Efficacy of PD-1 and PD-L1 Inhibitors in Triple-Negative Breast Cancer: A Meta-Analysis of Randomized Controlled Trials

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons)

School of Pharmacy
BRAC University
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled "Efficacy of PD-1 and PD-L1 Inhibitors in Triple-Negative Breast Cancer: A Meta-Analysis of Randomized Controlled Trials" submitted by Meharin Khandaker (21146034) of Spring, 2026 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This project does not involve any kind of animal and human trial.

Abstract

Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer. PD-1 and PD-L1 inhibitors have recently shown promise when combined with chemotherapy to treat TNBC. This thesis aimed to evaluate the efficacy and safety of PD-1/PD-L1 inhibitors in TNBC through a meta-analysis of randomized controlled trials. Nine randomized controlled trials were included. This study covers both early-stage and advanced or metastatic TNBC. The main efficacy outcomes were pathological complete response (pCR) in early-stage TNBC and objective response rate (ORR) in advanced or metastatic TNBC. Safety was assessed using Grade ≥3 adverse events. The pooled analysis showed that PD-1/PD-L1 inhibitor plus chemotherapy significantly improved pCR in early-stage TNBC (OR = 1.82, 95% CI: 1.43-2.31; $p < 0.00001$) and ORR in advanced or metastatic TNBC (OR = 1.28, 95% CI: 1.09-1.51; $p = 0.003$). Safety analysis showed no statistically significant increase in Grade ≥3 adverse events with immunotherapy-based treatment compared with control therapy (RR = 1.04, 95% CI: 0.99-1.11; $p = 0.14$). Overall, the findings suggest that PD-1/PD-L1 inhibitors combined with chemotherapy provide meaningful clinical benefit in TNBC.

Keywords: Triple-Negative Breast Cancer (TNBC), PD-1/PD-L1 Inhibitors, Immunotherapy, Pathological Complete Response (pCR), Objective Response Rate (ORR), Meta-analysis.

Dedication

I would like to express my gratitude to Almighty Allah for granting me the strength, patience, and perseverance to complete this work. I am sincerely grateful to my parents for their unwavering support, encouragement, and guidance throughout this journey.

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List of Acronyms

TNBC	Triple-Negative Breast Cancer
RCT	Randomized Controlled Trial
ORR	Objective Response Rate
pCR	Pathological Complete Response
OR	Odds Ratio
RR	Risk Ratio
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
ASIR	Age-Standardized Incidence Rate
ASDR	Age-Standardized Death Rate
ER	Estrogen receptor
PR	Progesterone receptor

Chapter 1

Introduction

1.1 Background of Breast Cancer

Breast cancer remains the most frequently diagnosed malignancy among women worldwide (Zhang et al., 2024). It represents a significant public health burden with millions of new cases reported annually. Breast cancer is not a single disease but a heterogeneous group of malignancies with different biological features. Based on biological features clinical behaviour and treatment responses also can be different (Smolarz et al., 2022). Following this breast cancer is commonly classified according to the expression of hormone receptors and human epidermal growth factor receptor 2 (HER2) (Smolarz et al., 2022). The major molecular subtypes include hormone receptor-positive/HER2-negative breast cancer, HER2-positive breast cancer and triple-negative breast cancer (TNBC) (Smolarz et al., 2022). Hormone receptor-positive breast cancers express estrogen receptor (ER), progesterone receptor (PR) or both. And hormone receptor-positive breast cancer are often treated with endocrine therapy (Smolarz et al., 2022). Furthermore, HER2-positive breast cancers show overexpression or amplification of the HER2 receptor and respond to HER2-targeted therapies (Smolarz et al., 2022). On the other hand, TNBC lacks ER, PR, and HER2 expression. Because of these characteristics make TNBC less responsive to endocrine or HER2-targeted treatment (Smolarz et al., 2022).

Although mortality rates have dropped in many high-resource communities through systematic screening and sophisticated medicines (Zhang et al., 2024). But incidence and death rates are still rising in low-resource communities. This highlights global inequities in access to early identification and equitable care. Furthermore, according to recent epidemiological data breast cancer accounts for approximately 30% of all new cancer cases in women with a mortality-to-

incidence ratio of roughly 15% (Zhang et al., 2024). In 2020, approximately 2.26 million new breast cancer cases were reported worldwide and this is making it one of the most common cancers globally (Zhang et al., 2024). The global burden of breast cancer has steadily increased over recent decades. Global Burden of Disease studies have found that incidence rates are increasing in many regions around the world (Zhang et al., 2024). It is mostly related to population expansion, age, urbanization, lifestyle changes, obesity, physical inactivity, alcohol consumption and reproductive variables (Zhang et al., 2024). Current projections indicate that the number of breast cancer cases will continue to rise substantially over the coming decades, creating significant challenges for healthcare systems worldwide (Zhang et al., 2024). The table 1, shows that the global burden of breast cancer among women is changing over time. The age-standardized incidence rate increased from 40.12 per 100,000 women in 1990 to 45.86 in 2019 (Table 1). And it is projected to reach 48.09 by 2030 (Table 1). This indicates that more women are being diagnosed with breast cancer globally. The increase may be related to population ageing, lifestyle changes, improved disease detection and better cancer registration. However, the age-standardized death rate decreased from 17.76 per 100,000 women in 1990 to 15.88 in 2019, and it is expected to decline slightly to 15.62 by 2030 (Table 1). This suggests that although breast cancer incidence is increasing but death from breast cancer is not increasing at the same rate. Improved screening, early diagnosis, better treatment facilities and increased awareness may have contributed to this reduction in mortality. The DALY rate also decreased from 524.87 per 100,000 women in 1990 to 473.83 per 100,000 women in 2019 (Table 1). But is projected to remain nearly stable at 474.28 per 100,000 women in 2030 (Table 1). This means that the overall health loss due to breast cancer has reduced compared with 1990. Overall, the table indicates a mixed pattern data such as breast cancer incidence is rising, while mortality and disability burden are slightly decreasing or remaining stable. Therefore stronger screening,

early detection and treatment access are still necessary to reduce the future burden of breast cancer.

Indicator	1990	2019	2030 (Projected)
ASIR (per 100,000)	40.12	45.86	48.09
ASDR (per 100,000)	17.76	15.88	15.62
DALY Rate (per 100,000)	524.87	473.83	474.28

Table 1: Global burden of breast cancer in women from 1990 to 2030 (Zhang et al., 2024)

1.2 Triple-Negative Breast Cancer

Triple-negative breast cancer (TNBC) is a distinct and particularly aggressive form of breast cancer (Xiong et al., 2024). It is also a clinically important and aggressive subtype of breast cancer (Xiong et al., 2024). It is called “triple-negative” because this type of cancer cells do not have estrogen receptors, progesterone receptors or excess HER2 protein (Xiong et al., 2024). As a result, TNBC does not respond to hormone therapy or HER2-targeted therapy. Because of this nature makes treatment more challenging than some other breast cancer subtypes (Xiong et al., 2024). Following this TNBC is commonly associated with faster disease progression, higher recurrence risk and also poorer prognosis (Xiong et al., 2024). It is alarming that, recent review evidence indicates that TNBC accounts for approximately 15-20% of diagnosed breast cancer cases (Xiong et al., 2024). Moreover, this disease is biologically heterogeneous and includes several molecular subtypes such as basal-like, mesenchymal, immunomodulatory, and luminal androgen receptor (LAR) subtypes (Xiong et al., 2024). Among these, the basal-like subtype is the most common and accounts for about 70-80% of TNBC cases (Xiong et al., 2024). After that the diagnosis process of TNBC also difficult.

Diagnosis begins with clinical history, TNM staging, symptoms, comorbidities and imaging methods such as mammography, ultrasound, MRI and radiography (Xiong et al., 2024). Furthermore, TNBC is not a single disease type. It includes several molecular subtypes (Xiong et al., 2024). For example, basal-like 1, basal-like 2, mesenchymal, luminal androgen receptor, mesenchymal stem-like and immunomodulatory subtypes (Xiong et al., 2024). Each subtype is linked with different molecular targets such as PARP1, EGFR, PI3K, mTOR, AR, STATs, and NF-κB. And its difficulties the diagnosis process (Xiong et al., 2024).

In addition, recent research has demonstrated that TNBC often exhibits higher levels of tumour-infiltrating lymphocytes and increased expression of immune-related biomarkers (Smolarz et al., 2022). This mechanism suggest that the immune system plays an important role in disease progression (Smolarz et al., 2022). These findings find out the promising approach in immunotherapy (Smolarz et al., 2022). Particularly PD-1 and PD-L1 inhibitors that help the immune system recognize and attack cancer cells more effectively (Smolarz et al., 2022).

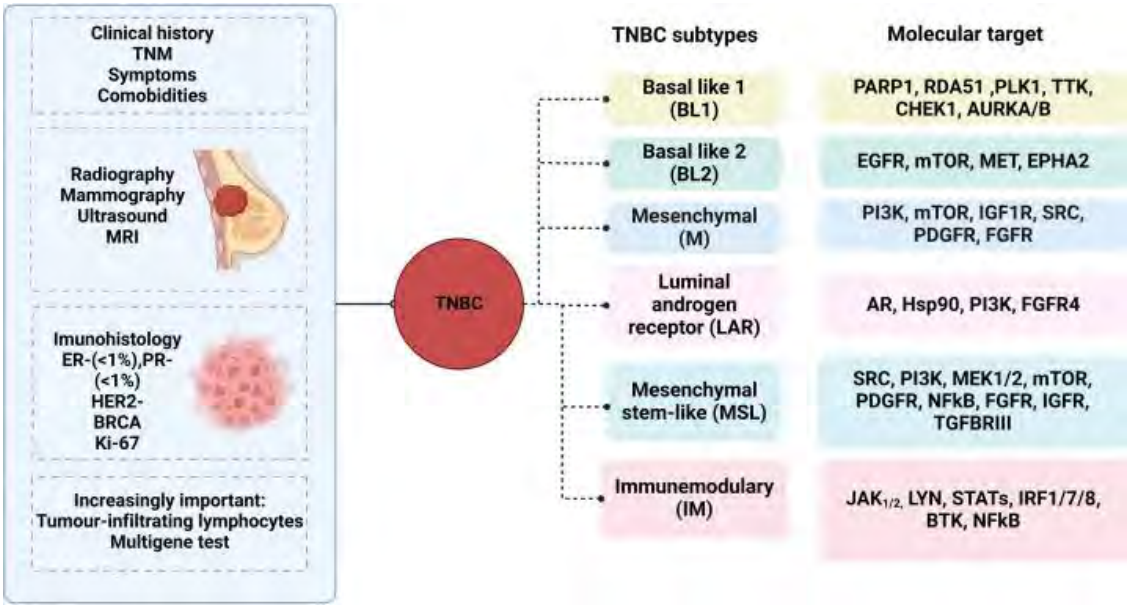

Figure 1: Diagnostic aspects of triple-negative breast cancer (Xiong et al., 2024)

1.3 PD-1 and PD-L1 Pathway in Cancer Immunity

The PD-1 and PD-L1 pathway is an important immune checkpoint mechanism because it helps to regulate immune responses and prevent excessive immune activation (Xiong et al., 2024). Programmed cell death protein 1 (PD-1) is mainly expressed on activated T cells (Xiong et al., 2024). On the other hand, programmed death-ligand 1 (PD-L1) may be expressed on tumour cells and immune cells within the tumour microenvironment (Xiong et al., 2024). Normally the interaction of PD-1 and PD-L1 helps to maintain the immune system in normal cells. But cancer cells can exploit this pathway to escape immune destruction (Xiong et al., 2024). In cancer immunity tumour cells expressing PD-L1 bind to PD-1 receptors on T cells and reduce T-cell activity. Because of exhibit this weakens the anti-tumour immune response by limiting T-cell activation, cytokine production, and cancer cell killing (Xiong et al., 2024). As a result, the tumour can avoid immune surveillance and continue to grow (Xiong et al., 2024). This process is relevant in aggressive cancers such as Triple-Negative Breast Cancer (TNBC), where immune evasion contributes to disease progression and treatment resistance (Xiong et al., 2024).

Following this, blocking the PD-1/PD-L1 pathway has become an important immunotherapeutic strategy (Xiong et al., 2024). Immune checkpoint inhibitors prevent the interaction between PD-1 and PD-L1. This process is allowing T cells to regain their anti-tumour activity (Xiong et al., 2024). Furthermore, drugs like atezolizumab (an anti-PD-L1 agent) and pembrolizumab (an anti-PD-1 agent) have been demonstrated to be effective in treating TNBC, especially in tumors that are positive for PD-L1 (Xiong et al., 2024). These therapies enhance T-cell-mediated immune responses and may improve treatment outcomes when combined with chemotherapy (Xiong et al., 2024). However, not all patients respond equally, so predictive biomarkers such as PD-L1 expression, tumour-infiltrating lymphocytes, tumour mutational burden and immune profiling are increasingly important for selecting

suitable patients (Xiong et al., 2024). Therefore, the PD-1/PD-L1 pathway represents both a key mechanism of tumour immune escape and also a major therapeutic target in modern cancer immunotherapy (Xiong et al., 2024).

Despite these mechanisms of response to PD-1/PD-L1 inhibitors is not uniform among all TNBC patients (Serrano García et al., 2024). Some patients show strong and durable responses while others receive limited benefit (Serrano García et al., 2024). This variation highlights the importance of predictive biomarkers. PD-L1 expression, tumour-infiltrating lymphocytes, tumour mutational burden, immune gene signatures and molecular subtype classification have been investigated as potential markers for patient selection (Serrano García et al., 2024). As a result, patients are more likely to benefit from immunotherapy (Serrano García et al., 2024).

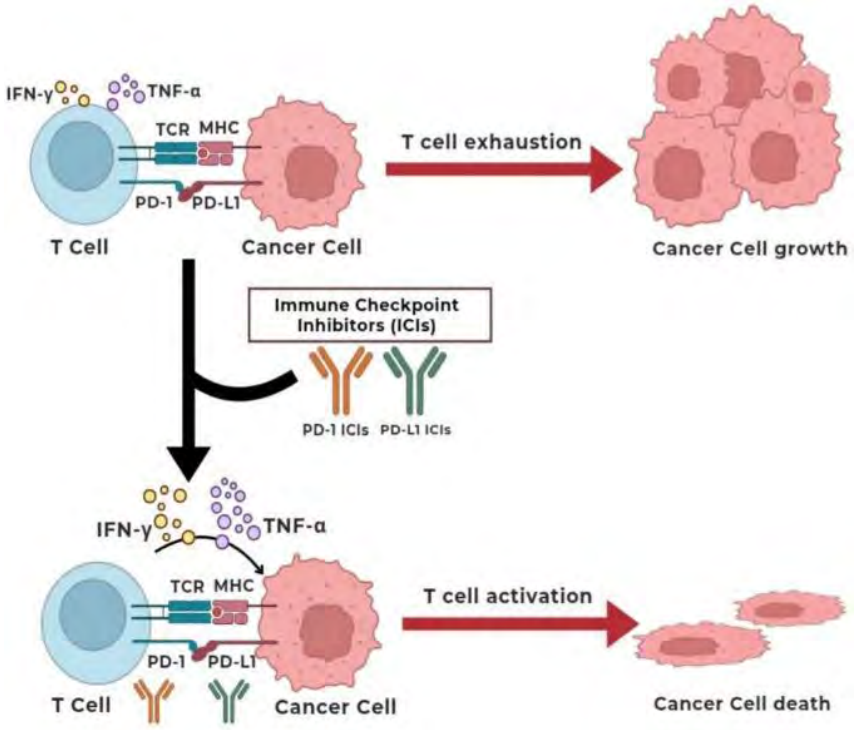

Figure 2: PD-1/PD-L1 interaction and immune-checkpoint inhibitors (Lin et al., 2025).

1.4 Aim of the Study

The specific aim of the study are:

- To assess whether PD-1/PD-L1 inhibitor plus chemotherapy improves pathological complete response in patients with early-stage TNBC compared with placebo or chemotherapy-based control treatment.
- To evaluate the effect of PD-1/PD-L1 inhibitor-based combination therapy on objective response rate in patients with advanced or metastatic TNBC.
- To compare the safety profile of PD-1/PD-L1 inhibitor plus chemotherapy with control treatment by analysing Grade ≥3 adverse events.
- To synthesize randomized controlled trial evidence in order to determine the overall clinical value of PD-1/PD-L1 inhibitors in TNBC treatment.

Chapter 2

Methodology

2.1 Research Design

This study was conducted as a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the efficacy and safety of programmed cell death protein-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors in patients with triple-negative breast cancer (TNBC). The methodology was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency, reproducibility, and methodological rigor. Published clinical trials comparing PD-1/PD-L1 inhibitor-based therapies with placebo or standard chemotherapy were identified and analyzed. The primary efficacy outcomes included pathological complete response (pCR) in early-stage TNBC and objective response rate (ORR) in advanced or metastatic TNBC. Safety was assessed using the incidence of Grade ≥3 adverse events.

2.2 Search Strategy

A comprehensive literature search was performed using the electronic databases PubMed, Scopus, ResearchGate, and ClinicalTrials.gov, with studies published up to May 2026. The following keywords were used: “Triple-negative breast cancer or TNBC”, “PD-1 inhibitor or PD-L1 inhibitor”, “Immune checkpoint inhibitor”, “Randomized controlled trial” and “Clinical trial”.

2.3 Eligibility Criteria

Studies were selected based on predefined inclusion and exclusion criteria.

2.3.1 Inclusion Criteria

- Randomized controlled trials (RCTs).
- Studies involving patients diagnosed with triple-negative breast cancer.
- Studies comparing PD-1 or PD-L1 inhibitors plus chemotherapy with placebo or chemotherapy alone.
- Studies reporting at least one efficacy outcome (pCR or ORR) or safety outcome (Grade ≥3 adverse events).
- Full-text articles published in peer-reviewed journals.
- Articles published in English.

2.3.2 Exclusion Criteria

- Non-randomized clinical trials.
- Studies without sufficient outcome data.
- Duplicate publications.
- Animal or in vitro studies.

2.4 PRISMA Framework

The study selection process followed the PRISMA framework. Initially, all records identified through database searching were imported into reference management software and duplicate records were removed. Titles and abstracts were screened to exclude irrelevant studies.

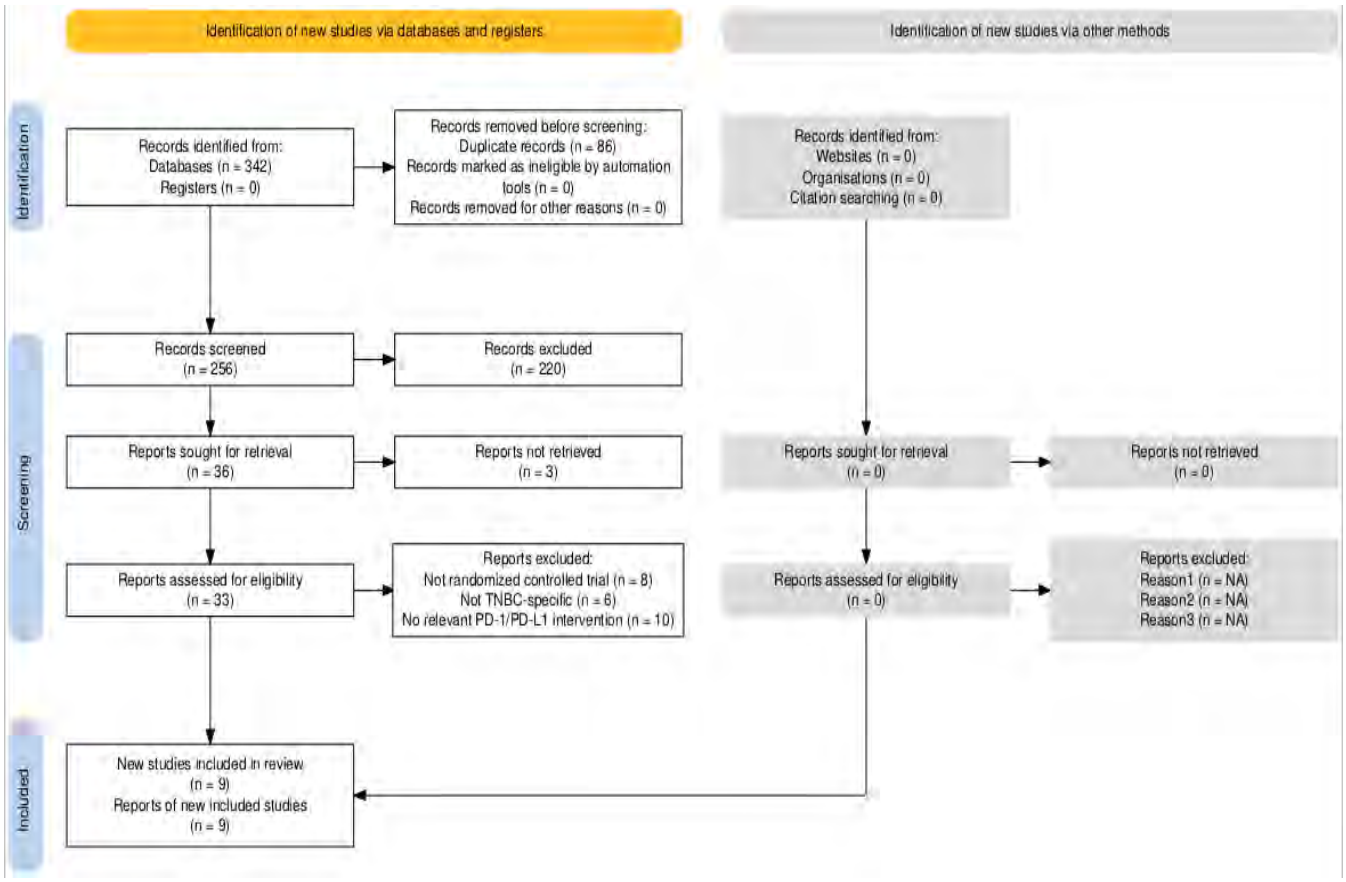

Figure 3: PRISMA flow chart for the included and excluded studies

2.5 Meta Analysis

Meta-analysis was performed using Review Manager (RevMan) version 5.4. Dichotomous outcomes were analyzed using odds ratios (ORs) or risk ratios (RRs) with corresponding 95% confidence intervals (CIs). For efficacy outcomes pooled odds ratios were calculated for pathological complete response (pCR) and objective response rate (ORR). Safety outcomes were analyzed using pooled risk ratios for Grade ≥3 adverse events.

Statistical heterogeneity among studies was assessed using Cochran's Q test and the I^2 statistic. An I^2 value below 25% was considered low heterogeneity, 25-50% moderate heterogeneity and greater than 50% substantial heterogeneity.

Risk of bias was evaluated using the Cochrane Risk of Bias (RoB 2) assessment tool. According this tools which examines bias arising from the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. The overall quality and reliability of the included studies were assessed based on these domains. And finally statistical significance was established at a p-value less than 0.05.

Chapter 3

Result

3.1 Characteristics Table of Included Studies (pCR & ORR)

The characteristics table summarizes the nine randomized controlled trials included in this meta-analysis. The studies evaluated PD-1/PD-L1 inhibitors combined with chemotherapy in patients with either early-stage or metastatic TNBC and reported efficacy outcomes. It includes pathological complete response (pCR) and objective response rate (ORR).

Study	**Population**	**Primary Outcomes**	**Intervention (Experimental arm vs Control arm)**	**Effect measure (Experimental vs Control)**	
				Events	**Total**
KEYNOTE-522 (Schmid et al., 2020)	Early-stage TNBC	pCR	Pembrolizumab + neoadjuvant chemotherapy	260	401
			Placebo + chemotherapy	103	201
IMpassion031 (Mittendorf et al., 2020)	Early-stage TNBC	pCR	Atezolizumab + neoadjuvant chemotherapy	95	165
			Placebo + chemotherapy	69	168
GeparNuevo (Loibl et al., 2019)	Early-stage TNBC	pCR	Durvalumab + neoadjuvant chemotherapy	46	86
			placebo + chemotherapy	39	88

NeoTRIPaPDL1 (Ademuyiwa et al., 2022)	Early stage TNBC	pCR	Atezolizumab + carboplatin + paclitaxel	25	45
			carboplatin + paclitaxel	3	16
KEYNOTE-355 (Cortes et al., 2022)	Metastatic TNBC	ORR	Pembrolizumab + chemotherapy	231	566
			placebo + chemotherapy	104	281
IMpassion130 (Schmid et al., 2018)	Metastatic TNBC	ORR	Atezolizumab + nab-paclitaxel	252	450
			Placebo + nab-paclitaxel	206	449
IMpassion131 (Miles et al., 2021)	Metastatic TNBC	ORR	Atezolizumab + paclitaxel	231	431
			placebo + paclitaxel	104	220
IMpassion132 (Dent et al., 2024)	Metastatic TNBC	ORR	Atezolizumab + chemotherapy	53	171
			Placebo + chemotherapy	54	168
ALICE (Røssevold et al., 2022)	Metastatic TNBC	ORR	Atezolizumab + PLD + cyclophosphamide	11	40
			Placebo + PLD + cyclophosphamide	5	28

Table 2: Characteristics Table of Included Studies

3.2 Safety Data Extraction Table

The safety data extraction table presents the incidence of Grade ≥3 adverse events reported across the included randomized controlled trials.

Study	Population	Safety outcome	Intervention (Experimental arm vs Control arm)	Effect measure (Experimental vs Control)	
				Events	Total
KEYNOTE-522 (Schmid et al., 2020)	Early-stage TNBC	Grade≥3 AE	Pembrolizumab + neoadjuvant chemotherapy	633	781
			Placebo + chemotherapy	295	389
IMpassion031 (Mittendorf et al., 2020)	Early-stage TNBC	Grade 3 or 4 AE	Atezolizumab + neoadjuvant chemotherapy	103	164
			Placebo + chemotherapy	101	167
GeparNuevo (Loibl et al., 2019)	Early-stage TNBC	Grade ≥3 AE	Durvalumab + neoadjuvant chemotherapy	30	92
			placebo + chemotherapy	29	82

NeoTRIPaPDL1 (Ademuyiwa et al., 2022)	Early stage TNBC	Grade ≥3 AE	Atezolizumab + carboplatin + paclitaxel	26	45
			carboplatin + paclitaxel	10	16
KEYNOTE-355 (Cortes et al., 2022)	Metastatic TNBC	Grade 3 - 4 AE	Pembrolizumab + chemotherapy	438	562
			placebo + chemotherapy	207	281
IMpassion130 (Schmid et al., 2018)	Metastatic TNBC	Grade 3 - 4 AE	Atezolizumab + nab-paclitaxel	220	452
			Placebo + nab-paclitaxel	185	438
IMpassion131 (Miles et al., 2021)	Metastatic TNBC	Grade 3 - 4 AE	Atezolizumab + paclitaxel	229	431
			placebo + paclitaxel	100	217
IMpassion132 (Dent et al., 2024)	Metastatic TNBC	Grade 3 - 4 AE	Atezolizumab + chemotherapy	195	293
			Placebo + chemotherapy	210	294
ALICE (Røssevold et al., 2022)	Metastatic TNBC	Grade 3 - 4 AE	Atezolizumab + PLD + cyclophosphamide	25	40
			Placebo + PLD + cyclophosphamide	12	28

Table 3: Safety Data Extraction Table

3.3 Risk of Bias

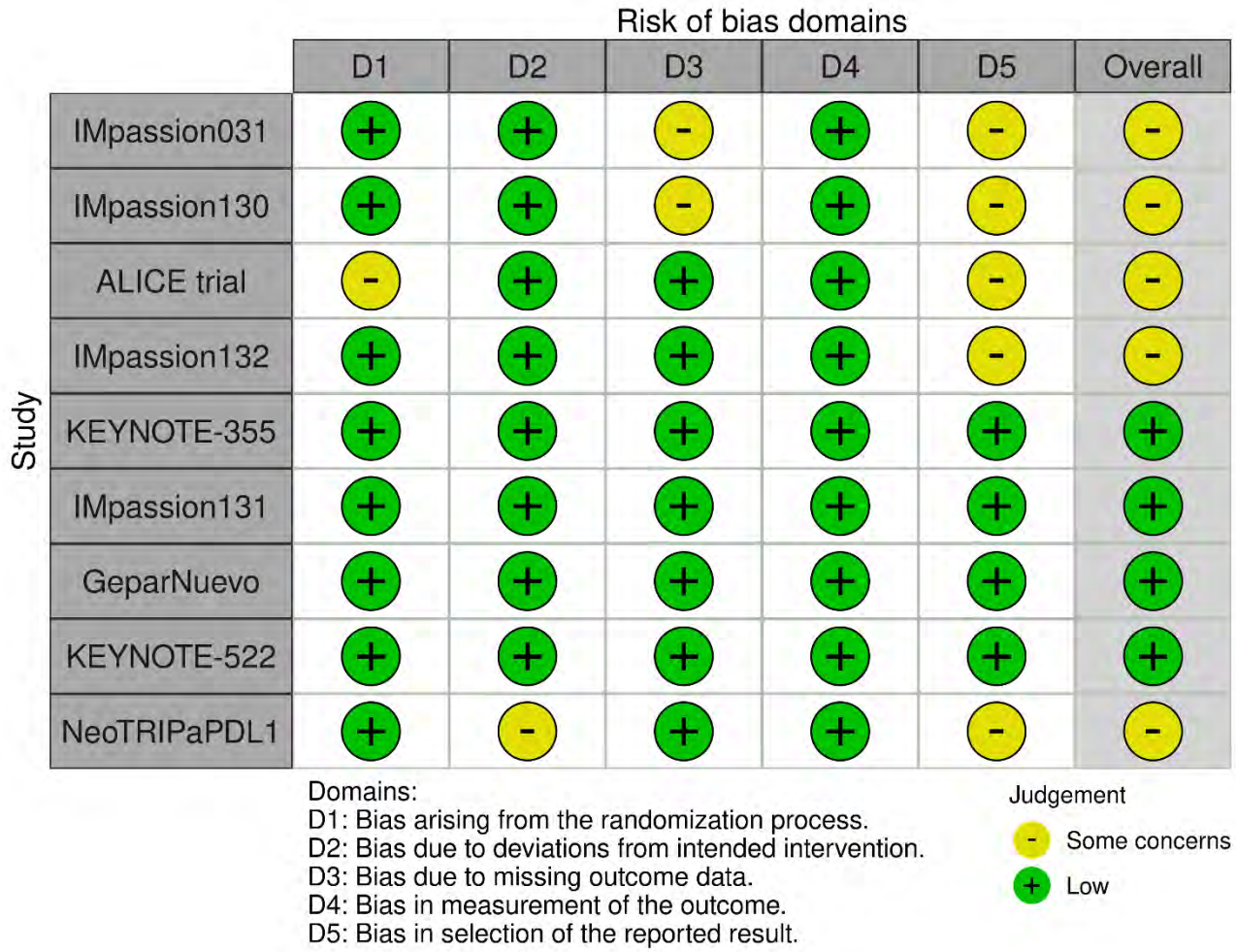

Figure 4: Risk of Bias Table

Among the nine studies, four trials (KEYNOTE-355, IMpassion131, GeparNuevo, and KEYNOTE-522) demonstrated a low risk of bias across all domains. This indicates strong study design and reliable outcome reporting.

However, five studies (IMpassion031, IMpassion130, ALICE trial, IMpassion132, and NeoTRIPaPDL1) showed some concerns in at least one domain and resulting in an overall judgment of "some concerns." The most frequently affected domain was D5 (bias in selection of the reported result), where five studies indicate potential reporting concerns. Additionally,

D3 (bias due to missing outcome data) showed concerns in IMpassion031 and IMpassion130. But on the other hand D1 (randomization process) raised concerns in the ALICE trial and D2 (deviations from intended intervention) in NeoTRIPaPDL1.

3.4 Pathological Complete Response (pCR) Meta-analysis

Four neoadjuvant trials with patients with early-stage triple-negative breast cancer were included for the meta-analysis of pathological complete response. Of the patients in the PD-1/PD-L1 inhibitor plus chemotherapy group, 426 of 697 achieved pCR, as received 214 of 473 patients in the placebo or chemotherapy control group in the included studies. The pooled analysis indicated a statistically significant improvement of pCR by immune checkpoint inhibition added to neoadjuvant chemotherapy (OR = 1.82, 95% CI: 1.43-2.31; Z = 4.83; $p < 0.00001$). This means that patients treated with PD-1/PD-L1 inhibitor-based therapy were significantly more likely to achieve pCR than those treated with chemotherapy alone or placebo plus chemotherapy.

The treatment effect was very consistent, with no statistical heterogeneity across studies ($Tau^2 = 0.00$; $Chi^2 = 3.09$, df = 3, p = 0.38; $I^2 = 0\%$). This suggests that the direction and magnitude of benefit are consistent regardless of trial design, type of immune checkpoint inhibitor or chemotherapy backbone. KEYNOTE-522 and IMpassion031 contributed most heavily to the pooled estimate and both preferred the experimental treatment. The KEYNOTE-522 trial showed a higher pCR rate with pembrolizumab plus chemotherapy versus placebo plus chemotherapy. IMpassion031 also showed improved pCR with atezolizumab plus chemotherapy. GeparNuevo also preferred durvalumab but the individual trial effect was not statistically significant. Individually, the NeoTRIPaPDL1 trial had the largest estimate of effect. However, the contribution of this study to the pooled result was small due to the smaller

sample size. Overall, these findings support the efficacy of adding PD-1/PD-L1 inhibitors to neoadjuvant chemotherapy in improving pCR in early-stage TNBC.

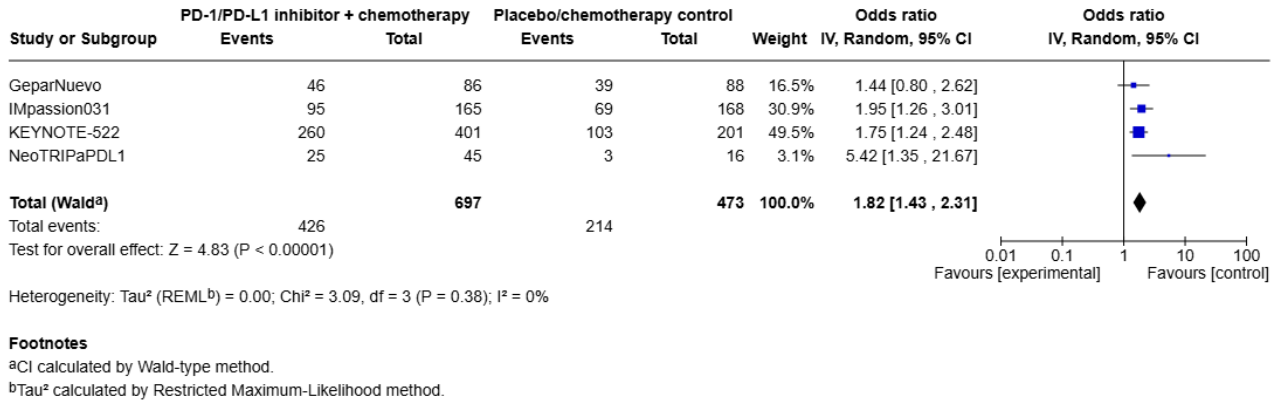

Figure 5: Pathological Complete Response (pCR) Meta-analysis

3.5 Objective Response Rate (ORR) Meta-analysis

The meta-analysis of objective response rates included five trials in patients with advanced or metastatic triple-negative breast cancer. Here objective response was achieved in 778 of 1,658 patients in the PD-1/PD-L1 inhibitor plus chemotherapy group compared with 473 of 1,146 patients in the placebo or chemotherapy control group across the included studies. The pooled analysis demonstrated a statistically significant improvement in ORR with the addition of immune checkpoint inhibitors to chemotherapy (OR = 1.28, 95% CI: 1.09-1.51; Z = 3.02; p = 0.003). This finding suggests that PD-1/PD-L1 inhibitor-based combination therapy was more likely to reach the objective tumour response compared to chemotherapy-based control treatment.

Furthermore, heterogeneity was very low across the included studies ($Tau^2 = 0.00$; $Chi^2 = 3.65$, df = 4, p = 0.45; $I^2 = 4\%$). This data suggest that the study findings were generally consistent.

Among individual trials, IMpassion130 showed a statistically significant improvement in ORR with atezolizumab plus nab-paclitaxel. ALICE and IMpassion131 showed a numerical trend favouring the experimental arm, although their confidence intervals crossed the line of no effect. On the other hand, KEYNOTE-355 also showed a modest non-significant trend favouring pembrolizumab plus chemotherapy. In contrast, IMpassion132 did not show an ORR advantage for atezolizumab plus chemotherapy, with an effect estimate close to no difference.

Overall, the ORR meta-analysis suggests that adding PD-1/PD-L1 inhibitors to chemotherapy provides a statistically significant improvement in tumour response among patients with advanced or metastatic TNBC.

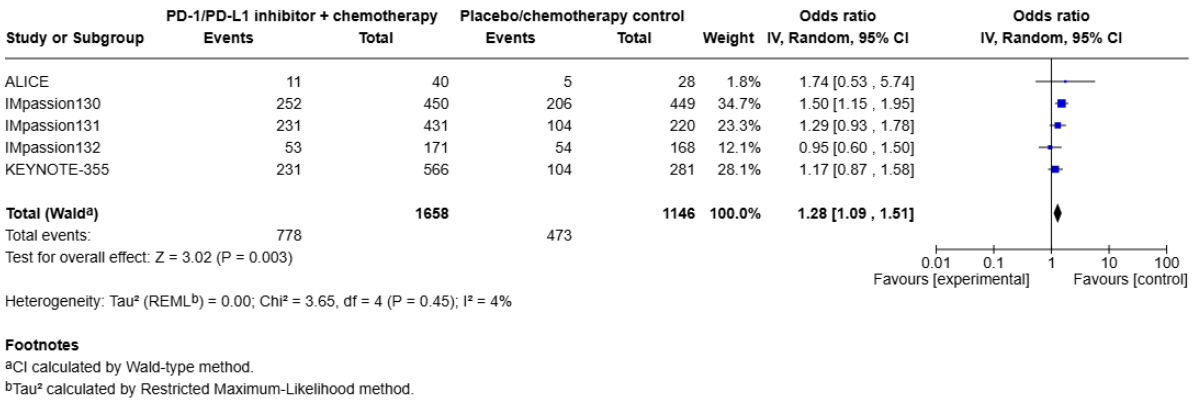

Figure 6: Objective Response Rate (ORR) Meta-analysis

3.6 Safety Meta-analysis of Grade ≥3 Adverse Events

The safety meta-analysis evaluated Grade ≥3 adverse events in patients receiving PD-1/PD-L1 inhibitor plus chemotherapy vs placebo or chemotherapy control. The number of patients with adverse events of Grade ≥3 was 1811 of 2861 in the experimental arm of included studies and 1116 of 1912 in the control arm. The pooled random effects estimate did not show a statistically significant difference in the risk of Grade ≥3 adverse events between the two treatment groups (RR = 1.04, 95% CI: 0.99-1.11; Z = 1.49; p = 0.14). This means that the addition of PD-1/PD-L1 inhibitors to chemotherapy did not result in a statistically significant increase in the overall rate of severe adverse events.

Subgroup analysis by treatment setting showed similar findings. In the early/neoadjuvant TNBC subgroup, the pooled effect was not statistically significant (RR = 1.05, 95% CI: 0.99-1.12; p = 0.12), with no observed heterogeneity (I^2 = 0%). In the advanced/metastatic TNBC subgroup, the pooled estimate also showed no statistically significant increase in Grade ≥3 adverse events (RR = 1.06, 95% CI: 0.96-1.17; p = 0.26). However, moderate heterogeneity was observed in this subgroup (I^2 = 57%), suggesting greater variability among metastatic trials, possibly due to differences in chemotherapy backbone, disease burden, treatment duration, and patient characteristics.

The test for subgroup differences was not significant (Chi^2 = 0.01, p = 0.92; I^2 = 0%), indicating that the safety effect did not differ meaningfully between early/neoadjuvant and advanced/metastatic TNBC settings. Overall heterogeneity was low to moderate (I^2 = 25%), supporting a generally consistent safety profile across the included studies. These findings suggest that PD-1/PD-L1 inhibitor-based chemotherapy improves efficacy outcomes without a clearly significant increase in severe adverse events, although careful toxicity monitoring remains necessary because immune checkpoint inhibitors can cause clinically important immune-related toxicities.

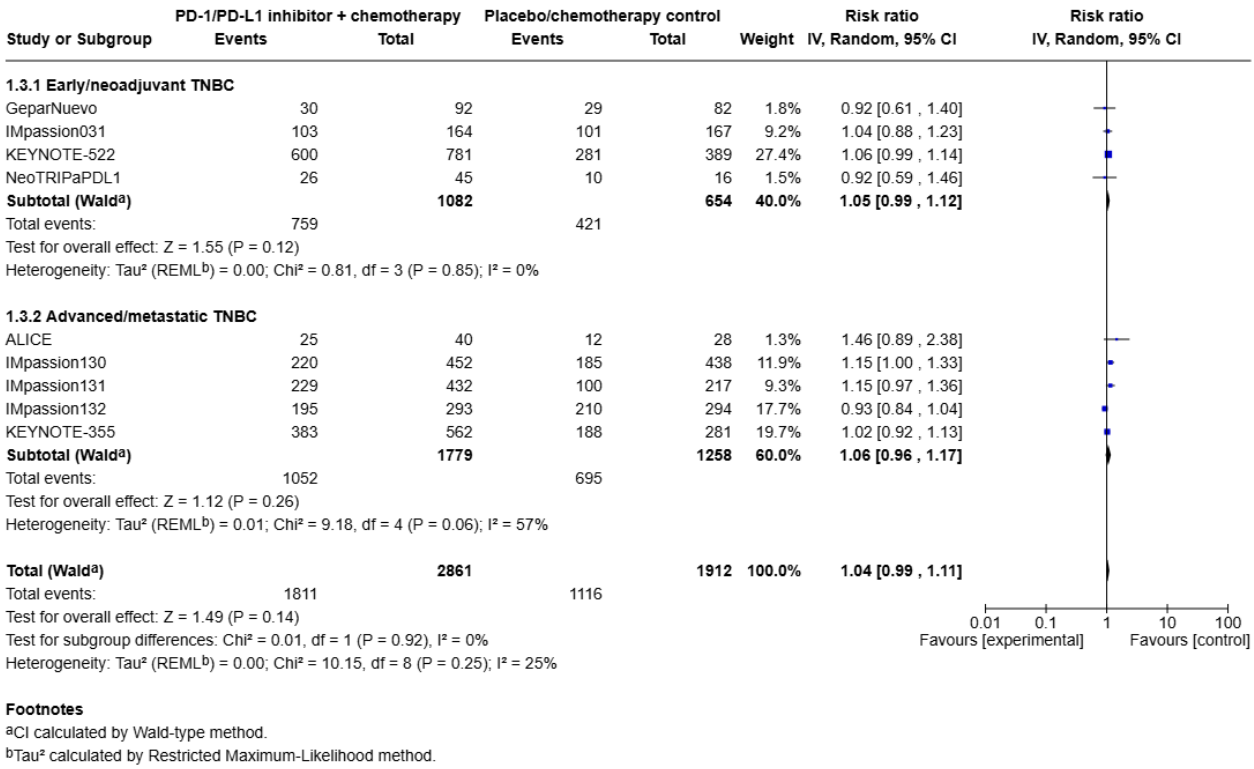

Figure 7: Safety Meta-analysis of Grade ≥3 Adverse Events

Chapter 4

Discussion

This meta-analysis was conducted to evaluate the efficacy and safety of PD-1 and PD-L1 inhibitors for patients with triple-negative breast cancer (TNBC) by pooling data from nine randomized controlled trials. Risk of bias assessment showed a good methodological standard of included studies. In the current review, four trials were considered to be at low risk of bias for all domains assessed, while the other studies were considered to be some concerns rather than high risk of bias. In this meta-analysis, the combination of PD-1/PD-L1 inhibitors and chemotherapy significantly improved rates of pathological complete response (pCR) in patients with early-stage TNBC. Pooled analysis demonstrated a significant increase in the probability of achieving pCR versus chemotherapy alone. Pathological complete response is an important surrogate marker of long-term survival outcomes in TNBC. Thus, the observed improvement suggests that the addition of immune checkpoint inhibitors to neoadjuvant therapies may improve disease control and possibly survival.

The pooled analysis in advanced/metastatic TNBC also showed a statistically significant improvement in ORR with combination therapy with PD-1/PD-L1 inhibitors. Findings suggest that immune checkpoint inhibition has clinically meaningful antitumor activity in metastatic disease, although the magnitude of benefit was more modest than that compared to the pCR end point. Several individual studies, especially IMpassion130 study, had strongly supported this positive effect.

In addition, the safety analysis showed that the addition of PD-1/PD-L1 inhibitors did not significantly increase the overall risk of Grade ≥3 adverse events compared with control treatments. These results are promising as they suggest that immunotherapy can be effective

without a significant increase in severe toxicity. Safety profiles were similar in the early and metastatic TNBC settings.

Chapter 5

Future Discussion

Future studies should place greater emphasis on long-term survival outcomes. In this meta-analysis pathological complete response was used for early-stage TNBC and objective response rate was used for advanced or metastatic TNBC. These are clinically useful outcomes but they do not fully represent long-term benefit. So, future randomized controlled trials should provide longer follow-up data on event-free survival, disease-free survival, progression-free survival and overall survival. This is particularly important because improvement in pCR or ORR does not always guarantee durable survival benefit for every patient with TNBC.

Furthermore, in this meta-analysis PD-1/PD-L1 inhibitors combined with chemotherapy did not significantly increase Grade ≥3 adverse events compared with control treatment. Future studies should give more attention to treatment safety. Future clinical trials should report safety outcomes in more details. It should include immune-related adverse events, reasons for treatment discontinuation, patient quality of life and long-term side effects after completion of therapy. This would help clinicians better understand the balance between treatment benefit and the treatment risk.

Chapter 6

Conclusion

According to this meta-analysis, Patients with triple-negative breast cancer have significantly improved treatment outcomes when chemotherapy is administered in combination with PD-1 and PD-L1 inhibitors. From meta-analysis analysis result, pathological complete response (pCR) rates in early-stage TNBC were improved when immune checkpoint inhibitors were added. And it also improved objective response rates (ORR) in advanced/ metastatic TNBC disease. Furthermore, there was no statistically significantly improve in Grade ≥3 adverse events was observed. This indicates an acceptable safety profile. Overall, the findings support the use of PD-1/PD-L1 inhibitor-based therapy as an effective treatment strategy for TNBC disease. Future studies with longer follow-up periods are required to better analyze long-term survival advantages and identify patients who will benefit the most from immunotherapy.

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