nivolumab).
- PD-L1 inhibitors (e.g., atezolizumab, durvalumab).
- CTLA-4 inhibitors (e.g., ipilimumab, tremelimumab).
- Key clinical outcomes such as pathologic complete response (pCR), event-free survival (EFS), and overall survival (OS). The search was restricted to English-language studies published in the last 10 years, with foreign-language articles included only if an English translation was available.

### 2.4. Data Collection

Relevant data were systematically extracted from multiple studies to ensure accuracy. The initial database search yielded studies based on author names, titles, keywords, and abstracts. Abstracts were screened based on exclusion criteria, and full-text articles were retrieved when abstracts lacked sufficient details.

The selection process focused on:

- Study design.
- Sample size.
- Assessed outcomes (pCR, EFS, OS).
- Study duration.
- Overall quality.

Following this, essential data were compiled to provide a comprehensive analysis.

### 2.5. Quality Assessment of Included Studies

A formal risk of bias assessment was conducted for all included studies using:

- Cochrane Risk of Bias (RoB) Tool for RCTs.
- Newcastle-Ottawa Scale (NOS) for cohort studies.
- ROBINS-I (Risk of Bias in Non-Randomized Studies of Interventions) for non-randomized studies.

A risk of bias summary table was generated to improve transparency and reliability.

### 2.6. Heterogeneity Assessment

To evaluate heterogeneity among studies, the following statistical measures were used:

- **$I^2$ statistic:** Quantifies heterogeneity, where $I^2 > 50\%$ suggests significant variation.
- **Cochran's Q test:** Assesses heterogeneity across included studies.
- **Subgroup analysis:** Conducted based on study design, tumor PD-L1 expression, and intervention type.
- **Sensitivity analysis:** Performed by removing individual studies to assess their impact on overall results.

### 2.7. Meta-Analysis

If sufficient homogeneous data were available, a meta-analysis was conducted

using:

- Fixed-effects or random-effects models, depending on heterogeneity levels.
- Forest plots to illustrate pooled estimates.
- Funnel plots to assess publication bias.

### 2.8. Study Selection Process

The database search identified 130 articles (Figure 1). After removing duplicates, 85 articles remained. Of these:

- 55 were excluded based on title and abstract screening.
- 26 full-text articles were excluded for not meeting the inclusion criteria.
- Finally, 4 publications met the criteria and were included in this review.

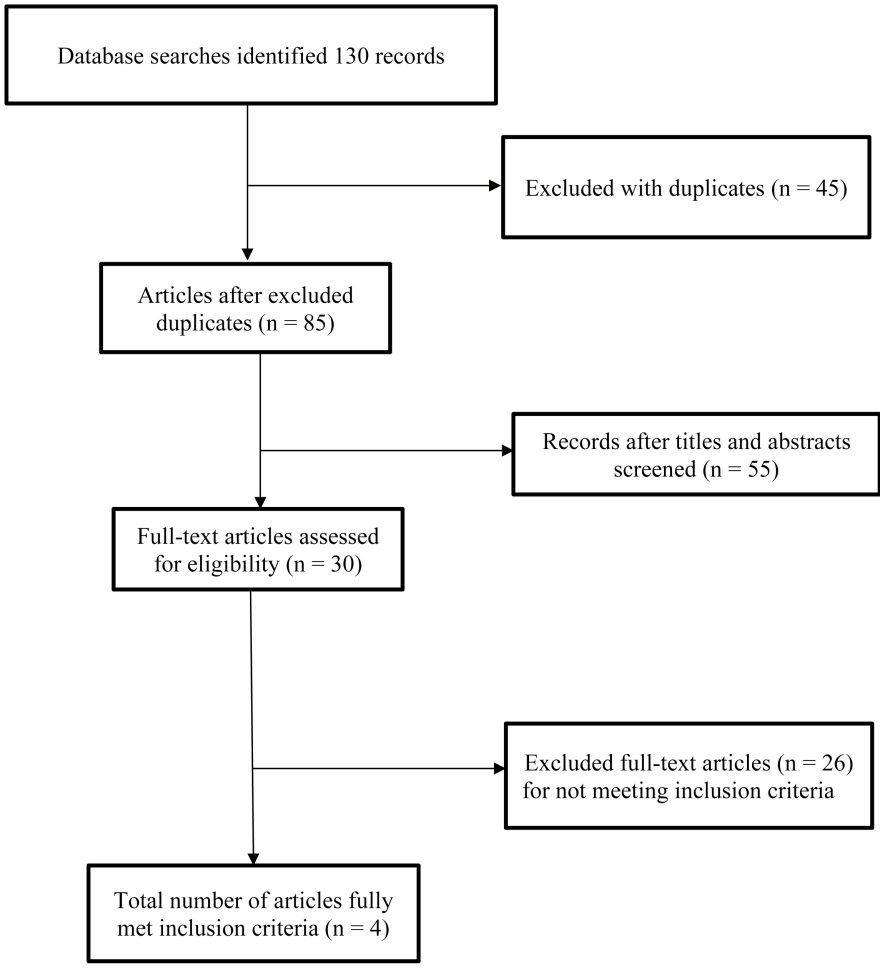



Figure 1. Flow chart of systematic review of literature selection process for the present research.

## 3. Result

Gianni L *et al.* [23] conducted the NeoTRIP Michelangelo trial, a Phase III randomized, multicenter study designed to assess the neoadjuvant use of atezolizumab, an anti-PD-L1 immune checkpoint inhibitor, in combination with car-

boplatin and nab-paclitaxel for early-stage triple-negative breast cancer (TNBC). The study included 280 patients, with 138 receiving the atezolizumab combination therapy and 142 receiving the placebo combination therapy. The primary endpoint was pathological complete response (pCR), and secondary endpoints included event-free survival (EFS) and other clinical outcomes (Table 1).

**Table 1.** Summary of published clinical trials on neoadjuvant immune checkpoint inhibitors on early-stage triple negative breast cancer.

| Reference | Trial | Experimental arm | Control arm | Drug target | Number of patients enrolled | Median time to follow-up (in months) | Primary outcomes | pCR (%) |
|---|---|---|---|---|---|---|---|---|
| Gianni L *et al.* [23] Italy | NeoTRIP Michelangelo (Phase III) | Neoadjuvant atezolizumab, carboplatin and nab-paclitaxe | Nerve root blocks were performed with and without a stimulator, accompanied by an epidurogram. | PD-L1 | 280 (138 experimental vs. 142 control) | 60† | EFS | 48.6% experimental vs. 44.4% control |
| Loibl S *et al.* [24] Germany | GeparNuevo (Phase II) | Neoadjuvant durvalumab plus anthracycline/ taxane based chemotherapy | Needle-based mechanical stimulation and SNRB were compared to surgery. | PD-L1 | 174 (88 experimental vs. 86 control) | 43.7 | pCR | 53.4% experimental vs. 44.2% control |
| Nanda R *et al.* [8] United States | i-SPY2 (Phase II) | Neoadjuvant pembrolizumab plus anthracycline/ taxane based chemotherapy | SNRB was performed after laminectomy, followed by surgical re-exploration. | PD-1 | 250 (69 experimental vs. | 33.6 | pCR | 22% experimental vs. 60% control |
| Schmid P *et al.* [7] UK | KEYNOTE-522 (Phase III) | Neoadjuvant pembrolizumab + carboplatin/ paclitaxel | Neoadjuvant carboplatin/ paclitaxel | PD-1 | 1174 (784 experimental vs. 390 control) | 15.5 | pCR | 64.8% experimental vs. 51.2% control |

†5-year EFS. pCR, pathologic complete response; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; EFS, event free survival.

The results revealed that the pCR rate in the atezolizumab group was 48.6%, compared to 44.4% in the placebo group. However, this difference was not statistically significant (odds ratio (OR) 1.18; 95% CI, 0.74 - 1.89; P = 0.48). These findings suggest that adding atezolizumab did not provide a statistically significant improvement in the pCR rate over the placebo, although the data did indicate a higher response in the atezolizumab group (Figure 2).

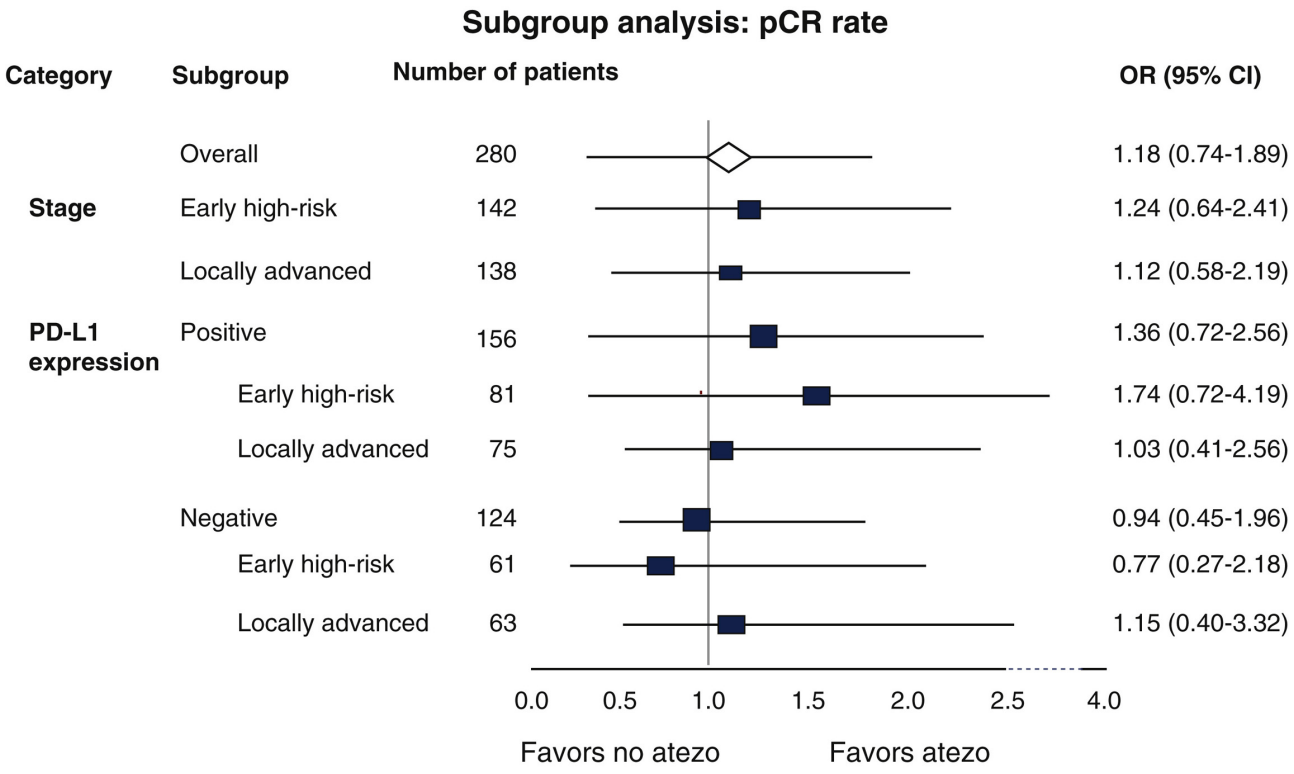



**Figure 2.** Subgroup analysis of pathological complete response (pCR) rate.

Loibl S *et al.* [24] conducted the GeparNuevo trial, a randomized, double-blind Phase II study to evaluate the efficacy of durvalumab, an anti-PD-L1 immune checkpoint inhibitor, in combination with neoadjuvant chemotherapy in patients with early-stage triple-negative breast cancer (TNBC). The study enrolled 174 patients between June 2016 and October 2017, with 88 patients receiving durvalumab plus chemotherapy and 86 patients receiving placebo plus chemotherapy. The chemotherapy regimen consisted of both anthracycline-based and taxane-based therapies, which are commonly used in neoadjuvant treatment for TNBC. The primary endpoints of the study included pathological complete response (pCR), as well as 3-year invasive disease-free survival (iDFS), distant disease-free survival (DDFS), and overall survival (OS).

While the study showed a non-significant increase in pCR rates in the durvalumab group, significant improvements were observed in survival outcomes. The 3-year iDFS was 85.6% in the durvalumab group, compared to 77.2% in the placebo group (hazard ratio (HR) 0.48, 95% CI 0.24 - 0.97, P = 0.036). Additionally, the DDFS improved from 78.4% in the placebo group to 91.7% in the durvalumab group (HR 0.31, 95% CI 0.13 - 0.74, P = 0.005), and OS was significantly better in the durvalumab group at 95.2% compared to 83.5% in the placebo group (HR 0.24, 95% CI 0.08 - 0.72, P = 0.006) (**Figure 3**). Durvalumab enhanced iDFS, DDFS, and OS in patients with and without pCR as compared to a placebo (**Figure 4**). In the pCR analysis, the window cohort's addition of durvalumab resulted in a significantly higher pCR rate than the non-window cohort [OR 2.22 (95% CI 1.06 -

4.64) versus OR 0.61 (95% CI 0.21 - 1.75), interaction P 1/4 0.048], but the durvalumab effect did not differ in iDFS between the window and non-window cohorts (Figure 5).

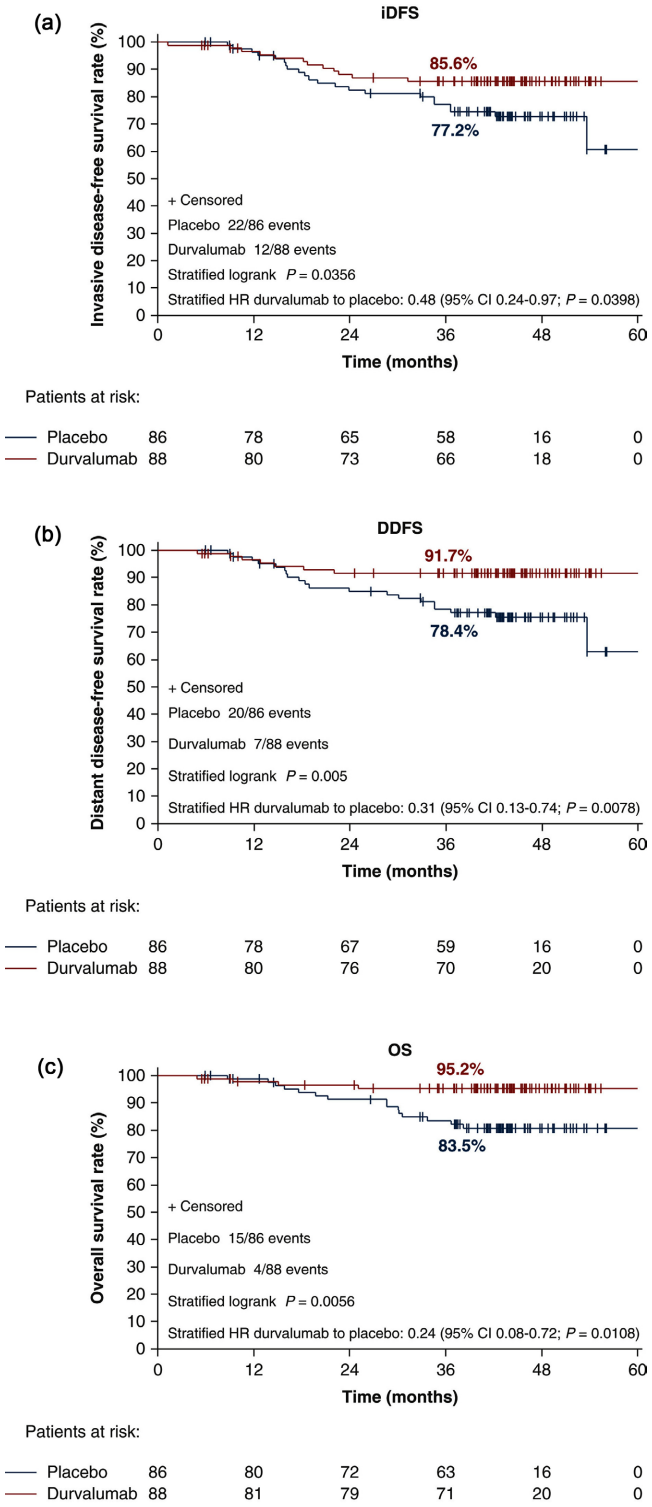



Figure 3. (a) invasive disease-free survival (iDFS), (b) distant disease-free survival (DDFS) and (c) overall survival (OS) by treatment arm.

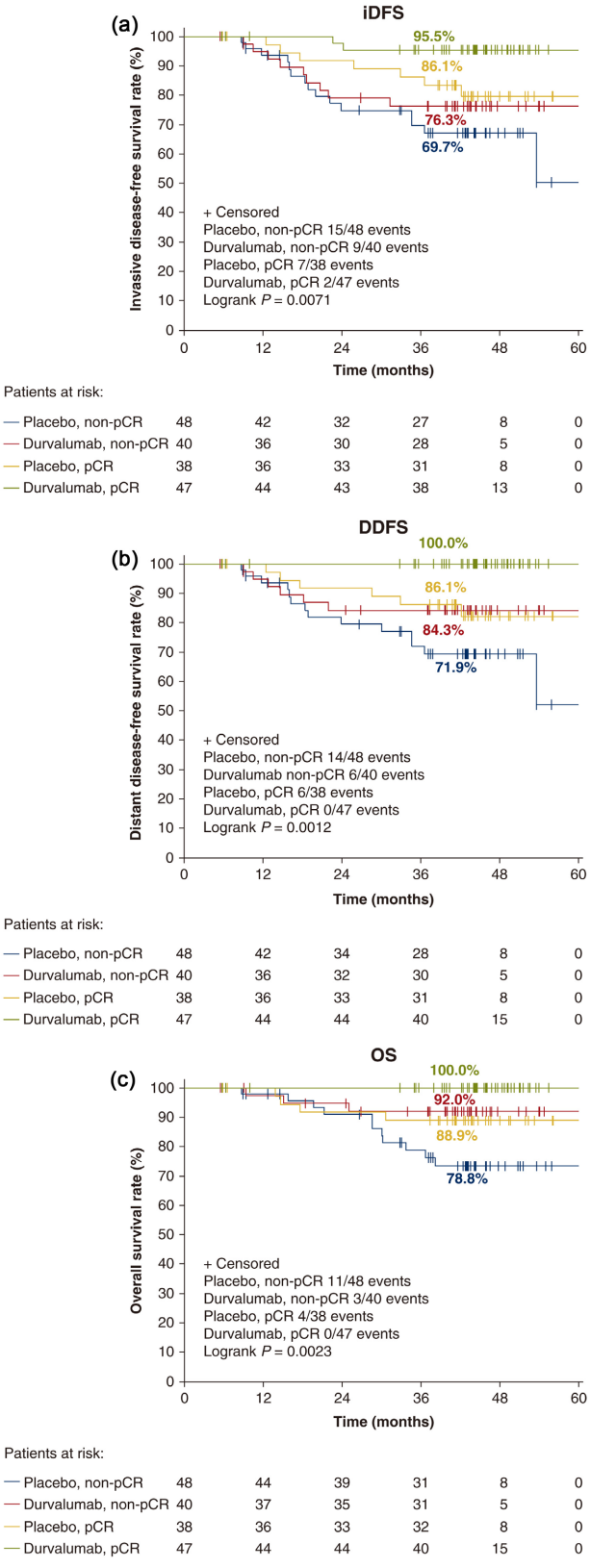



**Figure 4.** (a) invasive disease-free survival (iDFS), (b) distant disease-free survival (DDFS) and (c) overall survival (OS) by pCR and treatment arm. The event-free rates at 36 months in each group are displayed above and below the curves.

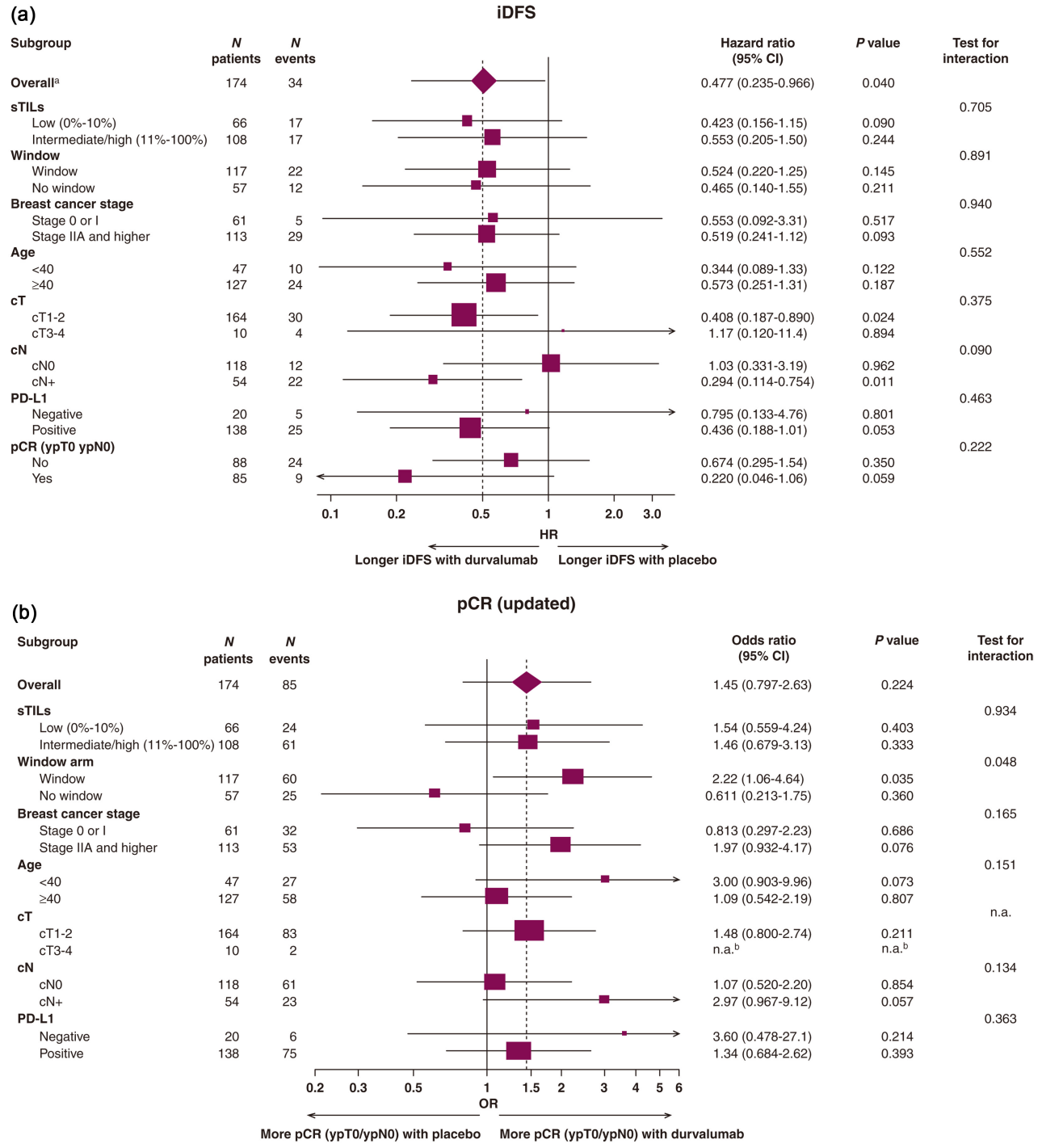



**Figure 5.** Subgroup analysis of (a) invasive disease-free survival (iDFS) (univariate Cox regression model) and (b) pCR (univariate logistic regression model).

Nanda R *et al.* [8] conducted the i-SPY2 trial, a Phase II study evaluating the neoadjuvant use of pembrolizumab combined with paclitaxel and AC chemotherapy in early-stage breast cancer, including triple-negative breast cancer (TNBC). Of the 250 women enrolled, 69 received pembrolizumab. The study found a significant increase in pathological complete response (pCR) rates, with 60% of

TNBC patients in the pembrolizumab group achieving pCR, compared to 22% in the control group. Pembrolizumab also shifted the residual cancer burden to a lower disease stage and was associated with a 93% event-free survival at 3 years. Only four out of 69 patients randomly assigned to pembrolizumab had three or more years of follow-up; the median follow-up durations for patients in the control and pembrolizumab arms were 3.5 and 2.8 years, respectively. For the entire cohort, EFS was qualitatively similar across the pembrolizumab and control groups (Figure 2); however, due to the small number of patients, care must be used when drawing inferences. Regardless of arm, patients who attained pCR had outstanding results (Figure 6).

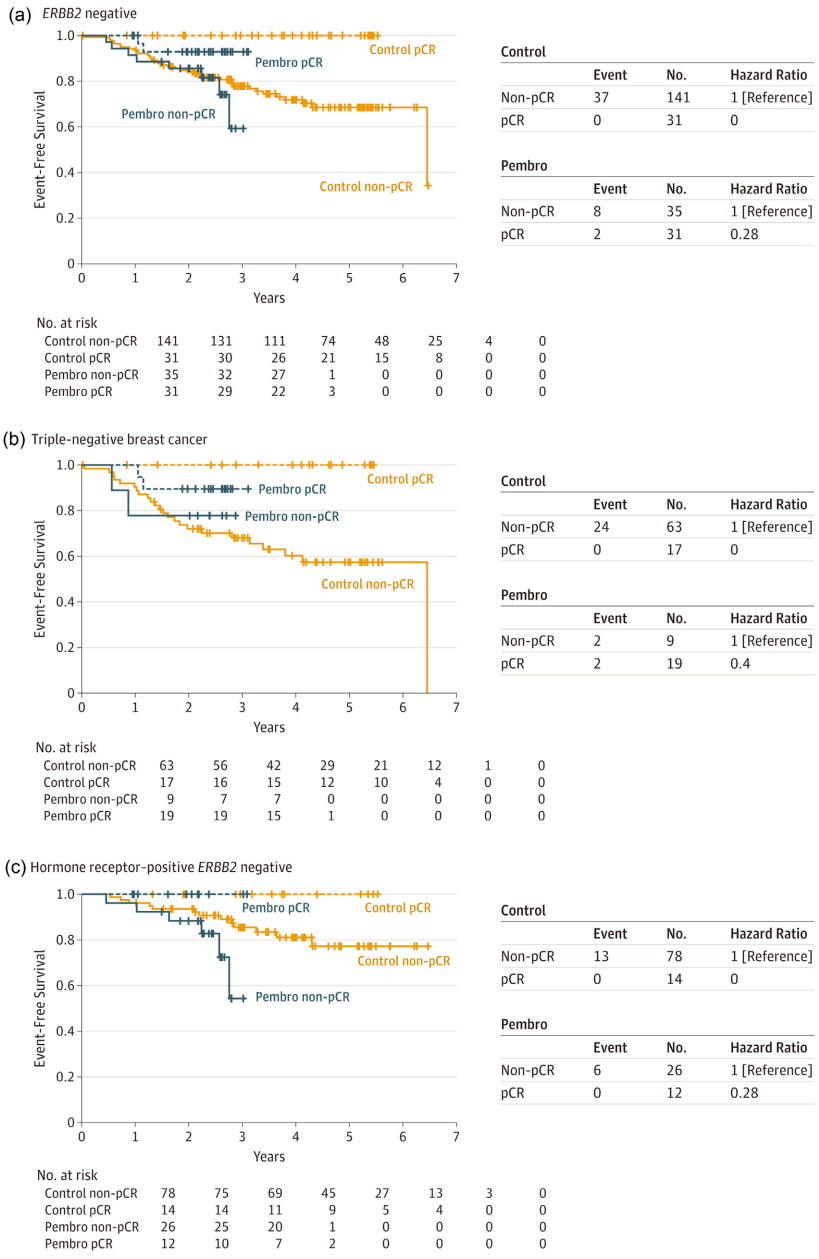



**Figure 6.** Event-Free survival by signature and pathologic complete response (pCR).

Schmid P *et al.* [7] conducted the Phase III KEYNOTE-522 trial, a randomized, double-blind, placebo-controlled study, to evaluate the effectiveness of pembrolizumab (anti-PD-1) combined with neoadjuvant chemotherapy in early-stage triple-negative breast cancer (TNBC). A total of 1174 patients were randomized into two groups: one received pembrolizumab plus chemotherapy (carboplatin and paclitaxel), and the other received a placebo plus the same chemotherapy regimen. At the first interim analysis, the pembrolizumab combination significantly improved the pathological complete response (pCR) rate to 64.8%, compared to 51.2% in the placebo group ($P < 0.001$). After a median follow-up of 15.5 months, the pembrolizumab group showed a 37% reduction in the risk of disease progression or recurrence (7.4% vs. 11.8%; HR 0.63, 95% CI, 0.43 - 0.93). However, Grade 3 or higher treatment-related adverse events were slightly more common in the pembrolizumab group (78.0% vs. 73.0%), including rare instances of treatment-related mortality. The proportions of patients in the PD-L1-positive population who experienced a pathological complete response (stage ypT0/Tis ypN0) were 68.9% (230 of 334) among those who received pembrolizumab-chemotherapy, 54.9% (90 of 164) among those who received placebo-chemotherapy, 45.3% (29 of 64 patients), and 30.3% (10 of 33 patients) among those who received placebo-chemotherapy in the PD-L1-negative population (Figure 7). The hazard

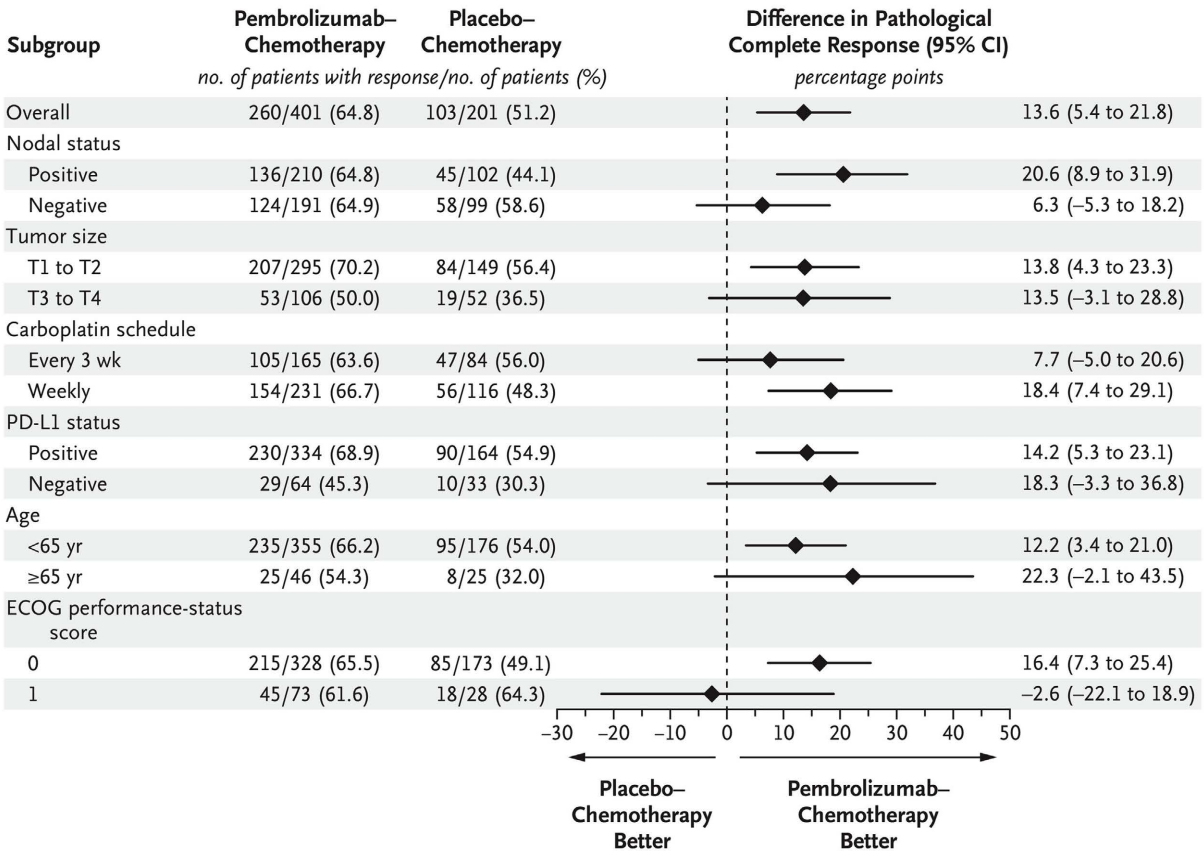



**Figure 7.** Subgroup analysis of difference in percentages of patients with a pathological complete response (stage ypT0/Tis ypN0).

ratio for disease progression (precluding definitive surgery), local or distant recurrence or a second primary tumor, or death from any cause favored the pembrolizumab-chemotherapy group (hazard ratio, 0.63; 95% CI, 0.43 to 0.93). The Kaplan-Meier estimates of the percentage of patients who were alive at 18 months without disease progression that precluded definitive surgery, without local or distant recurrence, and without a second primary tumor were 85.3% (95% CI, 80.3 to 89.1) in the placebo-chemotherapy group and 91.3% (95% CI, 88.8 to 93.3) in the pembrolizumab-chemotherapy group; neither group reached the median (Figure 8).

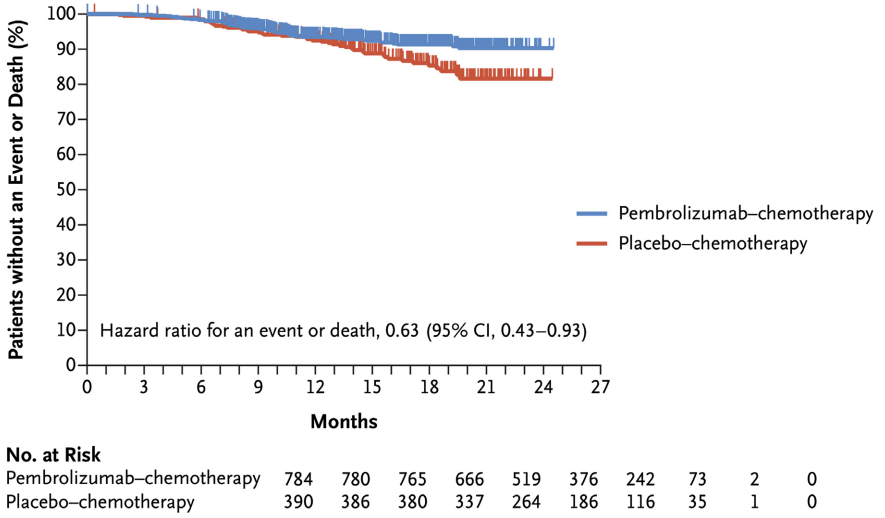
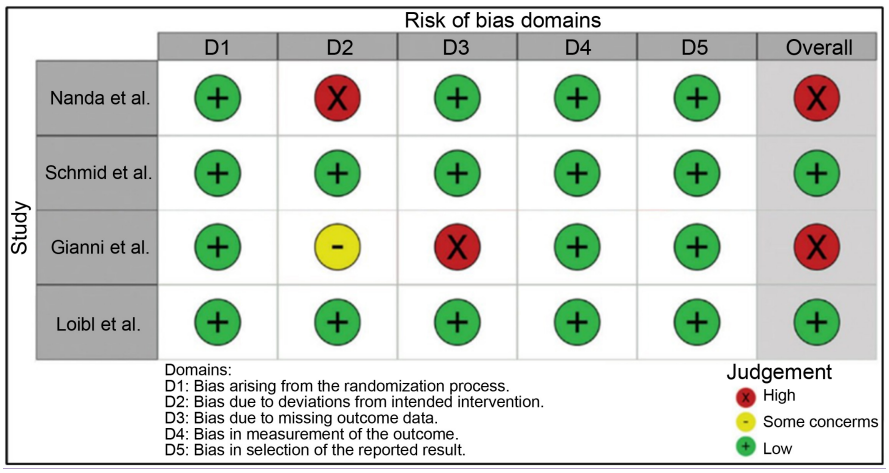



Figure 8. Kaplan-Meier estimates of event-free survival, according to trial group in the intention-to-treat population.

**Risk of Bias:**




The overall ROB was recorded as low in three RCTs. The risk of bias was recorded as high for Nanda *et al.* [8] (due to its small pembrolizumab-treated cohort and adaptive trial design) and Gianni *et al.* [23] (due to its small sample size and

lack of PD-L1 stratification).

## 4. Discussion

Triple-Negative breast cancer (TNBC) remains one of the most challenging subtypes of breast cancer due to its aggressive nature and lack of targeted therapies [25]. The approval of several targeted therapies, such as PARP inhibitors (olaparib and talazoparib) [12] and the PD-L1 inhibitor (atezolizumab) [21], for treating advanced or metastatic TNBC has driven a surge in clinical trials investigating their efficacy in early-stage disease. Currently, neoadjuvant chemotherapy (NACT) remains the standard approach for managing early-stage breast cancer [26]. The integration of immune checkpoint inhibitors (ICIs) into the treatment landscape for early-stage TNBC has shown promising results, particularly in combination with neoadjuvant chemotherapy. This systematic review focuses on key clinical trials and emerging real-world evidence. Historically, achieving a pathological complete response (pCR) in TNBC has shown a strong correlation with event-free survival (EFS) rates [27]. As a result, pCR is widely recognized as a surrogate endpoint for predicting long-term clinical outcomes in early-stage cancers. In 2014, the FDA issued guidance endorsing pCR as an endpoint for the accelerated approval of neoadjuvant treatments in TNBC and related breast cancers [28]. Our findings suggest that the addition of ICIs, particularly PD-1/PD-L1 inhibitors such as pembrolizumab and atezolizumab, to neoadjuvant chemotherapy significantly improves pathological complete response (pCR) rates. Studies, including KEYNOTE-522 [7] have demonstrated a substantial increase in pCR, which is strongly correlated with improved event-free survival (EFS) and overall survival (OS). Furthermore, exploratory analyses indicate that patients with PD-L1-positive tumors derive the greatest benefit, though some response is observed in PD-L1-negative subgroups as well.

In the durvalumab study, [24] showed a non-significant increase in pCR rates in the durvalumab group, significant improvements were observed in survival outcomes. The 3-year iDFS was 85.6% in the durvalumab group, compared to 77.2% in the placebo group (hazard ratio (HR) 0.48, 95% CI 0.24 - 0.97, P = 0.036). Additionally, the DDFS improved from 78.4% in the placebo group to 91.7% in the durvalumab group (HR 0.31, 95% CI 0.13 - 0.74, P = 0.005), and OS was significantly better in the durvalumab group at 95.2% compared to 83.5% in the placebo group (HR 0.24, 95% CI 0.08 - 0.72, P = 0.006). One of the major concerns regarding ICI use in early-stage TNBC is the risk of immune-related adverse events (irAEs). Immune-related adverse events (irAEs) were observed in 28% of patients treated with anti-PD-1 therapies and 53% of those receiving anti-PD-L1 inhibitors, as reported by Patrinely JR *et al.* (2021). Among specific agents, atezolizumab (74%) and nivolumab (81%) exhibited notably higher irAE rates compared to pembrolizumab (18%) and avelumab (10%) [29]. For mild dermatologic irAEs, symptomatic management is recommended without discontinuing ICIs, often involving topical corticosteroids and antihistamines [30]. In moderate cases,

temporary suspension of ICI therapy may be necessary. Severe irAEs may require permanent discontinuation of treatment, along with high-dose corticosteroids (1 - 2 mg/kg/day of prednisone or equivalent). If symptoms persist, additional immunosuppressive agents like infliximab or mycophenolate mofetil may be needed [31]. The presence of irAEs has important implications for treatment adherence, survival outcomes, and quality of life in TNBC patients. Research suggests that the development of irAEs may be associated with improved treatment response and overall survival, potentially indicating a connection between immune activation and tumor control. The review highlights that while most irAEs are manageable with standard immunosuppressive therapy, a subset of patients experiences severe toxicities that may necessitate treatment discontinuation. Endocrine-related toxicities, including hypothyroidism and adrenal insufficiency, are particularly long-term monitoring. Balancing the potential h toxicity risks remains a crucial challenge in patient selection and treatment planning. Real-world data are beginning to complement findings from clinical trials, offering insights into treatment patterns and long-term outcomes in diverse patient populations. However, the generalizability of clinical trial results to broader patient cohorts, including those with comorbidities and older age groups, remains an area requiring further exploration. Ongoing and future studies are expected to refine treatment algorithms and provide guidance on the optimal duration of immunotherapy in the neoadjuvant and adjuvant settings.

Furthermore, the development of biomarkers to predict patient response and select the best candidates for immunotherapy could significantly improve treatment outcomes and minimize adverse effects, providing a more personalized approach to care. Biomarkers associated with immune activation, tumor microenvironment changes, and immune checkpoint expression can help identify patients who are most likely to benefit from ICIs. This could lead to a more refined selection of patients for personalized treatment plans, optimizing therapeutic efficacy while minimizing unnecessary toxicities.

## 5. Limitations

The current review of neoadjuvant immunotherapy in Triple-Negative breast cancer (TNBC) has several limitations. The existing literature is limited, with variability in study design and patient populations, impacting the generalizability of findings. Most studies focus on short-term outcomes, lacking long-term survival data. There is also a lack of standardized biomarkers to predict treatment response, and limited research on immune-related toxicities. Additionally, the review primarily centers on immune checkpoint inhibitors, with little exploration of combination therapies. The inclusion criteria were limited to English-language studies, potentially omitting relevant research in other languages.

## 6. Conclusion

The review ICIs represent, a significant advancement in the management of early-

stage TNBC, demonstrating improved pCR and survival outcomes. However, optimizing patient selection, mitigating immune-related toxicities, and identifying reliable biomarkers remain critical challenges. Future research should focus on refining treatment strategies to maximize benefits while minimizing risks, ultimately improving outcomes for patients with early-stage TNBC.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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