EFFECTS OF THE COMBINATION OF NEOADJUVANT IMMUNOTHERAPY WITH CHEMOTHERAPY VERSUS PLACEBO WITH CHEMOTHERAPY ON PATHOLOGIC COMPLETE RESPONSE IN EARLY TRIPLE-NEGATIVE BREAST CANCER: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction One of the most aggressive forms of breast cancer is triple-negative breast cancer (TNBC). TNBC has a poor prognosis and few therapy options. Therefore, therapeutic intervention is strongly suggested even though treatment with the intention of cure is still possible. Chemotherapy and immune checkpoint-inhibiting drugs have already been utilized to raise the pathologic complete response (pCR) rates in TNBC patients.
Objectives The study aims to assess the efficacy of neoadjuvant immunotherapy in combination with chemotherapy, in the early-stage TNBC, with the primary endpoint of pCR (ypT0/is ypN0).
Methods The medical term "Immunotherapy", "Pembrolizumab", "Atezolizumab", "Durvalumab", "Neoadjuvant treatment", and "Triple-negative breast cancer", were used in Pubmed and Google Scholar to discover studies of the efficacy of immunotherapy combined with chemotherapy in early-stage TNBC by following the PICO framework up to January 2023. All phase 1, 2, and 3 clinical studies that demonstrated safety and efficacy data were included. Two independent reviewers excluded the non-RCTs and other clinical studies irrelevant to the study question. Five remaining studies were reviewed and screened for the inclusion criteria, based on the relevance to the study subject and clinical outcomes.
Results Based on five studies included in this review, a combination of immunotherapy (pembrolizumab, atezolizumab, or durvalumab) with chemotherapy has shown superior effects of increasing pCR rates, compared to the chemotherapy alone, regardless of PD-L1 status, in early-stage TNBC. Adverse events were not more frequently reported with the immunotherapy compared to placebo.
Conclusions A combination of neoadjuvant immunotherapy with chemotherapy has revealed superior effects of increasing pCR rates, compared to the chemotherapy alone in early-stage TNBC, irrespective of PD-L1 status, with an acceptable safety profile. However, further studies are needed to explore this issue.

Keywords: Immunotherapy, Pembrolizumab, Atezolizumab, Durvalumab, Neoadjuvant Treatment, Triple-Negative Breast Cancer

1. INTRODUCTION

"Breast cancer is a universal health problem. According to statistics from Global Cancer, breast cancer is the most common cause of death among women from neoplasms, accounting for 15.5% of all tumor-related deaths in 2020" [1]. "One of the most dangerous

types of breast cancer is triple-negative breast cancer (TNBC)" [2]. TNBC is more aggressive than other subtypes, and the majority of patients experience recurrence and metastasis within 3 years, with a dismal prognosis [3]. TNBC frequently has a high death rate and early recurrence [4]. TNBC treatment choices are scarce, and its prognosis is dismal. Therefore, therapeutic intervention is strongly advised when receiving treatment for a cure [5]. "The majority of stage II and stage III triple-negative breast cancer (TNBC) and HER2-positive breast cancer cases are currently being treated with neoadjuvant targeted therapy, which has proven to be the most effective treatment option for locally progressed and inflammatory breast cancer" [6]. "Following neoadjuvant therapy, a pathologic complete response (pCR) has been linked to enhanced event-free survival (EFS) and overall survival (OS) in early-stage breast cancer" [7]. "According to the available data, patients with TNBC experience marginally higher rates of pathologic complete response (pCR) when PD-1/PD-L1 inhibitors are added" [8]. "However, neoadjuvant immune checkpoint inhibitors' efficacy in treating early TNBC hasn't been examined in real-world research" [9].

2. OBJECTIVES

The study aims to assess the efficacy of neoadjuvant immunotherapy in combination with chemotherapy, in the early-stage TNBC, with the primary endpoint of pCR (ypT0/is ypN0).

3. METHODS

3.1 Inclusion and Exclusion Criteria

Research publications on the effectiveness of neoadjuvant immunotherapy in combination with chemotherapy in early-stage TNBC, with the outcome being pCR (ypT0/is ypN0), were included in the inclusion criteria for this literature search, original research, full-text journal, All phase 1, 2, and 3 clinical trials that provided safety and efficacy data were included. The exclusion criteria in this study are research studies with samples of non-humans, all case reports, case series, preclinical studies, review articles, meta-analyses, clinical studies irrelevant to the study question, and journals published in unknown databases. All journals used must be published in reputable journals in English. Out of the total of 13.702 research articles, five studies, which met the inclusion and exclusion criteria were selected and used as materials for our systematic review. The research strategy used the following English keywords: "Immunotherapy", "Pembrolizumab", "Atezolizumab", "Durvalumab", "Neoadjuvant treatment", and "Triple-negative breast cancer". This was to ensure that the obtained articles are relevant and appropriate. Subsequently, the five full text studies were downloaded and stored.

3.2 Screening

Following the initial identification of titles and abstracts, 13.702 articles were collected after collecting 12.900 from Google Scholar and 802 from PubMed following the PICO framework through January 2023. 350 papers were found after the research was reviewed by title and abstract. The researcher examined the full-text category. 302 journals were eliminated because they didn't adhere to the rules. 43 of the 48 remaining journals were eliminated after a thorough assessment because the studies did not meet the minimum requirements for inclusion. In the last stage, 5 papers were examined and screened for inclusion based on the relevance to the topic and results.

3.3 Review Literature Methods

There were several stages to the selection process: The results were initially evaluated for eligibility following the criteria for inclusion and exclusion. Regarding the inclusion criteria, we selected peer-reviewed journal original research articles written in English and published between 2019 and 2023 for the second stage. Journals published in unidentified databases and non-original publications like letter editors, abstract-only publications, and editorials were removed from the study. According to the examiners' subjective judgments, excluded records were considered methodological of a lower standard. The clinical efficacy of neoadjuvant immunotherapy combined with chemotherapy in early-stage TNBC is the main objective of this systematic review. We shall first describe the results to improve this interpretation in Fig. 1; the selection procedure for the papers is depicted.

Fig 1. Article Search Process

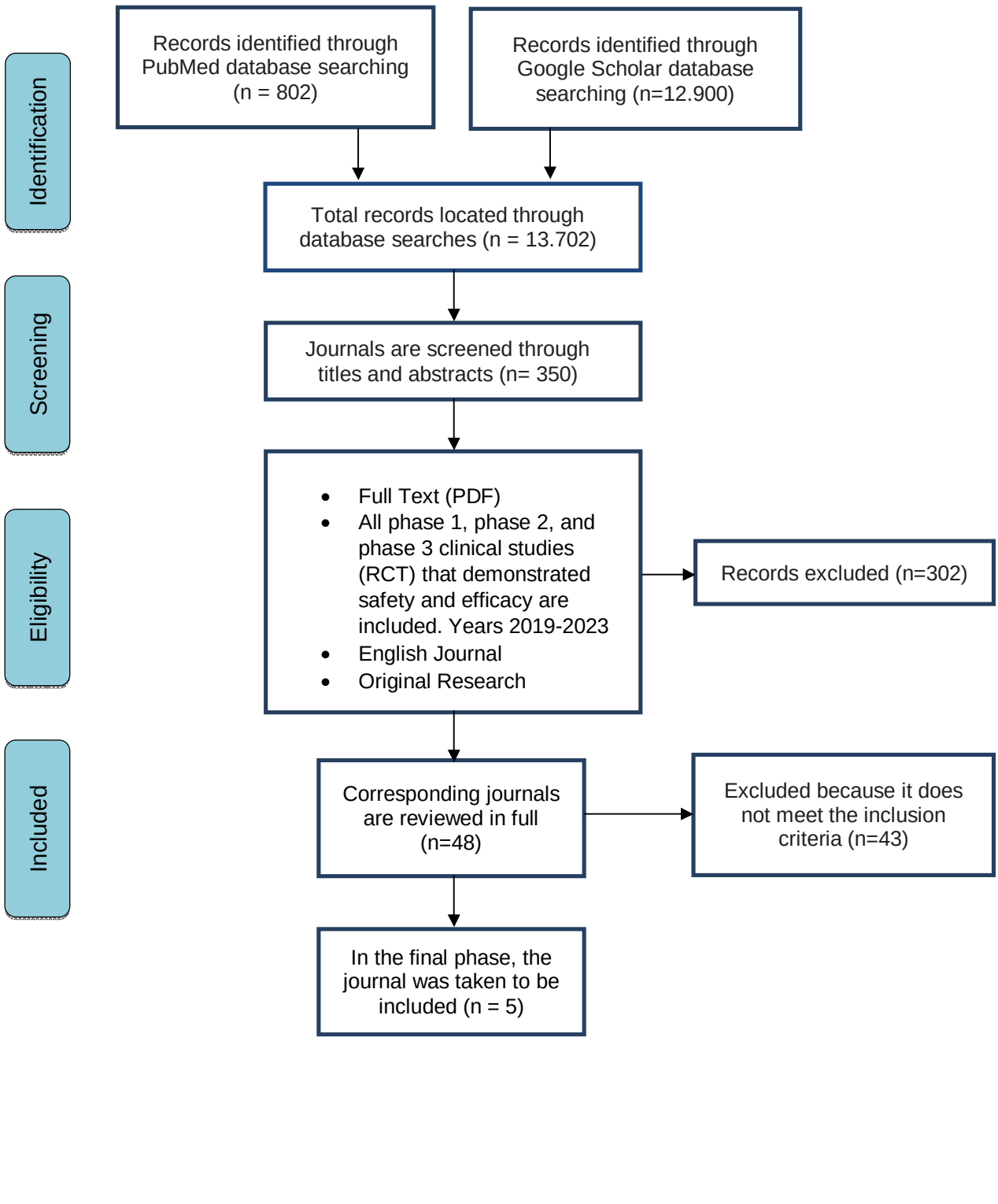

Table 1. Studies Characteristic

	Author	Title	Objectives	Method study/ design study	Sample	Result
1.	(Mittendorf et al., 2020) Randomized, double-blind, placebo-controlled, phase III trial (USA) [10].	Patients with early-stage triple-negative breast cancer (IMpassion031): a Randomized, double-blind, phase 3 trial, comparing chemotherapy and placebo with neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy.	To evaluate the effectiveness and safety of neoadjuvant atezolizumab in combination with nab-paclitaxel, followed by doxorubicin and cyclophosphamide in patients with early-stage TNBC who were treatment-naive.	Phase III trial employing a two-stage adaptive enrichment design that was randomized, multicenter, international, and double-blind.	(n=333)	Patients with early-stage TNBC experienced a considerably higher pathological complete response rate with an acceptable safety profile while receiving neoadjuvant atezolizumab therapy in combination with nab-paclitaxel and anthracycline-based chemotherapy.
2.	(Saji et al., 2022) Randomized placebo-controlled phase III trial (Japan) [5].	Neoadjuvant atezolizumab or placebo, in combination with nab-paclitaxel and anthracycline-based chemotherapy, in early triple-negative breast cancer: subgroup analysis of Japanese patients in a phase III randomized, controlled research.	To evaluate the efficacy and security of atezolizumab combined with neoadjuvant chemotherapy, including doxorubicin, cyclophosphamide, and nab-paclitaxel in patients with early-stage TNBC who have not yet received treatment. Pathologic complete response (ypT0/is ypN0) in the population treated with intention and PD-L1-positive (1% PD-L1 expressing tumor-infiltrating immune cells) were the co-primary objective.	Phase III trial evaluation that was double-blind, random, and placebo-controlled.	(n=36)	In this small exploratory analysis of Japanese patients with early-stage triple-negative breast cancer, atezolizumab added to neoadjuvant chemotherapy quantitatively increased pathological complete response against placebo; this finding was directionally consistent with the results of the other research. There were no additional red flags discovered.

3.	(Schmid, Peter et al., 2020) Randomized controlled trials (London) [4].	Pembrolizumab for Early Triple-Negative Breast Cancer.	To assess the efficacy and safety of adjuvant, neoadjuvant pembrolizumab treatment against adjuvant, placebo treatment in patients with early-stage triple-negative breast cancer. The primary outcomes were a pCR during definitive surgery and event-free survival (EFS) in the treated group.	pPacebo-controlled, double-blind, randomized study.	(n=602)	Compared to individuals who received a placebo plus neoadjuvant chemotherapy, those who received pembrolizumab plus neoadjuvant chemotherapy showed a considerably higher rate of pathological complete responses.
4.	(Nanda et al., 2020) Randomized controlled trials (USA) [11].	Effect of Neoadjuvant Chemotherapy and Pembrolizumab in Early-Stage TNBC Patients.	PCR was the main result. Achieving 3-year event-free and distant recurrence-free survival were the secondary goals, along with eliminating of the cancer burden. The experimental arms have progressive prediction success percentages in a hypothetical confirmatory phase 3 trial..	Phase II multicenter trial with randomization. Non-Blinded	(n=210)	When pembrolizumab is combined with chemotherapy, the anticipated pCR rates for patients with HR-positive/ERBB2- and triple-negative breast cancer are increased by two times. This study demonstrates the possibility of success for a phase 3 trial combining checkpoint blockade in women with early-stage high-risk, high-risk, ERBB2-negative breast cancer.

5.	(Loibl et al., 2019) Randomized, double-blind, placebo-controlled, phase II trial (USA)[12]	Early triple-negative breast cancer patients participating in a randomized phase II study comparing durvalumab versus neoadjuvant taxane-based anthracycline treatment	The primary objective endpoint was (pCR)	Phase II (n=117) double-blind, randomized, placebo-controlled study.	According to our results, adding durvalumab to anthracycline/taxane-based NACT increases the pCR rate, especially in patients who had previously only received durvalumab.

3.4 Methodological Characteristics

Based on the five studies examined, one study used a randomized, double-blind, placebo-controlled, phase III trial evaluation [10], one study used a randomized, double-blind, multicentre, multinational study [5], and one study used a randomized, double-blind trial. Randomized controlled trial that was placebo-controlled [4], one study used a non-blinded randomized controlled trial [11], and one study used a randomized phase II double-blind placebo-controlled trial that was [12].

3.5 Intervention Methods

Based on five studies, four used randomized double-blind, placebo-controlled [4,5,10,12], and one used a non-blinded randomized controlled trial [11].

4. RESULTS

Out of the total of 13.702 research articles, five studies were assessed by full-text review. In this study, the effficacy was measured by pathologic complete response (pCR) in early-stage TNBC treatment. Based on five studies included in this review, Four studies showed, regardless of the presence or absence of PD-L1, immunotherapy (pembrolizumab or atezolizumab) combined with chemotherapy significantly increased pathological complete response rates with an acceptable safety profile in early-stage TNBC. One study shown that immunotherapy (durvalumab alone before the commencement of immunotherapy combined with chemotherapy) enhanced pCR in early-stage TNBC, and the immunotherapy durvalumab did not cause adverse effects to occur more frequently than a placebo.

Table 2. The Efficacy and Safety of Neoadjuvant Immunotherapy and Chemotherapy in Early-stage TNBC

No	Study	Intervention/ Comparison (Neoadjuvant)	Subject	Follow-up	Pathological Complete Response ypT0/Tis ypN0		Adverse Events
1.	(Mittendorf et al., 2020) Randomized, double-blind, placebo-controlled, phase III trial (USA)[10]	Atezolizumab intravenous 840 mg every 2 weeks (20 weeks) – Standard NACT	165	20·6 months	n=95 (58%, 95% CI 50–65)	Rate Difference 17%, (95% CI 6–27) *P*<0,05	One patient in each group (the atezolizumab plus chemotherapy group and the placebo plus chemotherapy group) experienced an unrelated grade 5 adverse event (a car accident or pneumonia, respectively) during the neoadjuvant period. Grade 3–4 side effects were evenly distributed, whereas significant side effects were recorded by 37 (23%) and 26 (16%) people, respectively.
		Placebo– Standard NACT	168	19·8 months	n=69 (41%, 34–49) patients		
2.	(Saji et al., 2022) Randomized placebo-controlled phase III trial (Japan)[5]	Atezolizumab intravenous 840 mg every 2 weeks (12 weeks) – Standard NACT	17	22.2 months	n=7 41%; 95% CI (18-67)	Absolute Treatment Difference 4% (95% CI, −28 to 36)	All AEs in both treatment arms were treatment-related. Grades associated with treatment: In the atezolizumab and placebo groups, 12 (71%) and 13 (68%) patients reported 3-4 AEs. Both treatment arms saw no grade 5 adverse events.
		Placebo– Standard NACT	19	21.9 months	n=7 37%; 95% CI (16-64)		
3.	(Schmid, Peter et al., 2020) Randomized controlled trials (London)[4]	Pembrolizumab 200 mg intravenous every 3 weeks (8 cycles) – Standard NACT	401	Median 15.5 months	n=260 64.8% 95% CI (59.9–69.5)	Estimated Treatment Difference 13.6% (95% CI(5.4–21.8) *P*<0,05	In the pembrolizumab-chemotherapy group, there were 78.0% treatment-related adverse events of grade 3 or higher across all treatment phases, compared to 73.0% in the placebo-chemotherapy group. Mortality rates were 0.4% (3 patients) and 0.3% (1 patient), respectively..
		Placebo– Standard NACT	201		n=103 51.2% 95% CI (44.1–58.3)		
4.	(Nanda et al., 2020) Randomized controlled trials (USA)[11]	Pembrolizumab 200 mg intravenous every 3 weeks (4 cycles) – Standard NACT	29	2,8 years	n=17 60% 95% PI (44-75)	Probability Superior to Control 99,6 *P*<0,05	9 of the 69 individuals who received pembrolizumab (13.0%) had either hypothyroidism or hyperthyroidism. 6 of the 69 individuals who got pembrolizumab (8.7%) had adrenal insufficiency. Steroids or dosage interruption were successfully used to address these AEs by the protocol.
		Placebo– Standard NACT	89	3,5 years	n=20 22% 95% PI (13-30)		
5.	(Loibl et al., 2019) Randomized, double-blind, placebo-controlled, phase II trial (USA)[12]	Durvalumab 0.75 g i.v. (once in two weeks), Durvalumab 1.5 g i.v. q4wks (7 Cycles) - Standard NACT	117	16 Months	61.0%	OR 2.22 95% CI 1.06–4.64; *P*<0.05	Except for thyroid dysfunction, AEs were not more commonly reported with durvalumab than with placebo. Overall, 59 individuals (29 in the durvalumab arm and 30 in the placebo arm) had at least one major adverse event (AE).
		Placebo– Standard NACT			41.4%		

Abbreviation: TNBC, Triple-negative breast cancer; NACT, Neoadjuvant chemotherapy; AEs, Adverse Events

5. DISCUSSION

This study obtained five out of 13.702 articles that were relevant to the subject and outcomes. “The present results are consistent with findings from previous or other studies of the efficacy and safety of neoadjuvant immunotherapy for the treatment of triple-negative breast cancer” [13]. Overall, the pCR rate was increased in all therapy groups. In randomized clinical studies comparing atezolizumab and chemotherapy, PD-L1 inhibitors like atezolizumab demonstrated promising outcomes in patients with early-stage TNBC, according to (Mittendorf et al., 2020). “The study found that pathological complete response rates were considerably increased with an acceptable safety profile when atezolizumab was used as neoadjuvant therapy in conjunction with nab-paclitaxel and anthracycline-based chemotherapy” [10]. “A small exploratory analysis of Japanese patients with early-stage triple-negative breast cancer proved that atezolizumab added to neoadjuvant chemotherapy numerically improved pathological complete response versus placebo (Saji et al., 2022), a trend that was directionally consistent with the findings of the larger study”. AEs in both treatment groups were all caused by the treatments. Grade to therapy: 12 (71%) and 13 (68%) participants, respectively, in the atezolizumab and placebo groups, had 3–4 AEs. There were no grade 5 adverse events (AEs) in either therapy group. No new warning signs for safety were found [5]. According to research (Schmid, Peter et al., 2020), pembrolizumab plus neoadjuvant chemotherapy significantly increased the percentage of patients with a pathological complete response compared to placebo plus neoadjuvant chemotherapy [4]. Similar outcomes were observed in the (Nanda et al., 2020) study, where pembrolizumab was added to traditional neoadjuvant chemotherapy. “Pembrolizumab more than doubled the estimated pCR rates for both HR-positive/ERBB2- negative and triple-negative breast cancer, demonstrating that checkpoint blockade in early-stage, high-risk, ERBB2-negative breast cancer patients is highly likely to be successful in a phase 3 trial” [11]. In the study (Loibl et al., 2019), we discovered that adding durvalumab to anthracycline-/taxane-based NACT increases the pCR rate, especially in patients treated with durvalumab alone before chemotherapy. We also found that adverse events, except thyroid dysfunction, were not reported more frequently with durvalumab than with a placebo. 59 individuals (29 in the durvalumab arm and 30 in the placebo arm) had at least one major adverse event (AE) [12]. A strength of this study is the percentage of patients with pathological complete response in the neoadjuvant immunotherapy combined chemotherapy group was consistent with those reported in other studies of neoadjuvant regimens [9]. Another strength of this study is the article we obtained from Multinational.

5.1 Limitation

The limitation of this study is an inhomogeneity of the data outcome. Due to these restrictions, the author was unable to perform a meta-analysis.. Another limitation of this study is that it needs to assess long-term effects such as overall and event-free survival. Despite the limitations of this study, this systematic study offers considerable information on the efficiency and security of several neoadjuvant immunotherapy combinations in TNBC. It emphasizes the efficiency of immunotherapy (pembrolizumab, atezolizumab, or durvalumab) in early-stage TNBC.

6. CONCLUSIONS

A combination of neoadjuvant immunotherapy with chemotherapy has revealed superior effects of increasing pCR rates, compared to the chemotherapy alone in early-stage TNBC, irrespective of PD-L1 status, with an acceptable safety profile. However, further studies are needed to explore this issue.

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COMPETING INTERESTS

No conflicts of interest in this study

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