Efficacy and Safety of Paclitaxel-Based PD-1/PD-L1 Immunotherapies for Triple-Negative Breast Cancer: A Systematic Review and Network Meta-Analysis

Clinical Medicine Insights: Oncology
Volume 18: 1–11
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DOI: 10.1177/11795549241308072

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ABSTRACT

BACKGROUND: Triple negative breast cancer (TNBC) is a deadly subtype of breast cancer with limited treatment options. Currently, programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitors have become the first choice for breast cancer immunotherapies. Despite paclitaxel being considered a cornerstone drug in breast cancer treatment, the effectiveness, safety, and optimal drug selection for its combination with PD-1/PD-L1 inhibitors remain uncertain.

METHODS: We conducted a systematic review and network meta-analysis, performing a comprehensive literature search across PubMed, Embase, and the Cochrane Library from the inception of each database through May 18, 2024. Selected trials were those that assessed the efficacy and safety of paclitaxel-based PD-1/PD-L1 therapies for the treatment of TNBC. The primary endpoint assessed was overall survival (OS), while secondary outcomes included progression-free survival (PFS), adverse events (AEs), overall response rate (ORR), and Pathological complete response (pCR). This study is registered in PROSPERO under registration number CRD42023429651.

RESULTS: A total of 8 RCTs meeting our eligibility criteria were included, involving 4626 patients who received either Paclitaxel (Paclitaxel-placebo/chemotherapy) or a combination of durvalumab, pembrolizumab, atezolizumab, toripalimab with paclitaxel. The pooled results demonstrated that Durvalumab combined with Paclitaxel significantly reduced the hazard ratio for OS (surface under the cumulative ranking [SUCRA]: 91.05%) and PFS compared with Paclitaxel alone (SUCRA: 83.52%). Additionally, Durvalumab plus Paclitaxel significantly improved the ORR compared with Paclitaxel (odds ratio [OR]: 2.30; 95% credible interval [CrI]: 1.10–5.20). For safety outcomes, Atezolizumab plus Paclitaxel showed a favorable profile in AEs, with no significant differences observed between groups. In the pCR study, Pembrolizumab plus Paclitaxel was the most effective treatment option (SUCRA: 81.85%).

CONCLUSIONS: When combined with paclitaxel, PD-1/PD-L1 inhibitors exhibit a favorable survival benefit. The combination of Durvalumab and paclitaxel represents the optimal treatment option. In the future, attention should be paid to the TNBC subtypes and drug dosage, as these factors may help to design personalized TNBC treatment programs.

KEYWORDS: Triple-negative breast cancer, Paclitaxel, PD-1/PD-L1, immunotherapy, network meta-analysis

RECEIVED: August 1, 2024. **ACCEPTED:** November 27, 2024.

TYPE: Meta-analysis

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

According to GLOBOCAN 2022, breast cancer is the most prevalent and second most lethal malignancy worldwide, after lung cancer, with nearly 2.3 million new cases, representing approximately 11.6% of all cancers globally. In 2020, breast cancer surpassed lung cancer as the most common cancer in women, marking a significant public health concern due to its substantial impact on both physical and mental well-being.[1,2] Among all kinds of breast cancer, triple-negative breast cancer (TNBC) accounts for about 20%.[3] TNBC is characterized by a unique immunohistochemical phenotype, wherein the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) is negative. The existing therapies such as endocrine therapy, molecular targeted therapy, and chemotherapy are not effective for TNBC, given its more aggressive, high risk of recurrence, and strong drug resistance.[4,5] Referring to the latest National Comprehensive Cancer Network (NCCN) guidelines,[6] Paclitaxel still remains the first-line chemotherapy drug for the treatment of breast cancer, and it is also widely used in the field of tumor immunotherapy. This tetracyclic diterpene compound acts as an effective cell cycle inhibitor, reinforcing the impact of tumor immunotherapy through multiple mechanisms.[7]

Over the past decade, the introduction of immunotherapy has revolutionized the field of oncology, with extensive research focused on agents such as PD-1/PD-L1 inhibitors and

CDK4/6 inhibitors.[8,9] Notably, research indicates that approximately 20% of TNBC patients exhibit positive PD-1/PD-L1 expression, a significantly higher rate compared to non-TNBC patients.[10] Thus, the introduction of immune-checkpoint inhibitors (ICRIs), particularly programmed cell death-ligated 1 (PD-1/PD-L1) monoclonal antibodies, has brought a new era in the combination treatment of TNBC.[11,12] According to The Society for Immunotherapy of Cancer (SITC) guidelines,[13] the PD-1/PD-L1 inhibitors used in breast cancer include Durvalumab, Pembrolizumab, Atezolizumab and Toripalimab. Several large randomized controlled trials (RCTs) have demonstrated that using PD-1/PD-L1 agents in Paclitaxel-based treatment schemes can reduce the recurrence risk of recurrence and improve OS and PFS. However, despite these advancements, numerous challenges and issues persist in the field. The guideline-recommended regimen of PD-1/PD-L1 plus Paclitaxel chemotherapy involves only Pembrolizumab plus Paclitaxel,[6,14] with newer PD-1/PD-L1 inhibitors like Durvalumab, Toripalimab yet not to be extensively reported.

Most of the current evidence is derived from studies focusing on individual agents, making it challenging to make direct comparisons and identify the optimal treatment choice. Therefore, we conducted a network meta-analysis (NMA) based on the available data to determine the effectiveness of these drugs in TNBC. The primary objectives of this study are to systematically evaluate the efficacy and safety of Paclitaxel-based PD-1/PD-L1 immunotherapies, explore and analyze the underlying mechanisms of their effects, and provide a theoretical foundation for clinical PD-1/PD-L1 immunotherapies in TNBC. (This study has been registered in PROSPERO under the registration number of CRD42023429651.

Methods

The protocol for this systematic review and NMA has been registered in PROSPERO. This analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) extended statement.[15]

Search strategy and selection criteria

We conducted a comprehensive search across 3 main databases, including Embase, PubMed, and Cochrane Library, from their inception to May 18, 2024. The search used a range of MeSH terms related to "randomized controlled trials," "Paclitaxel," "breast cancer," and "programmed cell death 1 receptor/antagonists and inhibitors." Further details are provided in Supplemental Table S1. We also searched gray literature and abstracts of breast cancer-related conferences. Two authors independently conducted the literature search, with any discrepancies resolved through consultation with a senior author. No restrictions were applied regarding the nationality, publication date, or publication status of the studies included.

Studies were eligible for inclusion if they met the following criteria: (1) patients diagnosed with TNBC confirmed by histopathology, with molecular confirmed expression of ER and PR less than 1%, and the IHC assay of HER2 was 0-1+,[16,17] regardless of tumor stage. participants aged ⩾18 years, of any gender, with an ECOG performance status of ⩽1; (2) trials reporting hazard ratios (HRs) with 95% confidence intervals (CIs) for overall survival (OS) and progression-free survival (PFS), overall response rate (ORR), grade 3/4 adverse events (AEs), or pathological complete response (pCR) in TNBC; (3) intervention group receiving paclitaxel combined with a PD-1/PD-L1 inhibitor, and a control group receiving paclitaxel (paclitaxel-placebo or other chemotherapy), with no restrictions on Paclitaxel type or dosage form; and (4) full-text randomized controlled trials (RCTs).

These following criteria led to study exclusion: (a) involved non-TNBC tumor types; (b) provided insufficient data or did not meet inclusion criteria; (c) were non-RCTs, animal studies, reviews, letters, editorials, conference abstracts, notes, or duplicate publications; or (d) were published in languages other than English.

Data extraction and quality assessment

Two researchers conducted a thorough examination of all accessible titles and abstracts using EndNote X9 independently. In addition, they manually reviewed all references cited by the included studies to identify any potentially eligible studies that may have been missed. All the literature was then screened according to the inclusion and exclusion criteria. In cases where multiple reports of the same trial were identified, only the most up-to-date publication was included in the analysis. In situations where disagreements arose between the 2 researchers, a third author was consulted to resolve any discrepancies.

Two investigators independently extracted the following information from the included articles: the first name of the author, publication year, gender identity, age, number of patients, type and stage of breast cancer, methods of treatment and specific doses in each arm, median follow-up, EGCO grade, efficacy for outcomes as OS, PFS, ORR, AEs (grade ⩾3), pCR, HRs, and 95% CIs. When available, intention-to-treat (ITT) analyses were extracted. If ITT data were not provided, we used the data reported by the authors. Data reported at the end of treatment were extracted unless unavailable. Our primary outcome was OS, measured as the time from randomization to death from any cause. We also assessed PFS as the time from randomization to the progression of TNBC. Adverse events, ORR, and pCR were considered as secondary endpoints. All discrepancies regarding data extraction were reached by consensus through discussion among the collaborators. The quality of the included studies was evaluated using the Cochrane framework ROB2.0 (version 5.1.0; The Cochrane

Institute), assessing aspects like random sequence generation, allocation concealment, and blinding, as outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Two investigators independently and in duplicate summarized the assessment of bias for each study. In the event of any disagreements, they sought guidance from the supervisor, and if needed, a third author was consulted to reach a resolution. The details of the quality assessment can be found in Appendix 2 and 3.

Statistical analysis

Our NMA applied the model proposed by Woods et al.[18] In contrast to traditional meta-analyses, our approach allowed for indirect comparisons of treatments based on common comparator groups using a Bayesian framework. This analysis was conducted in R (version 4.2.2) using the gemtc package (version 1.0-1) with Markov Chain Monte Carlo (MCMC) simulation.[19,20] This analysis follows the following the National Institute for Health and Care Excellence (NICE) framework.[21] The estimated treatment effects included both available direct and indirect evidence. HRs with 95% CrIs (credible interval) were used to represent OS and PFS for each study, while odds ratios (ORs) with 95% CrIs quantified the risk of AEs, ORR, and pCR. A random-effects model was selected for the network meta-analysis to produce conservative estimates by accounting for heterogeneity across trials within individual comparisons. The MCMC simulation was conducted with an initial burn-in of 20 000 iterations, followed by 50 000 iterations across 4 Markov chains. When HRs and 95% CIs were not directly available, data conversion was performed using relevant literature.[22] Heterogeneity was assessed both visually using forest plots and quantitatively using the I^2 statistic, with the analysis conducted through the "mtc.anohe" command.[23] An $I^2 > 50\%$ was considered to present statistically significant heterogeneity. Nodal analysis was employed for further testing of heterogeneity. Owing to the variability between the different studies included, a random effects model was used for analysis in this study. To rank preferences for each treatment, we calculated the surface under the cumulative ranking (SUCRA) probability. The SUCRA value ranges from 0% to 100%.[24] For effectiveness measures (OS, PFS, ORR, and pCR), a higher SUCRA value indicates greater therapeutic efficacy. Conversely, for the safety index (AEs), a lower SUCRA value signifies enhanced safety of the therapy. Publication bias was not assessed due to the insufficient number of eligible studies (<10 studies).[25] These methods have been previously used in similar NMAs on this subject.[26]

Results

Characteristics of the studies

The electronic search yielded approximately 469 Creations, and after the full-text screening, 17 articles were considered potentially eligible. Eventually, 8 trials were included from the database search,[27-34] involving a total of 4626 patients. Figure 1 shows the complete screening process. Table 1 summarizes the baseline characteristics of the included studies. The mean age of the participants in these studies ranged from 48.0 to 56.0 years, with almost 100% of the patients being women. Most of the participants were of the white race, except for one study by Masaya Hattori, which included participants from Japan. The duration of median follow-up in the trials varied between 14.0 and 44.7 months.

The risk of bias assessment was performed for each RCT and summarized in Supplemental Table S2 and Figure S1. Most of the studies were found to have a low risk of bias in categories such as random processes (5/8, 62.50%) and deviations from intended interventions (4/8, 50.00%). In the aspect of incomplete outcome data, measurement of the outcome, and selective reporting, all included studies were shown to be low risk. However, in terms of overall bias, 3 study (3/8, 37.50%) was deemed to have a low risk, while the remaining studies were unclear.

Network meta analyzes

After screening abstracts and conducting full-text reviews, a total of 8 trials met our inclusion criteria. Among these trials, 5 reported on OS, 6 reported on PFS, 6 reported on ORR, 7 reported on AEs, and 3 reported on pCR. The network was created using the paclitaxel arm of each trial as the comparator. The network was composed of 4 nodes and 3 edges, representing paclitaxel, atezolizumab plus paclitaxel, pembrolizumab plus paclitaxel, and durvalumab plus paclitaxel treatment strategies. Supplemental Figure S2 shows an NMA plot of the efficacy and safety of different paclitaxel-based PD-1/PD-L1 strategies.

Overall survival

The survival data from the randomized phase 3 study NCT03036488[34] and NCT002620280[29] were excluded from the analysis as they are currently immature and have not been reported. The remaining studies reported on OS and were included in the primary analysis. The result of the NMA is depicted in Figure 2A. Among the 4 interventions, none showed clear superiority over the others, as they were not statistically comparable. However, durvalumab plus paclitaxel demonstrated a distinct advantage, having the lowest HR compared to the paclitaxel group (HR 0.24, 95% CrI: 0.04-1.30). Estimated HRs for all comparisons of treatments are reported in Supplemental Table S3(A). The outcome of the heterogeneity test is depicted in Supplemental Figure S3, with the pembrolizumab-plus-paclitaxel group showing greater heterogeneity. The SUCRA indicated that there is a 91.05% probability that durvalumab plus paclitaxel is the preferred treatment to prolong OS. The second-ranked treatment was pembrolizumab plus paclitaxel (SUCRA, 56.38%), followed by toripalimab plus paclitaxel

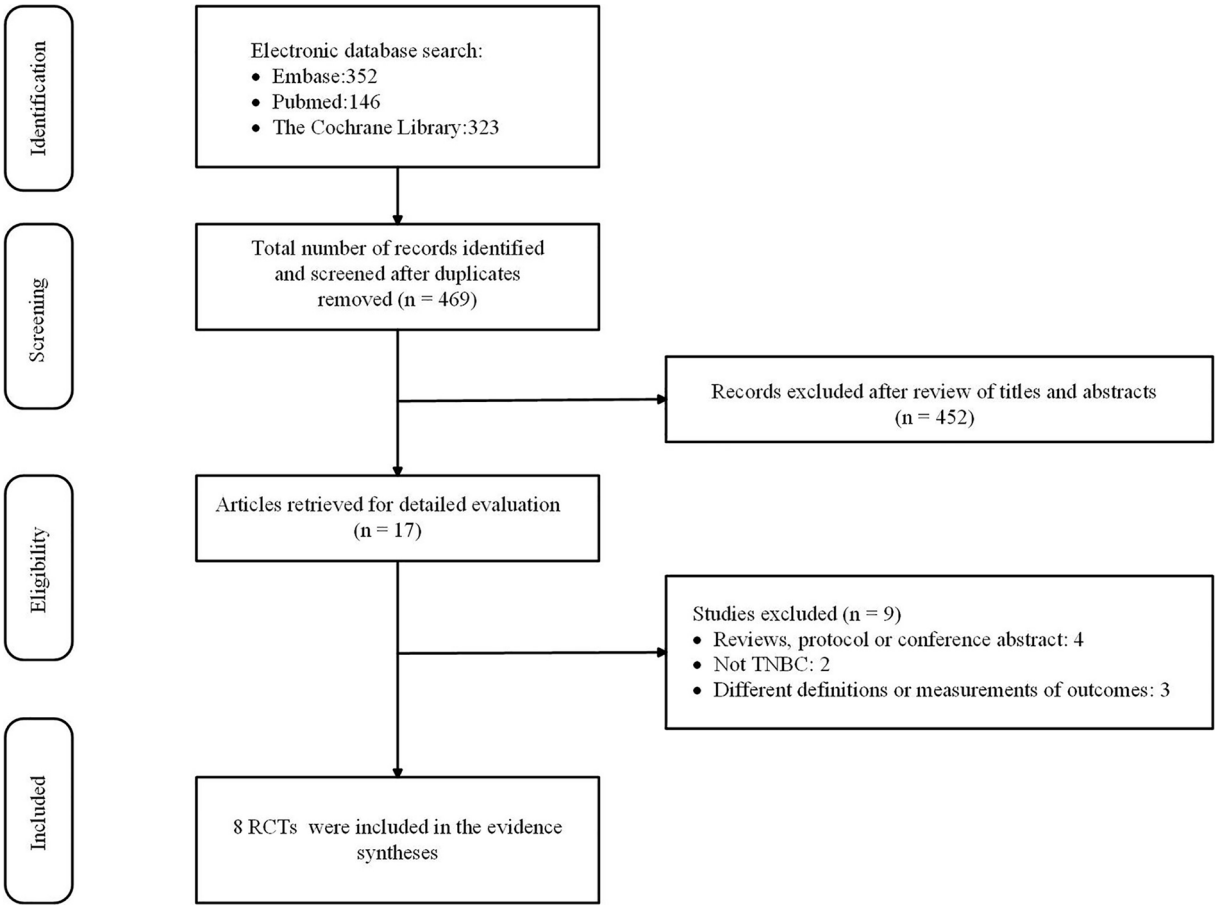

Figure 1. Flow chart of the search strategy.
RCT indicates randomized control trial.

(SUCRA, 54.47%), atezolizumab plus paclitaxel (SUCRA, 24.76%) ranked forth. The ranking results are presented in Figure 3A.

Progression-free survival

The PFS data of NCT002620280[29] is currently immature and has not been reported, leading to its exclusion from the analysis. However, the remaining 8 studies reported on PFS and were included in the primary analysis. The NMA results revealed that all 3 interventions were effective in prolonging PFS compared to the paclitaxel (Figure 2B). Among them, durvalumab plus paclitaxel had the absolute lowest HR compared with paclitaxel (HR 0.49, 95% CI: 0.42-1.70). Estimated HRs for all comparisons of treatments are reported in Supplemental Table S3(B). The outcome of the heterogeneity test is presented in Supplemental Figure S4, revealing no significant heterogeneity ($P > .05$). Therefore, a ranking probability chart was employed to assess the efficacy of the 11 dosage forms in improving PFS (Figure 3B). The highest-ranked treatment in terms of improving PFS was durvalumab plus paclitaxel (SUCRA, 84.52%), followed by toripalimab plus paclitaxel (SUCRA, 66.11%) in the second position, pembrolizumab plus paclitaxel (SUCRA, 54.63%) in the third position, and atezolizumab plus paclitaxel (SUCRA, 37.44%) ranked forth.

Adverse events

At the time of analysis, all trials have reported AEs grade $\geqslant 3$ results. Among these, toripalimab plus paclitaxel and pembrolizumab plus paclitaxel did not demonstrate a significant advantage in reducing AEs compared to paclitaxel alone. The analysis of AEs revealed that the risk of relative injury was higher in the durvalumab plus paclitaxel compared to other drugs. Among the interventions, atezolizumab plus paclitaxel had the absolute lowest OR compared with paclitaxel (OR 0.82, 95% CI: 0.41-1.50) (Figure 2C). The ranking probability diagram showed that the probability of adverse events (AEs) was highest for the pembrolizumab-plus-paclitaxel group (SUCRA, 71.07%), followed by toripalimab plus paclitaxel (SUCRA, 58.58%), paclitaxel in the third position (SUCRA, 50.01%), and durvalumab plus paclitaxel in the fourth position (SUCRA, 41.06%) (Figure 3C). The outcome of the heterogeneity test is presented in Supplemental Figure S5, with the atezolizumab-plus-paclitaxel group exhibiting greater heterogeneity ($I^2 = 82.13\%$). The estimated ORs for all treatment comparisons are reported in Supplemental Table S3(C).

Table 1. Basic characteristics of included studies.

AUTHOR	COUNTRY	ECOG	DISEASE STAGE	EXPERIMENTAL ARM TREATMENT	CONTROL ARM TREATMENT	NUMBER IN THE EXPERIMENTAL ARM (N)	NUMBER IN CONTROL ARM (N)	SEX (M/F)IN THE EXPERIMENTAL ARM	SEX (M/F)IN CONTROL ARM	AGE (YR) IN THE EXPERIMENTAL ARM	AGE (YR) IN CONTROL ARM	SURGERY	MEDIAN FOLLOW-UP	ENDPOINT	DATA TIME FRAME
Schmid et al[34]	Britain	0-1	Previously untreated stage II or stage III TNBC	Pembrolizumab-Paclitaxel	Paclitaxel-chemotherapy	784	390	0/784	0/390	49 (22–80)	48 (24–79)	Surgery after neoadjuvant treatment	15.5 mo	PCR, PFS, AEs, ORR	March 2017-April 24, 2019
Miles et al[33]	Britain	0-1	Metastatic or unresectable locally advanced measurable TNBC	Atezolizumab-Paclitaxel	Paclitaxel	431	220	1/430	0/220	54 (22-85)	53 (25-81)	/	14.2 mo	OS, PFS, AEs, ORR	25 August 2017-4 September 2020
Emens et al[28]	America	0-1	Unresectable, locally advanced, or metastatic TNBC	Atezolizumab-Paclitaxel	Paclitaxel	451	451	3/448	1/450	55 (46-64)	56 (47-65)	/	18.8 mo	OS, PFS,AEs,ORR	23 June 2015-14 April 2020
Loibl et al[32]	German	0-1	Untreated uni- or bilateral primary, non-metastatic invasive TNBC	Durvalumab-Paclitaxel	Paclitaxel-chemotherapy	88	86	0/88	0/86	49.5 (25-74)	49.5 (23-76)	Surgery after neoadjuvant treatment	43.7 mo	PCR, OS,PFS,AEs,ORR	June 2016-July 2021
Cortes et al[27]	Spain	0-1	Previously untreated locally recurrent inoperable or metastatic TNBC	Pembrolizumab-Paclitaxel	Paclitaxel	562	281	0/562	0/281	53 (44–63)	53 (43–63)	/	44.1 mo	OS, PFS,AEs,ORR	January 2017-June 15, 2021
Gianni et al[29]	Italy	0-1	Previously untreated histologically confirmed unilateral TNBC	Atezolizumab-Paclitaxel	Paclitaxel-chemotherapy	138	142	0/138	0/142	49.5 (25-79)	50 (24-77)	Surgery after neoadjuvant treatment	NA	PCR, AEs,ORR	May 2016-
Hattori et al[30]	Japan	0-1	Previously untreated locally recurrent inoperable or metastatic TNBC	Pembrolizumab-Paclitaxel	Paclitaxel-chemotherapy	61	26	0/61	0/26	54 (29–76)	51 (25–74)	/	44.7 mo	OS, PFS,AEs,ORR	January 2017-June 15, 2021
Jiang et al[31]	China	0-1	Newly diagnosed metastatic or recurrent locally advanced TNBC	Toripalimab-Paclitaxel	Paclitaxel	353	178	0/353	0/178	53.0 (23–84)	54.5 (27–76)	/	14.0mo	OS, PFS,AEs,ORR	25 December 2018 to 30 November 2022

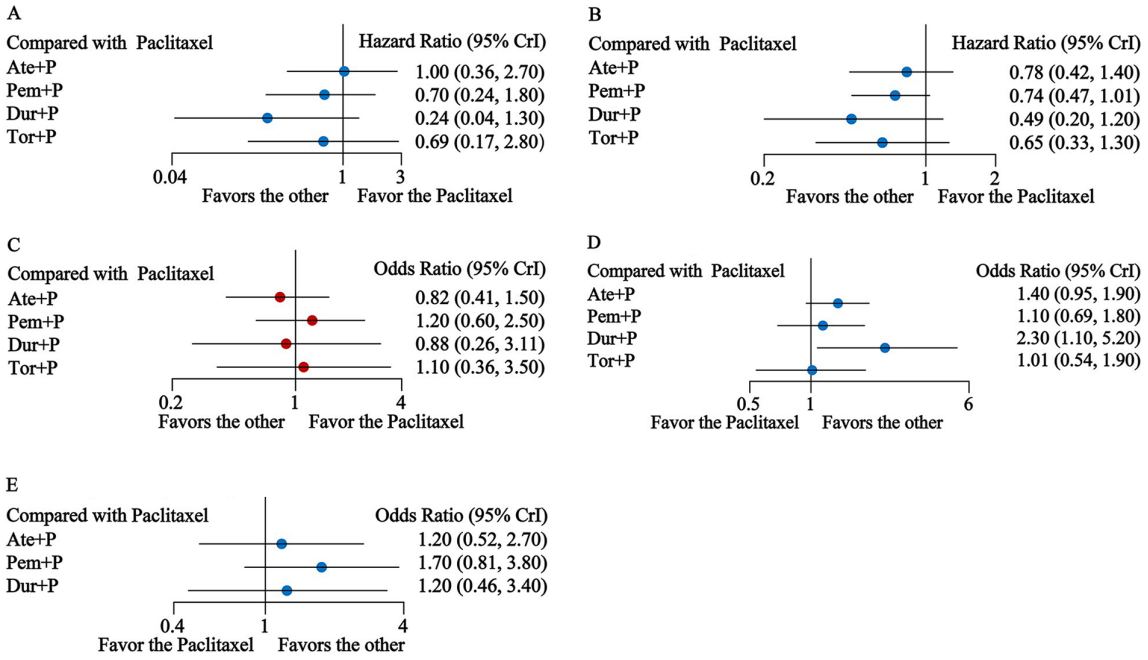

Figure 2. Forest plot of Bayesian random-effect consistency model for all studies compared with paclitaxel: ((A) Overall survival (OS); (B) Progression-free survival (PFS); (C) Adverse events (AEs); (D) Overall response rate (ORR); (E) Pathological complete response (pCR)).
Ate + p, atezolizumab plus paclitaxel; CrI, credible interval; Dur + P, durvalumab plus paclitaxel; HR, hazard ratios; OR, odds ratio; P, paclitaxel; Pem + P, pembrolizumab plus paclitaxel; Tor + P, toripalimab plus paclitaxel.

Overall response rate

The result of the NMA is depicted in Figure 2D, for which paclitaxel plus durvalumab showed the highest OR compared with paclitaxel (OR 2.30, 95% CrI: 1.10-5.20). All 3 interventions demonstrated significantly improved ORR compared with paclitaxel group. The calculated SUCRA suggests that there is a 94.87% probability that paclitaxel plus durvalumab is the preferred treatment option to improve ORR. The second-ranked treatment was atezolizumab plus paclitaxel (SUCRA, 65.83%), followed by pembrolizumab plus paclitaxel (SUCRA, 42.80%) in the third position, toripalimab plus paclitaxel (SUCRA, 26.72%) in the forth position. Figure 3D describes the ranking of the treatments in terms of the likelihood of being the superior treatment. The result of the heterogeneity test is reported in Supplemental Figure S6, showing no significant heterogeneity. Estimated ORs for all comparisons of treatments are reported in Supplemental Table S3(D). The total calculated SUCRA is shown in Supplemental Table S4.

Pathological complete response

Figure 2E illustrates the NMA result of pCR, showing that pembrolizumab plus paclitaxel had the highest or compared with the paclitaxel group (OR 1.70, 95% CrI: 0.81-3.80). All interventions demonstrated significantly improved pCR compared with the paclitaxel group. The calculated SUCRA suggests that there is 81.85% probability that pembrolizumab plus paclitaxel is the preferred treatment option to improve pCR. The second was paclitaxel plus durvalumab (SUCRA, 49.30%), the third was atezolizumab plus paclitaxel (SUCRA, 45.43%), the fourth was paclitaxel (SUCRA, 23.42%). Figure 3E provides a visualization of the ranking of treatments in terms of the likelihood of being the superior treatment. Estimated ORs for all treatment comparisons are reported in Supplemental Table S3(E). The total calculated SUCRA is provided in Supplemental Table S4.

Heterogeneity analyses

We conducted a thorough heterogeneity analysis for each outcome measure to identify potential influencing factors. However, for pathological complete response (pCR), the number of studies reporting data was insufficient to perform a heterogeneity analysis. In contrast, the ORR index exhibited no heterogeneity. When analyzing the PFS indicators, we found that the 3 studiesinvolving pembrolizumab plus paclitaxel demonstrated low heterogeneity, with an $I^2 = 13.7\%$. In the OS analysis, 2 studies related to pembrolizumab plus paclitaxel showed significant heterogeneity, with an I^2 value of 90.9%. In addition, in the AES index analysis, the 3 studies examining atezolizumab plus paclitaxel also revealed high heterogeneity, with an $I^2 = 90.8\%$ (Supplemental Figures S3-S6).

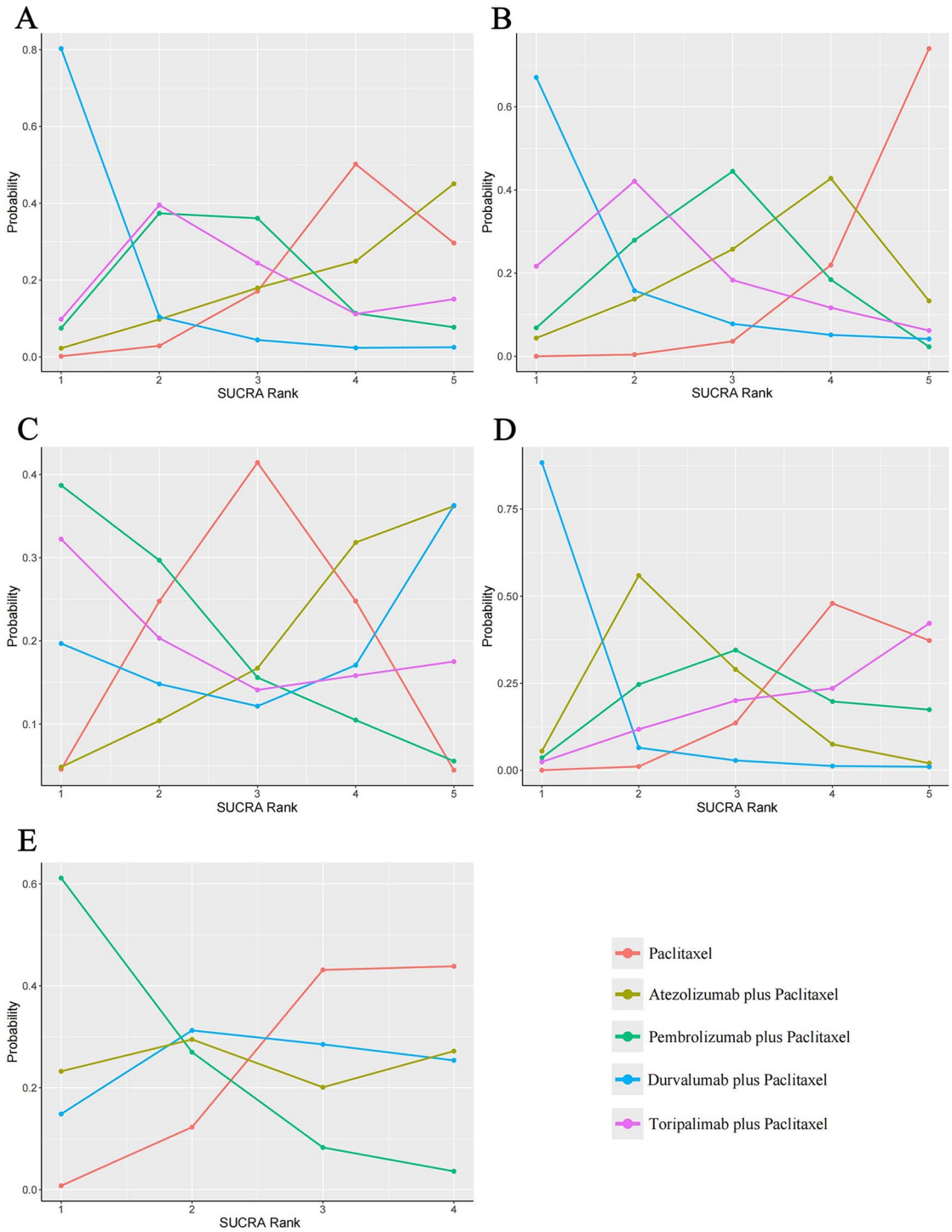

Figure 3. Rank gram of treatment modality. ((A) Overall survival (OS); (B) Progression-free survival (PFS); (C) Adverse events (AEs); (D) Overall response rate (ORR); (E) Pathological complete response (pCR)).
SUCRA, surface under the cumulative ranking.

Discussion

Triple-negative breast cancer is an exceptionally aggressive breast cancer subtype with poor survival, high mortality, and a tendency for recurrence and metastasis, making it challenging to find effective treatments in clinical settings.[35,36] Chemotherapy remains a cornerstone of treatment, with taxanes, such as paclitaxel, commonly administered as monotherapy or in combination with other therapeutic agents.[37] Immunotherapy targeting the PD-1/PD-L1 pathway has emerged as a promising novel approach in the management of TNBC.[38] Several studies have affirmed the potential of combining PD-1/PD-L1 inhibitors with paclitaxel to favorably impact patient outcomes. However, no studies have directly compared these treatment combinations to establish the optimal therapeutic strategy. To address this gap, a network meta-analysis of 8

RCTs was conducted to compare the efficiency and safety of currently approved PD-1/PD-L1 inhibitors combined with paclitaxel. This study aims to provide a scientific and rational treatment option by comparing the efficacy and safety of different combination therapies. By analyzing OS, the study seeks to identify the most effective treatment options, as OS is globally recognized as a key endpoint for supporting the approval of new anti-cancer therapies. In addition, the incidence of PFS, ORR, AEs, and pCR were used as secondary endpoints to provide a more comprehensive evaluation of therapeutic efficacy and safety.

Given that most outcomes were not statistically significant, we used SUCRA to compare treatment regimens and identify those with the most favorable outcomes. Our findings indicate that durvalumab plus paclitaxel exhibited superior efficacy in prolonging OS, PFS, and improving ORR. Since OS serves as the primary endpoint for assessing treatment effectiveness, we conclude that durvalumab plus paclitaxel is the optimal therapeutic option for treating TNBC. In terms of pCR, pembrolizumab plus paclitaxel exhibited significant advantages. Nonetheless, it is important to note that atezolizumab plus paclitaxel showed significant improvement in the incidence of AEs. However, toripalimab as a relatively emerging PD-L1 inhibitor, did not show a significant advantage in the comparison of these combinations. Further clinical trials are needed to validate the efficacy and safety of toripalimab.

The survival benefit may be partly attributed to the superior efficacy of paclitaxel. Paclitaxel functions as a mitotic inhibitor of tumor cells, effectively halting their proliferation. In addition, it has been shown to synergize with PD-1/PD-L1 inhibitors, enhancing their therapeutic effects.[39,40] Different from paclitaxel, PD-1/PD-L1 inhibitors reactivate T cell-mediated antitumor immunity by blocking the interaction of PD-1/PD-L1 targets in tumor cells.[10,41,42] In the tumor microenvironment, PD-1/PD-L1 plays an important role in tumor progression and survival.[43] Combining paclitaxel and PD-1/PD-L1 inhibitors offers a dual mechanism of action, directly targeting tumor cells while simultaneously modulating the immune system. Programmed death-1/PD-L1 inhibitors' immunotherapeutic effect enhances the immune cells' capabilities, counteracting the potential inhibitory impact of paclitaxel on the body's immune response.[11,40,44]

Durvalumab was first approved by the US Food and Drugs Administration (FDA) in 2017 for tumor immunotherapies and has since found widespread use in bladder cancer and non-small-cell lung cancer.[45] However, in the context of TNBC immunotherapies, it remains relatively new. Survival-related results of many trials, such as the I-SPY 2 trial, are still pending.[46] Up to now, the available research on durvalumab combined with paclitaxel in breast cancer treatment is still limited. According to the latest NCCN guidelines,[6] durvalumab is not included in the recommended drugs. The analysis of our study shows that durvalumab plus paclitaxel can significantly prolong OS and PFS, and improve ORR compared with other drug combinations. Durvalumab activates the patient's immune system, stimulating the production of tumor-specific T cells.[47] By restoring T cell activity, durvalumab helps mitigate immune evasion often induced by chemotherapy agents such as paclitaxel. This synergistic effect can significantly improve the therapeutic effect. However, the reasons behind these findings are yet to be fully understood due to the limited amount of literature and experiments available. Therefore, more RCTs are need to explore the optimal dosage form and compatibility to make informed decisions about its usage in TNBC treatment.

Atezolizumab was the first PD-L1 drug approved by the FDA for TNBC.[48] Whereas, it has not shown therapeutic advantage. The results from its large RCT trials, IMpassion130 and IMpassion131[33,49] also illustrated the same disappointing result. Another study, NCT002620280 which use pCR as primary outcomes also ended in failure.[29] In addition, the new trial IMpassion132 is still in progress,[50] so the results can be expected. Although the effectiveness of the treatment was not significant, our study's findings highlight that atezolizumab plus paclitaxel is the safest option. Atezolizumab is a high-affinity, low-immunogenicity humanized IgG1 monoclonal antibody with stable metabolism and a moderate half-life, minimizing the risk of accumulation and long-term toxicity.[51] The drug is primarily excreted through the kidneys, reducing residual effects and potential adverse reactions,[52] which may contribute to its favorable safety profile. However, significant heterogeneity was observed among the 3 studies on atezolizumab, which warrants consideration. Potential sources of heterogeneity include the inclusion of male patients in the studies by D. Miles and L.A. Emens, as well as the differences in median age between studies—less than 50 years in L. Gianni's study compared to approximately 60 years in the studies by D. Miles and L.A. Emens. The observed heterogeneity in AEs outcome analysis may partially explain the lack of statistical significance in these findings.

After reviewing the included literature, the primary adverse reactions identified were rashes, pruritus, gastrointestinal disorders, cardiotoxicity, and endocrine-related conditions. The adverse reactions observed in tumor patients may be attributed to the unique mechanism of action of PD-1/PD-L1 inhibitors, which can disrupt immune tolerance and trigger autoimmune and inflammatory responses in normal tissues.[53,54] In addition, research suggests that redox mechanisms is the primary cause of cardiotoxicity.[55] Patient variability, including factors such as gender and age, can also influence the incidence of adverse reactions. As indicated by heterogeneity analysis, both gender and age are significant determinants. Studies have shown that the prognosis for male breast cancer patients may be poorer compared to females, partly due to a lack of preventive programs, low awareness, and insufficient information among men, leading to later diagnoses and higher mortality rates at comparable stages and subtypes.[56-58] Furthermore, age is a critical risk factor for breast cancer, with a median age at diagnosis

of approximately 61 years.[59] Therefore, when considering drug safety, attention should be paid to the potential impact of differences in patient populations. While most immune-related AEs are usually manageable and reversible, it is crucial to closely monitor patients for any adverse effects.[60] Early detection and appropriate interventions are crucial to ensure patients continue to benefit from the combination of PD-1/PD-L1 inhibitors and chemotherapy, mitigating potential risks and maximizing treatment efficacy.

Pembrolizumab combined with paclitaxel is the recommended drug option for TNBC immunotherapies.[6] In our study, pembrolizumab combined with paclitaxel significantly improved pCR. Pembrolizumab can not only facilitate the direct elimination of tumor cells by T cells but also boosts the formation of immune memory.[61] These effects can reduce tumor cell burden and lower the risk of recurrence, potentially explaining its impressive improvement in pCR rates. However, pembrolizumab exhibited moderate performance in OS and PFS analyses. Heterogeneity analysis revealed discrepancies in OS and PFS outcomes between the 2 studies combining pembrolizumab with paclitaxel. These variations may be attributed to differences in TNBC stage, median follow-up time, and ethnic factors, which could explain the lack of significant improvements in OS and PFS. Notably, pCR, an emerging biomarker for evaluating the efficacy of neoadjuvant therapy, has been associated with prolonged OS and a reduced mortality risk in patients who achieve it.[62,63] Consequently, the current evidence supports the reliability of pembrolizumab combined with paclitaxel as a first-line treatment for TNBC. These findings further reinforce the therapeutic efficacy of this combination regimen.

Diagnosis of TNBC relies on the detection of ER, PR, and HER2 status. Imaging tests can identify TNBC prior to the onset of symptoms, facilitating early detection.[64] Research has shown a correlation between the molecular subtypes of cancer and their imaging characteristics. A deeper understanding of TNBC's molecular and imaging features may enhance early diagnosis and treatment strategies. Further studies are needed to optimize therapies and improve outcomes for TNBC patients.

Strength and Limitations

Our review has several strengths. First, the included studies were all large RCTs with high level of evidence, which greatly increased the number of participants included and ensured the reliability of evidence sources. Second, we included the latest results from the same studies. This can provide a more accurate range of results for evaluation than previously reported studies, instill confidence in the use of web meta-analysis, and produce reliable results. Furthermore, our study marks an important advancement from previous network meta-analyses. The inclusion of studies involving paclitaxel in combination with PD-1/PD-L1 agents, which were previously overlooked, has contributed to a more comprehensive understanding of the treatment options. This, in turn, has led to a different conclusion from previous NMAs, suggesting that the combination of PD-1/PD-L1 inhibitors with chemotherapy, specifically paclitaxel, may be the preferred treatment option.

The study has several limitations. Many conclusions rely on indirect comparisons, which are not an adequate substitute for direct comparisons of randomized data. In the analysis of outcome measures, 95% CI for some drugs did not show statistical significance, warranting cautious interpretation of the results. In addition, the quality of the RCT studies included in this analysis may have potential data bias issues. First of all, the patients included in this analysis were almost all women with a median age of 48.0 to 56.0, that is, perimenopause. Subgroup analysis by sex and age was not performed, which may affect the accuracy of the results. Second, some of the studies included in this analysis had a short median follow-up time. Shorter follow-ups may fail to capture long-term survival outcomes, potentially impacting the stability and reliability of the findings. Many of RCTs included have not yet reached maturity in terms of survival data. Moreover, we did not impose restrictions on the staging of TNBC, and variations in tumor stage—particularly the progression from early to advanced stages—can significantly influence patients' therapeutic responses and survival rates. Third, this study did not limit the race. Different races can exhibit variations in drug sensitivity, receptor sensitivity, and other factors, which can influence treatment outcomes significantly.[65,66] In addition, we did not conduct subgroup analyses for different TNBC subtypes anddifferent patient types. Therefore, there is a lack of discussion regarding potential drug interactions and the variability of their effects across different patient populations. Moreover, the limited number of studies available for inclusion in the durvalumab-and-toripalimab group may introduce bias into the analysis.

Conclusion

Based on our research, the combination of PD-1/PD-L1 inhibitors with paclitaxel demonstrates a survival advantage. Specifically, durvalumab plus paclitaxel emerges as a promising therapeutic option for the treatment of TNBC. Atezolizumab in combination with paclitaxel is identified as the safest regimen, while pembrolizumab combined with paclitaxel offers a unique advantage in improving pCR. These findings support current treatment strategies recommended by oncology guidelines and suggest potential new drug options. However, it is important to note that most drug comparisons did not yield statistically significant results, meaning the current evidence cannot definitively identify the preferred drug for TNBC treatment. Factors such as age, gender, race, and tumor staging may influence the efficacy and safety of these therapies. Future studies should integrate multiple diagnostic approaches, including imaging, to facilitate early detection and tumor

profiling. In addition, further RCTs are needed to provide more robust evidence comparing the efficacy and safety of additional PD-1/PD-L1 inhibitors combined with paclitaxel.

Acknowledgements
Not applicable.

Author Contributions
YD: Conceptualization, Methodology, Data retrieval, Data acquisition, Formal analysis, Software, Writing-Original draft preparation. **TR:** Conceptualization, Formal analysis, Data retrieval, Data curation, Writing-Original draft preparation. **WY:** Validation, Formal analysis, Data acquisition, Data curation, Investigation, Writing-Original draft preparation. **SL:** Conceptualization, Writing- Reviewing and Editing. **JC:** Conceptualization, Data acquisition, Writing-Reviewing and Editing. **YF:** Conceptualization, Writing-Reviewing and Editing. **QL:** Conceptualization, Writing-Reviewing and Editing.

Availability of Data and Materials
The data used to support the findings of this study are included within the article.

Consent for Publication
Not applicable.

Ethics Approval and Consent to Participate
Not applicable.

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Supplemental Material
Supplemental material for this article is available online.

REFERENCES
1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74:229-263. doi:10.3322/caac.21834
2. The Global Cancer Observatory. Latest global cancer data: cancer burden rises to 19.3 million new cases and 10.0 million cancer deaths in 2020. Published 2020. https://www.iarc.fr/fr/news-events/latest/
3. Gerratana L, Basile D, Buono G, et al. Androgen receptor in triple negative breast cancer: a potential target for the targetless subtype. *Cancer Treat Rev*. 2018;68:102-110. doi:10.1016/j.ctrv.2018.06.005
4. Bianchini G, Balko JM, Mayer IA, Sanders ME, Gianni L. Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. *Nat Rev Clin Oncol*. 2016;13:674-690. doi:10.1038/nrclinonc.2016.66
5. Garrido-Castro AC, Lin NU, Polyak K. Insights into molecular classifications of triple-negative breast cancer: improving patient selection for treatment. *Cancer Discov*. 2019;9:176-198. doi:10.1158/2159-8290.Cd
6. National Comprehensive Cancer Network. Breast cancer guideline. Published 2023. https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1419
7. Huang W, Ran R, Shao B, Li H. Prognostic and clinicopathological value of PD-L1 expression in primary breast cancer: a meta-analysis. *Breast Cancer Res Treat*. 2019;178:17-33. doi:10.1007/s10549-019
8. Cobec IM, Moleriu L, Moatar AE, Rempen A. First clinical experience with CDK4/6 inhibitors in breast cancer therapy. *Exp Ther Med*. 2021;21:522. doi:10.3892/etm.2021.9954
9. Keenan TE, Tolaney SM. Role of immunotherapy in triple-negative breast cancer. *J Natl Compr Canc Netw*. 2020;18:479-489. doi:10.6004/jnccn.2020.7554
10. Yang T, Li W, Huang T, Zhou J. Immunotherapy targeting PD-1/PD-L1 in early-stage triple-negative breast cancer. *J Pers Med*. 2023;13:526. doi:10.3390/jpm13030526
11. Alsaab HO, Sau S, Alzhrani R, et al. PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: mechanism, combinations, and clinical outcome. *Front Pharmacol*. 2017;8:561. doi:10.3389/fphar.2017.00561
12. Akinleye A, Rasool Z. Immune checkpoint inhibitors of PD-L1 as cancer therapeutics. *J Hematol Oncol*. 2019;12:92. doi:10.1186/s13045-019
13. Disis ML, Adams SF, Bajpai J, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of gynecologic cancer. *J Immunother Cancer*. 2023;11:e006624. doi:10.1136/jitc-2022
14. Morganti S, Tolaney SM. Role of immunotherapy in early- and late-stage triple-negative breast cancer. *Hematol Oncol Clin North Am*. 2023;37:133-150. doi:10.1016/j.hoc.2022.08.014
15. Panagopoulos A, Solou K, Tatani I, et al. What is the optimal surgical treatment for Neer type IIB (IIC) distal clavicle fractures? A systematic review and meta-analysis. *J Orthop Surg Res*. 2022;17:215. doi:10.1186/s13018-022
16. Derakhshan F, Reis-Filho JS. Pathogenesis of triple-negative breast cancer. *Annu Rev Pathol*. 2022;17:181-204. doi:10.1146/annurev-pathol
17. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol*. 2010;28:2784-2795. doi:10.1200/jco.2009.25.6529
18. Woods BS, Hawkins N, Scott DA. Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: a tutorial. *BMC Med Res Methodol*. 2010;10:54. doi:10.1186/1471-2288
19. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med*. 2010;29:932-944. doi:10.1002/sim.3767
20. Lumley T. Network meta-analysis for indirect treatment comparisons. *Stat Med*. 2002;21:2313-2324. doi:10.1002/sim.1201
21. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making*. 2013;33:607-617. doi:10.1177/0272989x12458724
22. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*. 2007;8:16. doi:10.1186/1745-6215
23. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539-1558. doi:10.1002/sim.1186
24. Mbuagbaw L, Rochwerg B, Jaeschke R, et al. Approaches to interpreting and choosing the best treatments in network meta-analyses. *Syst Rev*. 2017;6:79. doi:10.1186/s13643-017
25. Palma Pérez S, Delgado Rodríguez M. [Practical considerations on detection of publication bias]. *Gac Sanit*. 2006;20:10-16. doi:10.1157/13101085
26. Chen H, Lu W, Zhang Y, Zhu X, Zhou J, Chen Y. A Bayesian network meta-analysis of the efficacy of targeted therapies and chemotherapy for treatment of triple-negative breast cancer. *Cancer Med*. 2019;8:383-399. doi:10.1002/cam4.1892
27. Cortes J, Rugo HS, Cescon DW, et al. Pembrolizumab plus chemotherapy in advanced triple-negative breast cancer. *N Engl J Med*. 2022;387:217-226. doi:10.1056/NEJMoa2202809
28. Emens LA, Adams S, Barrios CH, et al. First-line atezolizumab plus nab-paclitaxel for unresectable, locally advanced, or metastatic triple-negative breast cancer: IMpassion130 final overall survival analysis. *Ann Oncol*. 2021;32:983-993. doi:10.1016/j.annonc.2021.05.355
29. Gianni L, Huang CS, Egle D, et al. Pathologic complete response (pCR) to neoadjuvant treatment with or without atezolizumab in triple-negative, early high-risk and locally advanced breast cancer: NeoTRIP Michelangelo randomized study. *Ann Oncol*. 2022;33:534-543. doi:10.1016/j.annonc.2022.02.004
30. Hattori M, Masuda N, Takano T, et al. Pembrolizumab plus chemotherapy in Japanese patients with triple-negative breast cancer: results from KEYNOTE-355. *Cancer Med*. 2023;12:10280-10293. doi:10.1002/cam4.5757
31. Jiang Z, Ouyang Q, Sun T, et al. Toripalimab plus nab-paclitaxel in metastatic or recurrent triple-negative breast cancer: a randomized phase 3 trial. *Nat Med*. 2024;30:249-256. doi:10.1038/s41591-023
32. Loibl S, Schneeweiss A, Huober J, et al. Neoadjuvant durvalumab improves survival in early triple-negative breast cancer independent of pathological complete response. *Ann Oncol*. 2022;33:1149-1158. doi:10.1016/j.annonc.2022.07.1940
33. Miles D, Gligorov J, André F, et al. Primary results from IMpassion131, a double-blind, placebo-controlled, randomised phase III trial of first-line paclitaxel with or without atezolizumab for unresectable locally advanced/metastatic triple-negative breast cancer. *Ann Oncol*. 2021;32:994-1004. doi:10.1016/j.annonc.2021.05.801

34. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med*. 2020;382:810-821. doi:10.1056/NEJMoa1910549
35. Varzaru VB, Vlad T, Popescu R, Vlad CS, Moatar AE, Cobec IM. Triple-negative breast cancer: molecular particularities still a challenge. *Diagnostics (Basel)*. 2024;14:1875. doi:10.3390/diagnostics14171875
36. Mayer IA, Abramson VG, Lehmann BD, Pietenpol JA. New strategies for triple-negative breast cancer—deciphering the heterogeneity. *Clin Cancer Res*. 2014;20:782-790. doi:10.1158/1078-0432.Ccr
37. Abu Samaan TM, Samec M, Liskova A, Kubatka P, Büsselberg D. Paclitaxel's mechanistic and clinical effects on breast cancer. *Biomolecules*. 2019;9:789. doi:10.3390/biom9120789
38. Won KA, Spruck C. Triplenegative breast cancer therapy: current and future perspectives (review). *Int J Oncol*. 2020;57:1245-1261. doi:10.3892/ijo.2020.5135
39. Marupudi NI, Han JE, Li KW, Renard VM, Tyler BM, Brem H. Paclitaxel: a review of adverse toxicities and novel delivery strategies. *Expert Opin Drug Saf*. 2007;6:609-621. doi:10.1517/14740338.6.5.609
40. Zhu L, Chen L. Progress in research on paclitaxel and tumor immunotherapy. *Cell Mol Biol Lett*. 2019;24:40. doi:10.1186/s11658-019
41. Rugo HS. ME01 Frontiers in Immunotherapy. *Ann Oncol*. 2022;33:S458. doi:10.1016/j.annonc.2022.05.086
42. Emens LA. Immunotherapy in triple-negative breast cancer. *Cancer J*. 2021;27:59-66. doi:10.1097/ppo.0000000000000497
43. Cimino-Mathews A, Thompson E, Taube JM, et al. PD-L1 (B7-H1) expression and the immune tumor microenvironment in primary and metastatic breast carcinomas. *Hum Pathol*. 2016;47:52-63. doi:10.1016/j.humpath.2015.09.003
44. Blenman KRM, Marczyk M, Karn T, et al. Predictive markers of response to neoadjuvant durvalumab with nab-paclitaxel and dose-dense doxorubicin/cyclophosphamide in basal-like triple-negative breast cancer. *Clin Cancer Res*. 2022;28:2587-2597. doi:10.1158/1078-0432.Ccr-21-3215
45. Hasegawa T, Ariyasu R, Tanaka H, et al. Subsequent treatment for locally advanced non-small-cell lung cancer that progressed after definitive chemoradiotherapy and consolidation therapy with durvalumab: a multicenter retrospective analysis (TOPGAN 2021-02). *Cancer Chemother Pharmacol*. 2023;92:29-37. doi:10.1007/s00280-023
46. Pusztai L, Yau C, Wolf DM, et al. Durvalumab with olaparib and paclitaxel for high-risk HER2-negative stage II/III breast cancer: results from the adaptively randomized I-SPY2 trial. *Cancer Cell*. 2021;39:989-998e985. doi:10.1016/j.ccell.2021.05.009
47. Wills S, Hochmuth LK, Bauer KS Jr, Deshmukh R. Durvalumab: a newly approved checkpoint inhibitor for the treatment of urothelial carcinoma. *Curr Probl Cancer*. 2019;43:181-194. doi:10.1016/j.currproblcancer.2018.08.010
48. Narayan P, Wahby S, Gao JJ, et al. FDA Approval summary: atezolizumab plus paclitaxel protein-bound for the treatment of patients with advanced or metastatic TNBC whose tumors express PD-L1. *Clin Cancer Res*. 2020;26:2284-2289. doi:10.1158/1078-0432.Ccr
49. Emens LA, Adams S, Barrios CH, et al. LBA16 IMpassion130: final OS analysis from the pivotal phase III study of atezolizumab + nab-paclitaxel vs placebo + nab-paclitaxel in previously untreated locally advanced or metastatic triple-negative breast cancer. *Ann Oncol*. 2020;31:S1148. doi:10.1016/j.annonc.2020.08.2244
50. Cortés J, André F, Gonçalves A, et al. IMpassion132 Phase III trial: atezolizumab and chemotherapy in early relapsing metastatic triple-negative breast cancer. *Future Oncol*. 2019;15:1951-1961. doi:10.2217/fon-2019-0059
51. Moroney JW, Powderly J, Lieu CH, et al. Safety and clinical activity of atezolizumab plus bevacizumab in patients with ovarian cancer: a phase Ib study. *Clin Cancer Res*. 2020;26:5631-5637. doi:10.1158/1078-0432.CCR-20-0477
52. Centanni M, Moes DJAR, Trocóniz IF, Ciccolini J, van Hasselt JGC. Clinical pharmacokinetics and pharmacodynamics of immune checkpoint inhibitors. *Clin Pharmacokinet*. 2019;58:835-857. doi:10.1007/s40262-019
53. Fabi A, Carbognin L, Botticelli A, et al. Real-world ANASTASE study of atezolizumab+nab-paclitaxel as first-line treatment of PD-L1-positive metastatic triple-negative breast cancer. *NPJ Breast Cancer*. 2023;9:73. doi:10.1038/s41523-023
54. Liu J, Chen Z, Li Y, Zhao W, Wu J, Zhang Z. PD-1/PD-L1 checkpoint inhibitors in tumor immunotherapy. *Front Pharmacol*. 2021;12:731798. doi:10.3389/fphar.2021.731798
55. Tocchetti CG, Cadeddu C, Di Lisi D, et al. From molecular mechanisms to clinical management of antineoplastic drug-induced cardiovascular toxicity: a translational overview. *Antioxid Redox Signal*. 2019;30:2110-2153. doi:10.1089/ars.2016.6930
56. Varzaru VB, Anastasiu-Popov DM, Eftenoiu AE, et al. Observational study of men and women with breast cancer in terms of overall survival. *Cancers (Basel)*. 2024;16:3049. doi:10.3390/cancers16173049
57. Lautrup MD, Thorup SS, Jensen V, et al. Male breast cancer: a nation-wide population-based comparison with female breast cancer. *Acta Oncol*. 2018;57:613-621. doi:10.1080/0284186x.2017.1418088
58. Potter AM, Bentz B, Crue L, et al. Men's lived experiences of breast cancer and changes in occupation. *Occup Ther Int*. 2023;2023:9641922. doi:10.1155/2023/9641922
59. VanderWalde A, Hurria A. Early breast cancer in the older woman. *Clin Geriatr Med*. 2012;28:73-91. doi:10.1016/j.cger.2011.10.002
60. Brown LC, Loi S. Immune checkpoint inhibition in the treatment of early stage triple negative breast cancer: 2021 update. *Breast*. 2022;62:S29-S33. doi:10.1016/j.breast.2021.12.018
61. Li C, Zhao S, Zheng Y, et al. Preoperative pembrolizumab combined with chemoradiotherapy for oesophageal squamous cell carcinoma (PALACE-1). *Eur J Cancer*. 2021;144:232-241. doi:10.1016/j.ejca.2020.11.039
62. Kang S, Lee SH, Lee HJ, et al. Pathological complete response, long-term outcomes, and recurrence patterns in HER2-low versus HER2-zero breast cancer after neoadjuvant chemotherapy. *Eur J Cancer*. 2022;176:30-40. doi:10.1016/j.ejca.2022.08.031
63. Waser NA, Quintana M, Schweikert B, et al. Pathological response in resectable non-small cell lung cancer: a systematic literature review and meta-analysis. *JNCI Cancer Spectr*. 2024;8:pkae021. doi:10.1093/jncics/pkae021
64. Burciu OM, Sas I, Popoiu TA, et al. Correlations of imaging and therapy in breast cancer based on molecular patterns: an important issue in the diagnosis of breast cancer. *Int J Mol Sci*. 2024;25:8506. doi:10.3390/ijms25158506
65. Kroenke CH, Kurtovich E, Aoki R, et al. Evaluation of approaches to recruitment of racially and ethnically diverse breast cancer patients from an integrated health care setting for collection of observational social network data. *Cancer Causes Control*. 2023;34:705-713. doi:10.1007/s10552-023
66. Terman E, Sheade J, Zhao F, et al. The impact of race and age on response to neoadjuvant therapy and long-term outcomes in Black and White women with early-stage breast cancer. *Breast Cancer Res Treat*. 2023;200:75-83. doi:10.1007/s10549-023