Review Article

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

ABSTRACT

Introduction Triple-negative breast cancer (TNBC) is one of the most aggressive forms of breast cancer. Therapeutic options for TNBC, which has poor outcomes, are limited. Therefore, therapeutic intervention is highly recommended when treatment with curative intent may still be possible. Combining immune checkpoint inhibitors agents with chemotherapy has previously improved pathological complete response (pCR) rates in patients with TNBC.

Objectives The study aims to assess the efficacy of neoadjuvant immunotherapy combination with chemotherapy in early-stage TNBC, with the primary endpoint was 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 trials that provided safety and efficacy are included. Two independent reviewers excluded non-RCT and clinical studies irrelevant to the study question.

Five remaining studies were reviewed and screened for inclusion based on relevance to the subject and outcomes.

Results Based on five studies in this review, a combination of immunotherapy pembrolizumab, atezolizumab, or durvalumab with chemotherapy has shown superior outcomes on increasing pCR rate than chemotherapy alone in early-stage TNBC, irrespective of PD-L1 status. Adverse events were not more frequently reported with immunotherapy than with a placebo.

Conclusions Neoadjuvant immunotherapy combination with chemotherapy has shown superior outcomes on increasing pCR rate than chemotherapy alone in early-stage TNBC, irrespective of PD-L1 status, with an acceptable safety profile.

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

INTRODUCTION

Breast Cancer (BC) is a universal health issue. According to the Global Cancer Observatory statistics, breast cancer led to 15.5 % of all deaths caused by tumors in 2020, and it is the leading cause of death among women due to neoplasms(1). Triple-negative breast cancer (TNBC) is one of the most aggressive forms of breast cancer(2). Triple-negative breast cancer is frequently associated with early recurrence and high mortality(3). Therapeutic options for TNBC, which has poor outcomes, are limited. Therefore, therapeutic intervention is highly

recommended when treatment with curative intent may still be possible(4). Pathologic complete response (pCR) following neoadjuvant therapy has been associated with improved event-free survival (EFS) and overall survival (OS) in early-stage breast cancer(5). Combining immune checkpoint inhibitors agents with chemotherapy has previously improved pathological complete response (pCR) rates in patients with TNBC.

MATERIAL AND METHODS

Inclusion and Exclusion Criteria

The inclusion criteria for this literature search include research journals about the efficacy of neoadjuvant immunotherapy combination with chemotherapy in early-stage TNBC, with the endpoint was pCR (ypT0/is ypN0), original research, full-text journal, all phase 1, 2, and 3 clinical trials that provided safety and efficacy are 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. Of the total of 13.702 research journals, five journals related to the inclusion and exclusion criteria of researchers were used as material for systematic reviews. The research strategy used the English keyword “Immunotherapy”, “Pembrolizumab”, “Atezolizumab”, “Durvalumab”, “Neoadjuvant treatment”, and “Triple-negative breast cancer”, this is to ensure that all articles obtained are relevant and appropriate. The full texts are downloaded and stored.

Screening

After initial identification of titles and abstracts, 12.900 articles were obtained from Google scholar, and 802 were acquired from PubMed by following the PICO framework up to January 2023, so the total number of result articles was 13.702. The research was screened by title and abstract, and then 350 articles were obtained. The researcher reviewed the full-text category. 302 journals were excluded because they did not meet the requirements. 48 remaining journals were reviewed in full, and 42 were excluded because they were not eligible for inclusion criteria. In the final stage, 5 remaining studies were reviewed and screened for inclusion based on relevance to the subject and outcomes.

Review Literature Methods

The selection process had several stages: In the first stage, the results were screened for eligibility according to the inclusion and exclusion criteria. In the second stage, related to inclusion criteria, we selected peer-reviewed journal original research articles published between 2019 and 2023, written in English. Journals published in unknown databases, Publications that are not original, such as letter editors, abstract only, and editorial, were excluded from the study. The selection and refining of the studies using the PRISMA 2009 flow diagram. Excluded records were considered methodologically of a lower quality according to the subjective opinions of the reviewers. The main focus of this systematic review is the efficacy of neoadjuvant immunotherapy combination with chemotherapy in early-stage TNBC. To optimize this interpretation, we will first clarify the findings. The search flow is summarized in figure 1 image.

Fig 1. Article Search Process

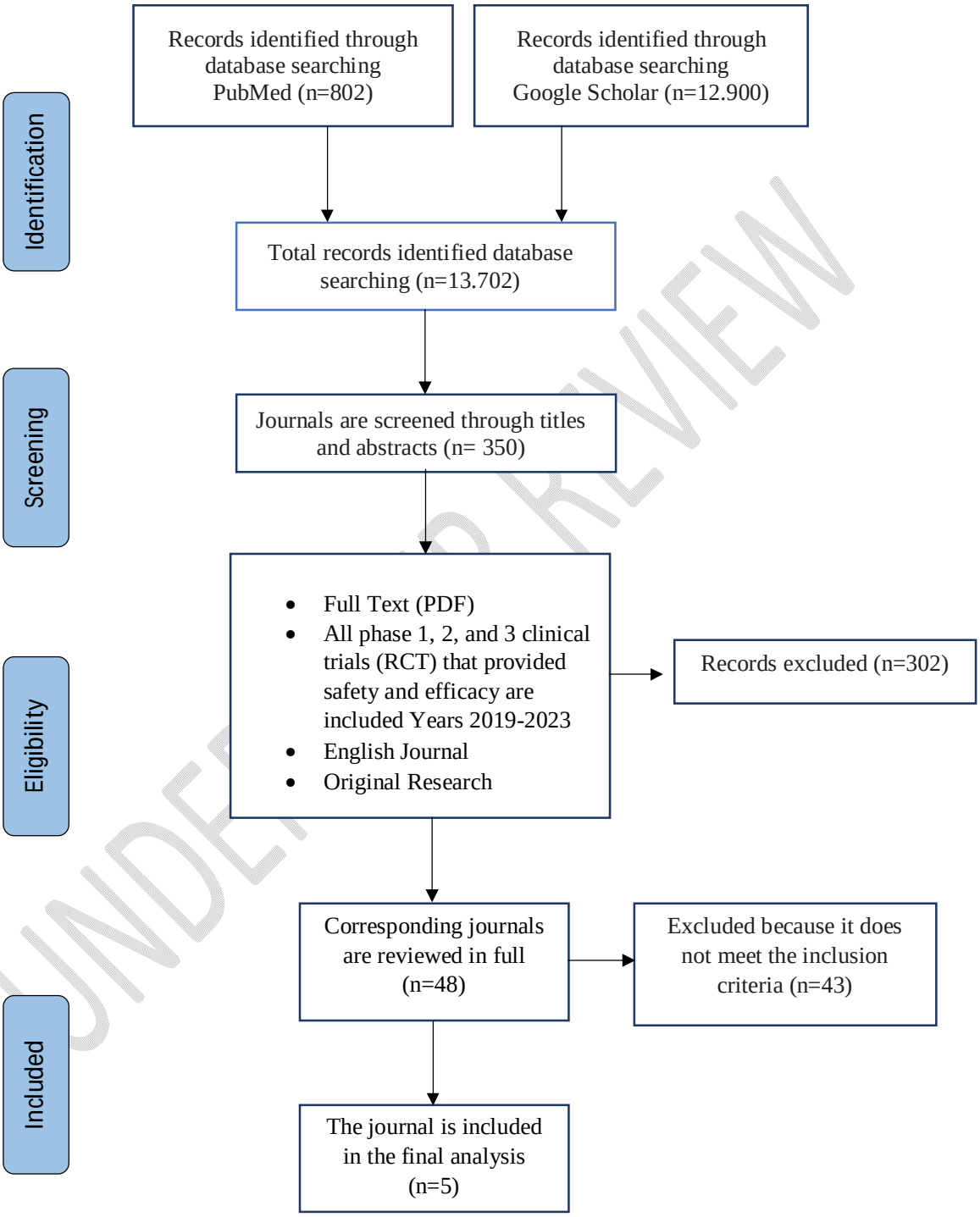

Table 1. Studies Characteristic

No	Author	Title	Objectives	Method study/ design study	Instrument	Sample	Result
1.	(Mittendorf et al., 2020) Randomized, double-blind, placebo-controlled, phase III trial (USA)(6)	Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early- stage triple-negative breast cancer (IMpassion031): a Randomized, double-blind, phase 3 trial Elizabeth.	To assess the efficacy and safety of neoadjuvant atezolizumab in combination with nab-paclitaxel followed by doxorubicin plus cyclophosphamide in patients with early-stage TNBC who were treatment-naïve.	Randomized, multicentre, multinational, double-blind, phase 3 study with a two-stage adaptive enrichment design.	Two groups	(n=333)	In patients with early-stage TNBC, neoadjuvant treatment with atezolizumab in combination with nab-paclitaxel and anthracycline-based chemotherapy significantly improved pathological complete response rates with an acceptable safety profile.
2.	(Saji et al., 2022) Randomized placebo-controlled phase III trial (Japan)(4)	Subgroup analysis of Japanese patients in a phase III randomized, controlled study of neoadjuvant atezolizumab or placebo, combined with nab-paclitaxel and anthracycline-based chemotherapy in early triple-negative breast cancer.	To evaluate the efficacy and safety of atezolizumab plus neoadjuvant chemotherapy consisting of nab-paclitaxel followed by doxorubicin and cyclophosphamide in treatment-naive patients with early-stage TNBC. Pathological complete response (ypT0/is ypN0) in the intention-to-treat and PD-L1-positive (≥1% PD-L1 expressing tumor-infiltrating immune cells) populations were co-primary endpoints.	Randomized, double-blind, placebo-controlled, phase III trial evaluation.	Two groups	(n=36)	Atezolizumab added to neoadjuvant chemotherapy numerically improved pathological complete response versus placebo in this small exploratory analysis of Japanese patients with early-stage triple-negative breast cancer, a trend directionally consistent with the global study results. No new safety signals were identified.

3.	(Schmid, Peter et al., 2020) Randomized controlled trials (London)(3)	Pembrolizumab for Early Triple-Negative Breast Cancer.	To evaluate the efficacy and safety of neoadjuvant pembrolizumab–chemotherapy compared with neoadjuvant placebo–chemotherapy, followed by adjuvant pembrolizumab or placebo in patients with early triple-negative breast cancer. The primary endpoints were a pathological complete response at the time of definitive surgery and event-free survival in the intention-to-treat population.	Randomized, double-blind trial.	Two groups	(n=602)	The percentage with a pathological complete response was significantly higher among those who received pembrolizumab plus neoadjuvant chemotherapy than among those who received placebo plus neoadjuvant chemotherapy.
4.	(Nanda et al., 2020) Randomized controlled trials (USA)(7)	Effect of Pembrolizumab Plus Neoadjuvant Chemotherapy on Pathologic Complete Response in Women With Early-Stage Breast Cancer.	The primary endpoint was pathologic complete response (pCR). Secondary endpoints were residual cancer burden (RCB) and 3-year event-free and distant recurrence-free survival. Investigational arms graduated when demonstrating an 85% predictive probability of success in a hypothetical confirmatory phase 3 trial.	Randomized phase 2 multicenter trial.	Two groups	(n=210)	When added to standard neoadjuvant chemotherapy, pembrolizumab more than doubled the estimated pCR rates for both HR-positive/ERBB2- negative and triple-negative breast cancer, indicating that checkpoint blockade in women with early-stage, high-risk, ERBB2-negative breast cancer is highly likely to succeed in a phase 3 trial.
5.	(Loibl et al., 2019) Randomized, double-blind, placebo-controlled, phase II trial (USA)(8)	A Randomized phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer.	The primary objective was pathological complete response (pCR) (ypT0 ypN0).	Randomized phase II double-blind placebo-controlled.	Two groups	(n=117)	Our results suggest that adding durvalumab to anthracycline-/taxane-based NACT increases the pCR rate, particularly in patients treated with durvalumab alone before the start of chemotherapy.

Methodological Characteristics

Based on the five studies reviewed, five used randomized controlled trials (Mittendorf et al., 2020) Randomized, double-blind, placebo-controlled, phase III trial (USA)[5], (Saji et al., 2022) Randomized placebo-controlled phase III trial (Japan)[4], (Schmid, Peter et al., 2020) Randomized controlled trials (London)[3], (Nanda et al., 2020) Randomized controlled trials (USA)[6], (Loibl et al., 2019) Randomized, double-blind, placebo-controlled, phase II trial (USA)[7].

Intervention Methods

Out of the five studies, five studies used two groups random control (Mittendorf et al., 2020) Randomized, double-blind, placebo-controlled, phase III trial (USA)[5], (Saji et al., 2022) Randomized placebo-controlled phase III trial (Japan)[4], (Schmid, Peter et al., 2020) Randomized controlled trials (London)[3], (Nanda et al., 2020) Randomized controlled trials (USA)[6], (Loibl et al., 2019) Randomized, double-blind, placebo-controlled, phase II trial (USA)[7].

RESULTS

Of 13.702 records initially identified, five studies were assessed by full-text review. Four showed that immunotherapy (pembrolizumab or atezolizumab) combined with chemotherapy significantly improved pathological complete response rates with an acceptable safety profile in early-stage TNBC, irrespective of PD-L1 status. One study showed that immunotherapy (durvalumab alone before the start of immunotherapy combined with chemotherapy) improved pathological complete response rates in early-stage TNBC, and the adverse events were not more frequently reported with immunotherapy durvalumab than with a placebo.

No	Study	Population	Intervention/ Comparison (Neoadjuvant)	Subject	Follow-up	Pathological Complete Response ypT0/Tis ypN0	Adverse Events

Table 2 . Study of the efficacy of neoadjuvant immunotherapy toward its outcome.

1.	(Mittendorf et al., 2020) Randomized, double-blind, placebo-controlled, phase III trial (USA)(6)	Early-stage TNBC	Atezolizumab intravenous 840 mg every 2 weeks (20 weeks) – Standard NACT	165	20·6 months	95 (58%, 95% CI 50–65)	Rate Difference 17%, (95% CI 6–27) *P*<0,05	In the neoadjuvant phase, grade 3–4 adverse events were balanced and treatment-related serious adverse events occurred in 37 (23%) and 26 (16%) patients, with one patient per group experiencing an unrelated grade 5 adverse event (traffic accident in the atezolizumab plus chemotherapy group and pneumonia in the placebo plus chemotherapy group)
			Placebo– Standard NACT	168	19·8 months	69 (41%, 34–49) patients		
2.	(Saji et al., 2022) Randomized placebo-controlled phase III trial (Japan)(4)	Early-stage TNBC	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. Treatment-related grade 3–4 AEs were experienced by 12 (71%) and 13 (68%) patients in the atezolizumab and placebo arms, respectively. No grade 5 AEs occurred in either treatment arm
			Placebo– Standard NACT	19	21.9 months	n=7 37%; 95% CI (16-64)		
3.	(Schmid, Peter et al., 2020) Randomized controlled trials (London)(3)	Early-stage TNBC	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	Across all treatment phases, the incidence of treatment-related adverse events of grade 3 or higher was 78.0% in the pembrolizumab–chemotherapy group and 73.0% in the placebo–chemotherapy group, including death in 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)(7)	Early-stage TNBC	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	Hypothyroidism and hyperthyroidism occurred in 9 of the 69 patients who recieved pembrolizumab (13.0%). Adrenal insufficiency in 6 of the 69 patients who received pembrolizumab (8.7%) These AEs were successfully treated per protocol with dose interruption or steroids.
			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)(8)	Early-stage TNBC	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	AEs were not more frequently reported with durvalumab than with placebo, with the exception of thyroid dysfunction, Overall 59 patients had at least one serious AEs, 30 in the durvalumab and 29 in the placebo arm.
			Placebo– Standard NACT			41.4%		

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

DISCUSSION

In total, the systematic review obtained five articles that were relevant to the subject and outcomes. Based on (Mittendorf et al., 2020)[5] PD-L1 inhibitors like Atezolizumab

showed promising result in early-stage TNBC patients, seen in randomized clinical trials on atezolizumab and chemotherapy. (Mittendorf et al., 2020)[5] study concluded that neoadjuvant treatment with atezolizumab in combination with nab-paclitaxel and anthracycline-based chemotherapy significantly improved pathological complete response rates with an acceptable safety profile in patients with early-stage TNBC. Similar results were seen in (Saji et al., 2022)[4] that atezolizumab added to neoadjuvant chemotherapy numerically improved pathological complete response versus placebo in this small exploratory analysis of Japanese patients with early-stage triple-negative breast cancer, a trend directionally consistent with the global study results. All AEs in both treatment arms were treatment-related. Treatment-related grade 3–4 AEs were experienced by 12 (71%) and 13 (68%) patients in the atezolizumab and placebo arms, respectively. No grade 5 adverse events (AEs) occurred in either treatment arm. No new safety signals were identifie. Based on (Schmid, Peter et al., 2020)[3] study we found that the percentage with a pathological complete response was significantly higher among those who received pembrolizumab plus neoadjuvant chemotherapy than among those who received placebo plus neoadjuvant chemotherapy. Similar results were seen in (Nanda et al., 2020)[6] study when pembrolizumab added to standard neoadjuvant chemotherapy, pembrolizumab more than doubled the estimated pCR rates for both HR-positive/ERBB2- negative and triple-negative breast cancer, indicating that checkpoint blockade in women with early-stage, high-risk, ERBB2-negative breast cancer is highly likely to succeed in a phase 3 trial**.** In (Loibl et al., 2019)[7] study found that the addition of durvalumab to anthracycline-/taxane-based NACT increases pCR rate particularly in patients treated with durvalumab alone before start of chemotherapy and the adverse event were not more frequently reported with durvalumab than with placebo, with the exception of thyroid dysfunction, Overall 59 patients had at least one serious AEs, 30 in the durvalumab and 29 in the placebo arm.

CONCLUSIONS

Neoadjuvant immunotherapy combination with chemotherapy has shown superior outcomes on increasing pCR rate than chemotherapy alone in early-stage TNBC, irrespective of PD-L1 status, with an acceptable safety profile.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

REFERENCES

1. Estimated number of deaths in 2020 , World , females , all ages. 2020;996:2020.
2. Cui Y, Xu Y, Li Y, Sun Y, Hu J, Jia J, et al. Antibody Drug Conjugates of Near-Infrared Photoimmunotherapy (NIR-PIT) in Breast Cancers. Technol Cancer Res Treat. 2023;22.
3. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020;382(9):810–21.
4. Saji S, Ohsumi S, Ito M, Hayashi N, Kobayashi K, Masuda N, et al. Subgroup analysis of Japanese patients in a phase III randomized , controlled study of neoadjuvant atezolizumab or placebo , combined with nab -paclitaxel and anthracycline-based chemotherapy in early triple-negative breast cancer (IMpassion031). 2022;52(June):1124–33.
5. Huang M, Shaughnessy JO, Zhao J, Haiderali A, Cort J, Ramsey SD, et al. Association of Pathologic Complete Response with Long-Term Survival Outcomes in Triple-Negative Breast Cancer : A Meta-Analysis. 2020;(October 2018):5427–34.
6. Mittendorf EA, Zhang H, Barrios CH, Saji S, Jung KH, Hegg R, et al. Articles Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early- stage triple-negative breast cancer (IMpassion031): a randomised , double-blind . 2020;2(20):1–11.
7. Nanda R, Liu MC, Yau C, Shatsky R, Pusztai L, Wallace A, et al. Effect of Pembrolizumab Plus Neoadjuvant Chemotherapy on Pathologic Complete Response in Women with Early-Stage Breast Cancer: An Analysis of the Ongoing Phase 2 Adaptively Randomized I-SPY2 Trial. JAMA Oncol. 2020;6(5):676–84.
8. Loibl S, Schneeweiss A, Huober J, Braun M, Rey J, Blohmer J, et al. Neoadjuvant durvalumab improves survival in early triple-negative breast cancer independent of pathological complete response 5. Ann Oncol [Internet]. 2022;33(11):1149–58.