

PD-1/PD-L1 inhibitor-based immunotherapy in locally advanced or metastatic triple-negative breast cancer: A meta-analysis

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Abstract. Triple-negative breast cancer (TNBC) is a subtype of breast cancer that is negative for oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 expression. Locally advanced and metastatic TNBC not only have a worse prognosis and are more invasive than TNBC, but are also the most immunogenic subtypes of breast cancer. There is still a lack of clarity regarding the optimal treatment of locally advanced or metastatic TNBC. The present study aimed to assess the efficacy and safety of programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitor-based immunotherapy [i.e., immune checkpoint inhibitors (ICIs)] alone or in combination with other therapies for the treatment of locally advanced or metastatic TNBC. The PubMed, Cochrane Library, Embase and MEDLINE databases were searched up to July 19, 2023 to identify studies that examined the efficacy and safety of ICIs for treating TNBC. The primary outcomes were progression-free survival (PFS) and overall survival (OS). The secondary outcomes were safety and adverse events. The data were analysed using Review Manager 5.4. A total of 8 studies (3,338 patients) were included in the present meta-analysis. Compared with other therapies, ICIs had a significantly different effect on OS [hazard ratio (HR)=0.83; 95% confidence interval (CI)=0.69-1.00; $P<0.05$; $I^2=59\%$] in patients with locally advanced or metastatic TNBC. In addition, ICIs significantly prolonged PFS compared with other therapies (intent-to-treat: HR=0.81; 95% CI=0.75-0.88; $P<0.00001$; $I^2=0\%$). Immunotherapy based on PD-1/PD-L1 inhibitors showed variable efficacy on OS and PFS in TNBC, while a significant improvement was observed for PD-L1(+). Future studies should focus on PD-L1 subgroup status, which may help optimize personalized treatment regimens for TNBC.

Introduction

Breast cancer (BC) is one of the most common malignant tumours worldwide (1); however, 70-80% of early-stage non-metastatic BC cases are curable (2). BC's Molecular typing is based on the expression of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). BC can be further subdivided into luminal A- and B-type BC, HER2-positive BC and triple-negative BC (TNBC). Among these subtypes, TNBC lacks the expression of ER, PR and HER2, and accounts for 15-20% of all BC cases. Furthermore, TNBC is characterized by a high rate of systemic metastasis, insensitivity to conventional treatments and susceptibility to drug resistance, thus leading to a poor prognosis. The poor response of TNBC to treatment remains a major problem in the field of BC research (3-5).

Locally advanced or metastatic TNBC, which is the most invasive and immunogenic subtype, has the poorest prognosis among all BC types (6). For decades, various treatment options, including chemotherapy, radiotherapy (RT) and surgery, have been available for TNBC; in particular, chemotherapy has been the primary first-line treatment (7,8). Surgical treatment of TNBC is confined to local therapy and consists of surgical removal of the breast tumour mass by mastectomy or breast-conserving surgery, followed by radiation therapy [breast-conserving therapy (BCT)]. According to previous studies, surgical treatment of TNBC and BC did not differ in local control rates, and these studies have demonstrated a higher rate of local recurrence in patients with TNBC subtypes following BCT (9-11). Although the current guidelines for adjuvant RT for TNBC are not much different from those for other BC subtypes, the recommended RT regimen for TNBC depends on the extent of surgery and lymph node status; however, no significant prolongation of survival and a high recurrence rate are observed after treatment (12). Although chemotherapy is effective, the treatment of TNBC still faces a series of challenges. Chemotherapy is successful in early-stage TNBCs, but it is relatively ineffective in advanced-stage patients, as reflected in the fact that metastatic TNBC has a 5-year survival rate of only 12% (13) due to its molecular heterogeneity, poor cell differentiation, high degree of malignancy, lack of molecular targets, rapid metastasis and resistance to chemotherapy drugs (14,15).

Although BC is not traditionally considered a particularly immunogenic tumour, previous studies have shown that

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immune checkpoint inhibitors (ICIs) or immunotherapies exert promising effects on a wide range of malignancies that are refractory to solid tumours (including advanced non-small cell lung cancer, metastatic melanoma and metastatic bladder cancer) (16-18). While TNBC has a higher degree of stromal and intratumoural tumour-infiltrating lymphocytes that recognize and attack tumour cells, non-TNBC has a lower mutational load than other solid tumours, which is correlated with the number of somatic mutations present in the tumour, high mutational loads in TNBC and higher programmed death ligand 1 (PD-L1) expression on the cell surface of TNBC compared with other BC subtypes. These correlations suggest that some aggressive TNBCs may be immunogenic (3,19,20). Thus, the use of ICIs, including programmed cell death protein 1 (PD-1), PD-L1 and cytotoxic T-lymphocyte associated protein 4 (CTLA-4), have promising potential for the treatment of BC. In TNBC, tumour immune infiltration, neoantigen levels, mutational load, high genomic instability and high levels of immune markers (such as PD-1 and PD-L1) are closely associated with tumour response, recurrence and prognosis. Immunotherapy can improve the prognosis of TNBC by remodelling the tumour microenvironment and stimulating antitumour immune responses (21,22). Programmed cell death proteins that are expressed on T cells bind to the ligand PD-L1, which is expressed on tumour cells, thereby mediating tumour immune escape by inhibiting antigen-specific T-cell immune responses. Interfering with PD-1/PD-L1 interactions via anti-PD-1 monoclonal antibodies (mAbs) or anti-PD-L1 mAbs activates antitumour immune responses. In addition, PD-L1 is expressed in other tumour-infiltrating immune cells, mainly antigen-presenting cells such as dendritic cells and macrophages, and PD-L1 expression on these immune cells plays an indispensable role in the efficacy of PD-1/PD-L1 blockade therapy (23-25). However, the results of several trials such as IMPASSION130 and IMPASSION131 that examined the use of ICI immunotherapy or combination chemotherapy to treat TNBC appear to be inconsistent.

To further understand the clinical efficacy of immunosuppressants in patients with locally advanced or metastatic TNBC, the current meta-analysis examined randomized controlled trials (RCTs) on patients with TNBC treated with ICIs, thus providing a comprehensive assessment of the efficacy and safety graded of PD-1/PD-L1 immunosuppressant treatment for locally advanced or metastatic TNBC according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) (26).

Materials and methods

Data sources and literature search. The PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Cochrane Library (<https://www.cochranelibrary.com/>), Embase (<https://www.embase.com/>) and MEDLINE (<https://www.nlm.nih.gov/medline>) databases were searched from December 2010 to July 19, 2023, to identify trials that examined the efficacy and safety of immunotherapy with ICIs for treating unresectable locally advanced or metastatic TNBC. The following keywords were used in the literature search: 'Triple-negative breast cancer', 'programmed cell death ligand 1 inhibitor' and 'immunotherapy'. The full search strategy was as follows:

'Triple-Negative Breast Cancer' OR 'Triple-Negative Breast Cancers' OR 'Triple-Negative Breast Neoplasm' OR 'Triple Negative Breast Neoplasm' OR 'Triple-Negative Breast Neoplasms' AND 'Immune Checkpoint Inhibitors' OR 'PD-1 inhibitor' OR 'PD-L1 inhibitor' OR 'PD-1/PD-L1 inhibitor' OR 'CTLA-4 inhibitor' OR 'Immune Checkpoint Blockade' OR 'PD-1 Blockade' OR 'PD-L1 blockade' OR 'CTLA-4 blockade' OR 'pd-1/pd-l1 blockade'. When duplicate studies were identified, the most recent article or the higher-quality article was selected. Furthermore, the reference lists of the retrieved studies and recently published reviews were thoroughly searched to identify additional relevant studies. The objective of the present meta-analysis was to examine the study population, treatments/exposure factors, comparative measures, outcome indicators and environmental criteria. The current study was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses 2020 checklist (27).

Screening criteria. The primary objective of the present meta-analysis was to compare the safety and efficacy of immunotherapy involving ICIs (PD-1/PD-L1 and CTLA-4 inhibitors) with the safety and efficacy of other treatments for locally advanced or metastatic TNBC. The inclusion criteria were as follows: i) RCTs or other types of clinical trials; ii) patients with unresectable locally advanced or metastatic TNBC only; and iii) patients in the experimental group of the RCT received immunotherapy based on ICIs, whereas the control group received other treatments. The exclusion criteria were as follows: i) Patients without TNBC; ii) animal experiments; iii) reviews, study reports, case reports, guidelines, letters, conference abstracts and meta-analyses; iv) incomplete studies; v) preclinical or phase 1 studies; and vi) early TNBC and adjuvant therapies.

Two authors (YC and LS) adopted a screening strategy for the retrieved literature and independently reviewed all the titles and abstracts of the studies to determine whether they met the inclusion criteria. Studies that did not meet the inclusion criteria were promptly excluded. In cases of doubt, the full text of the studies was screened. Disagreements regarding the inclusion of a study were resolved by discussion with a third author (WY); if a consensus could not be reached, the study was excluded.

Data extraction. The following data were extracted from the included studies: Name of the first author, year of publication, duration of the trial, authors' country, name of the RCT, phase of the trial, number of patients, patients' age group, patients' ethnicity, clinicopathological characteristics of the population enrolled, treatment regimen, follow-up time, and primary and secondary outcomes of the trial (Tables I and SI). It was also noted whether patients were included in the intent-to-treat (ITT) population, which included all the patients who had undergone randomization, and PD-L1 status subgroups were also extracted. To ensure the validity and accuracy of the extracted data, the aforementioned two authors independently extracted the data from the studies that met the inclusion criteria, and the data were then cross-validated. Disagreements between the two authors were resolved by consulting with the aforementioned third author.

Table I. Basic characteristics of the studies included in the present meta-analysis.

First author/s, year	Trial name	Trial phase	Primary outcomes	Secondary outcomes	Treatment plan		Patients with triple-negative breast cancer (n)		(Refs.)
					Experimental	Control	Experimental	Control	
Schmid <i>et al</i> , 2018	IMpassion130	III	PFS, OS	OR, CR, PR, DOR, AEs	Atezolizumab plus nab-paclitaxel	Placebo plus nab-paclitaxel	451	451	(29)
Brufsky <i>et al</i> , 2021	COLET	II	PFS, OR, PR, CR	AEs, DOR, OS	Cobimetinib plus atezolizumab plus paclitaxel	Cobimetinib plus paclitaxel	32	47	(35)
Cortes <i>et al</i> , 2022	KEYNOTE-355	III	PFS	OR, DOR, DCR	Pembrolizumab plus chemotherapy	Placebo plus chemotherapy	566	281	(32)
Bachelot <i>et al</i> , 2021	SAFIR02-BREAST IMMUNO	II	PFS	OS, ORR, AEs	Durvalumab	Maintenance chemotherapy	47	35	(31)
Hattori <i>et al</i> , 2023	KEYNOTE-355	III	PFS, OS	AEs, ORR, DOR, DCR	Pembrolizumab plus chemotherapy	Placebo plus chemotherapy	61	26	(33)
Miles <i>et al</i> , 2021	IMpassion131	III	PFS	OS, ORR, AEs	Atezolizumab plus paclitaxel	Placebo plus paclitaxel	431	220	(36)
Røssevold <i>et al</i> , 2022	ALICE	IIb	PFS	ORR, DOR, DRR, CBR, OS	Atezolizumab plus chemotherapy	Placebo plus chemotherapy	40	28	(30)
Winer <i>et al</i> , 2021	KEYNOTE-119	III	OS	PFS, ORR, DOR, DCR, AEs	Pembrolizumab	Chemotherapy	312	310	(34)

PFS, progression-free survival; OS, overall survival; OR, odds ratio; RR, relative risk; AEs, adverse events; ORR, objective response rate; PR, partial response; CR, complete response; DCR, disease control rate; DOR, duration of response; CBR, clinical benefit rate; nab, albumin-bound nanoparticles.

Literature quality assessment. The quality of each RCT was assessed using the Cochrane Collaboration tool in the Review Manager version 5.4 software (The Cochrane Collaboration). The quality of the literature was assessed across the following domains: i) Randomization sequence; ii) allocation concealment; iii) blinding of participants and investigators; iv) blinding of outcome assessors; v) completeness of outcome data; vi) selective reporting of outcomes; and vii) other risks of bias. Each domain was rated as 'low risk', 'high risk' or 'unclear risk'. Two authors independently assessed the quality of the literature, and disagreements were resolved via discussion with a third author to reach a consensus.

Statistical analysis. Statistical analyses were performed using Review Manager version 5.4, and hazard ratio (HR) and standard error were calculated and recorded by selecting the generalized inverse variance from the collected HR data for progression-free survival (PFS) and overall survival (OS). By contrast, dichotomous data types were selected to calculate the objective response rate (ORR) and adverse events. The heterogeneity of the studies was estimated by using the Cochrane Q test and the I^2 statistic, where $P < 0.1$ or $I^2 > 50\%$ were considered to indicate significant heterogeneity among the included studies. A random effects model was used regardless of $I^2 > 50\%$ or $\leq 50\%$. Sensitivity analyses were not performed because < 10 articles were included, and therefore it would have been difficult to detect the cause of asymmetry with such a small, number of studies included in the present meta-analysis (28).

Results

Research options. The study selection process is shown in Fig. 1. A total of 1,880 articles related to TNBC and PD-1/PD-L1 inhibitors were retrieved from the PubMed, Cochrane Library, Embase and MEDLINE databases. No additional articles were retrieved from other sources. A total of 181 articles were excluded due to being duplicates; 108 of these articles were identified via duplicate searches performed by the literature manager, and the authors deleted the remaining 73 articles by comparing the years, journals, titles and abstracts between the articles. A total of 1,573 articles were excluded after screening the titles and abstracts. The full texts of the remaining 126 articles were screened. A total of 118 articles were excluded for the following reasons: 28 were not RCTs; 7 were preclinical or phase I clinical trials; 58 involved adjuvant therapy but not immunotherapy for TNBC; 20 were trials of early-stage TNBC or other stages rather than locally advanced or metastatic breast cancer; and 5 reported the same data as other included studies.

Research characteristics and quality assessment. In total, eight studies (29-36) were ultimately included in the present meta-analysis. All of them used immunotherapy with immune checkpoint inhibition to treat locally advanced or metastatic TNBC. A total of 3,338 patients were included in the above studies, with 1,940 patients in the experimental group and 1,398 patients in the control group. Six of the RCTs examined the use of immunosuppressants in combination with other treatments versus other treatments alone, while two RCTs

compared the use of immunosuppressant monotherapy and chemotherapy. Regarding the blinding method used across the study trials, three studies were open-label trials, three were double-blind (participants and investigators) and the other two were quadruple-blind (participants, investigators, care providers and outcome assessors). Among the eight included studies, seven reported OS outcomes for all patients with TNBC. The subjects were divided into PD-L1-negative [PD-L1(-)] and PD-L1-positive [PD-L1(+)] subgroups according to PD-L1 expression. Six studies reported OS for PD-L1(+) patients; all the studies reported PFS for patients with TNBC and four studies reported PFS for PD-L1(+) patients. All the studies defined the PD-L1(+) population as patients in whom the number of PD-L1-stained tumour-infiltrating immune cells in the total tumour area in the metastatic lesion samples was > 1 . By contrast, the PD-L1(-) population was defined as patients in whom the number of PD-L1-stained tumour-infiltrating immune cells was $\leq 1\%$ of the total tumour area in metastatic lesion samples in the ITT population.

The results of the Cochrane risk of bias assessment are shown in Fig. 2. All eight studies had a relatively high standard of inclusion, and most of them had a low risk of bias. In the risk of bias assessment chart, green indicates a low risk of bias, while red indicates a high risk of bias and yellow indicates an unclear risk of bias.

Antitumour efficacy results

OS in the ITT population, and in the PD-L1-positive and PD-L1-negative populations. Seven of the eight studies reported OS for the ITT population, while seven studies reported OS for the PD-L1(+) population and three studies reported OS for the PD-L1(-) population. The OS of the experimental group was significantly superior to that of the control group in the PD-L1(+) population [hazard ratio (HR)=0.83; 95% confidence interval (CI)=0.70-0.98; $P < 0.05$; $I^2 = 38\%$] (Fig. 3B) and in the ITT population (Fig. 3A) (HR=0.83; 95% CI=0.69-1.00; $P < 0.05$; $I^2 = 59\%$). By contrast, there was no significant difference in the OS of the PD-L1(-) population (Fig. 3C). Forest plot results in Fig. 3 showed that PD-1/PD-L1 inhibitor-based immunotherapy improved OS in the ITT population as well as in the PD-L1(+) population; however, there was no effect on OS in the PD-L1(-) subgroup-based population, which indicates that PD-1/PD-L1 inhibitor-based immunotherapy has an impact on OS in metastatic and advanced locally unresectable TNBC, and correlates with PD-L1 subtype subgroups, since the PD-L1(+) group in the ITT population is affected.

PFS in the ITT population, and in the PD-L1-positive and -negative population. Eight studies reported PFS for the ITT population, five of which (29,30,32,33,36) reported PFS for the PD-L1(+) population. Of these, two (29,30) reported PFS for the PD-L1(-) population, while the others did not report PFS for the PD-L1 subgroup. The PFS in the experimental group was significantly higher compared with that in the control group for both the ITT population (Fig. 4A) and the PD-L1(+) population (Fig. 4B) (ITT: HR=0.81, 95% CI=0.75-0.88, $P < 0.05$, $I^2 = 0\%$; PD-L1-positive: HR=0.71, 95% CI=0.62-0.81, $P < 0.05$, $I^2 = 0\%$). However, the PFS of the experimental and control groups was not statistically significant in the PD-L1(-) population (Fig. 4C). Forest plot results in Fig. 4 illustrate that PD-1/PD-L1 inhibitor-based immunotherapy

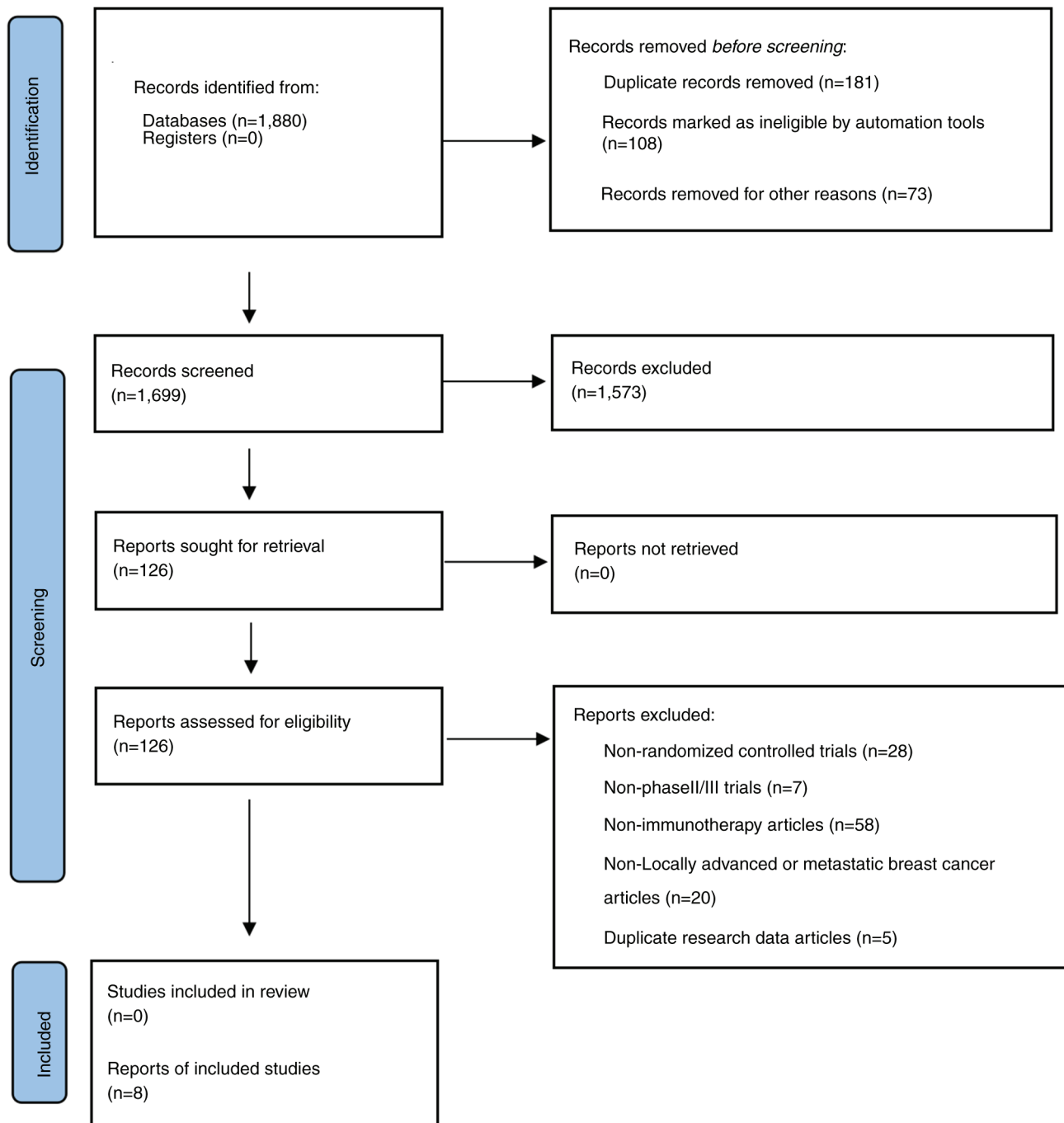


Figure 1. Flow diagram of the study selection process.

significantly prolongs PFS in the ITT population as well as in PD-L1(+) population, confirming the strong association between PD-1/PD-L1 inhibitor therapy for TNBC and PD-L1 subtype status.

Safety analysis. Adverse event rates were used to assess the safety of ICI-based immunotherapy or immunotherapy in combination with other drugs. Specifically, the rates of serious adverse events (SAEs) and immune-related adverse events (irAEs) in the included studies were examined to determine the safety of the therapies. There was no significant difference in the rate of adverse events between the immunotherapy alone group and the immunotherapy combined with chemotherapy

group. Therefore, the main adverse events examined were SAEs (grade ≥ 3). Table SII shows that immunosuppressant treatment combined with other therapies for TNBC was associated with the following adverse events: Alopecia [relative risk (RR)=0.89; 95% CI=0.70-1.14; P=0.36], anaemia (RR=0.96; 95% CI=0.75-1.22; P=0.72), cough (RR=1.29; 95% CI=1.06-1.57; P=0.01), diarrhoea (RR=0.83; 95% CI=0.59-1.19; P=0.31), loss of appetite (RR=0.64; 95% CI=0.29-1.39; P=0.26), fatigue (RR=1.02; 95% CI=0.92-1.13; P=0.74), hypothyroidism (RR=4.52; 95% CI=2.95-6.94; P<0.00001), nausea (RR=0.93; 95% CI=0.76-1.14; P=0.49), neutropenia (RR=0.97; 95% CI=0.68-1.38; P=0.86), fever (RR=1.42; 95% CI=1.15-1.83; P=0.002), rash (RR=1.10; 95%

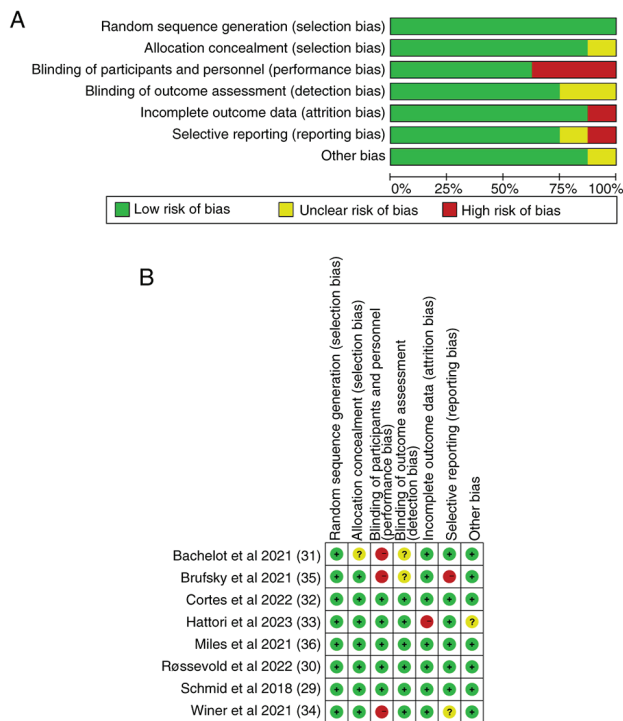


Figure 2. Migration risk assessment: Review of the enrolled studies. (A) Risk of bias graph: Judgements about each risk of bias item presented as percentages across all included studies and (B) risk of bias summary: Judgements about each risk of bias item for all included studies.

CI=0.90-1.33; $P=0.36$), pruritus (RR=0.80; 95% CI=0.26-2.48; $P=0.70$) and weakness (RR=1.00; 95% CI=0.81-1.23; $P=0.99$). Among them, only hypothyroidism, fever and cough showed significant associations with the ICI + chemotherapy combination treatment ($P<0.05$). Six studies documented SAEs (Fig. 5A); immunotherapy based on ICIs in combination with other therapies was associated with 691 SAEs among 1,828 patients compared with 405 SAEs among the 1,302 control patients receiving other therapies. Furthermore, there was no significant difference in the rate of SAEs associated with immunotherapy with ICIs alone or combined with other therapies and the rate of SAEs associated with other therapies ($P=0.31$; $P>0.05$).

In six of the included studies, there was a significant difference in irAEs between the experimental group and the control group ($P=0.0005$) (Fig. 5B), suggesting that immunotherapy based on ICIs alone or in combination with other treatments is more likely to cause irAEs in patients with TNBC. Furthermore, this finding suggests that the occurrence of irAEs is predominantly associated with abnormalities in thyroid function (including hyperthyroidism and hypothyroidism) (Fig. 6).

Discussion

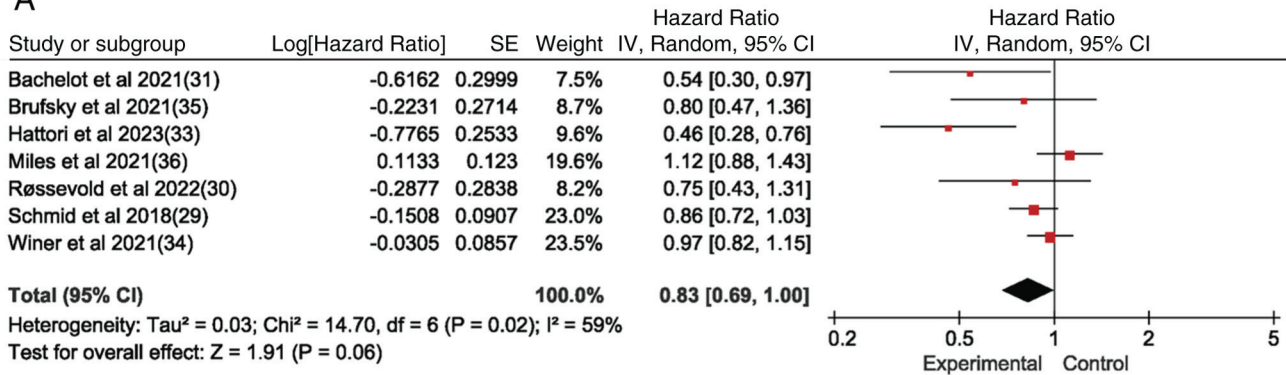
TNBC is characterized by high immunogenicity, high invasiveness and poor prognosis (37). In recent years, immunotherapy has emerged as an effective treatment for cancer (38-40). The present meta-analysis aimed to assess the efficacy and safety of PD-L1/PD-1 inhibitors for patients with TNBC by evaluating whether the ICIs were combined with chemotherapy, and

to determine the clinical significance of PD-L1 status with respect to the use of ICIs to treat patients with TNBC (34). The results revealed that immunotherapy based on ICIs alone or combined with other therapies for the treatment of locally advanced or metastatic TNBC affected the PFS of the ITT population ($P<0.05$) but did not significantly impact the OS of patients with TNBC. Subgroup analyses stratified based on PD-L1 receptor status revealed that ICI-based immunotherapy alone or in combination with other therapies significantly prolonged PFS and OS in the PD-L1(+) subgroup; however, no statistically significant differences were observed in the PD-L1(-) subgroup.

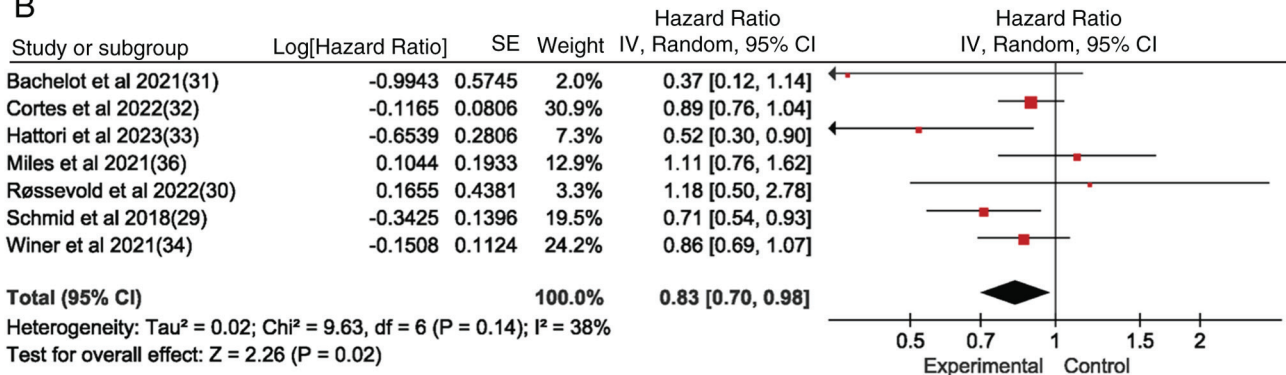
Analysis of several RCTs revealed that ICIs alone or combined with chemotherapy prolonged patients' OS and PFS. The phase III RCT KEYNOTE119 (34), which compared pembrolizumab immunotherapy and chemotherapy for the treatment of metastatic TNBC, revealed that PD-1/PD-L1 inhibitor monotherapy did not significantly improve the ORR or OS of patients with metastatic TNBC who had received other therapies, while pembrolizumab treatment was effective among individuals with increased PD-L1 levels in the tumour microenvironment, thus suggesting that the clinical benefits produced by pembrolizumab monotherapy for metastatic TNBC may be associated with the expression of PD-L1 in the tumour microenvironment; thus, the use of immune checkpoint inhibition alone in the treatment of locally advanced or metastatic TNBC is ineffective and prone to drug resistance. On the other hand, the randomized, double-blind, controlled phase III IMpassion130 clinical trial (29) evaluated the efficacy and safety of atezolizumab in combination with nab-paclitaxel versus placebo in combination with nab-paclitaxel for the treatment of locally advanced or metastatic TNBC. The results revealed that there was no significant difference in OS for ICI + nab-paclitaxel versus placebo + paclitaxel, although ICI + nab-paclitaxel was superior to placebo + paclitaxel in the ITT population. There was a significant difference in the PD-L1(+) population, suggesting that ICI atezolizumab + nab-paclitaxel has a clinically meaningful effect on OS and PFS in the PD-L1(+) population. In the KEYNOTE-355 trial (27), the use of pembrolizumab plus chemotherapy for TNBC led to improvements in PFS and OS compared with placebo plus chemotherapy. By contrast, the Impassion 131 trial (36), a randomized, placebo-controlled, double-blind trial that evaluated the efficacy of first-line paclitaxel alone or in combination with atezolizumab for treating unresectable locally advanced or metastatic TNBC, revealed that atezolizumab in combination with paclitaxel exhibited significant efficacy for treating metastatic TNBC.

A safety analysis was conducted in the present study, which focused on adverse events caused by PD-1/PD-L1 inhibitors, SAEs (grade ≥ 3 adverse events) and immune-related adverse events. The safety analysis of immunosuppressant treatment for patients with TNBC revealed that there was no statistically significant difference in the incidence of SAEs, but there was a statistically significant difference in the incidence of irAEs between the experimental group and the control group. Specifically, the incidence rates of hypothyroidism, hyperthyroidism, pneumonitis, hepatitis and adrenal insufficiency significantly increased after the addition of ICIs (41). Adverse events may affect the patient's choice of treatment; therefore, it

A



B



C

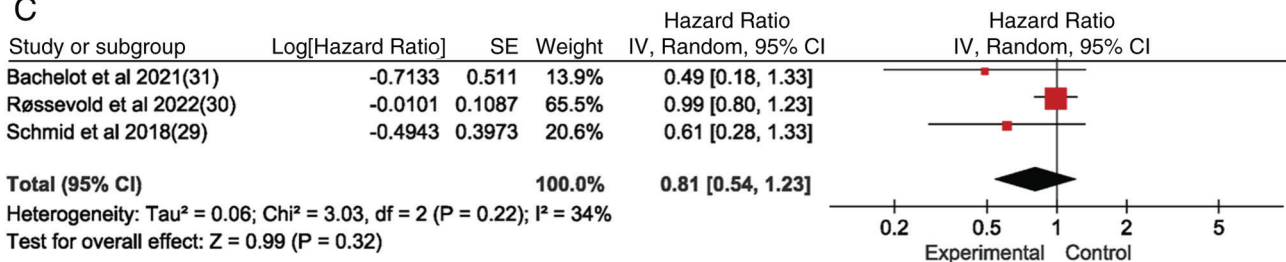


Figure 3. Forest plot of OS for immunotherapy using immunosuppressive agents versus other therapies for patients with locally advanced or metastatic triple-negative breast cancer. (A) Intent-to-treat population OS: $P=0.06$. (B) PD-L1(+) OS: $P=0.002$. (C) PD-L1(-) OS: $P=0.32$. OS, overall survival; PD-L1, programmed death ligand 1; SE, standard error; CI, confidence interval; df, degrees of freedom.

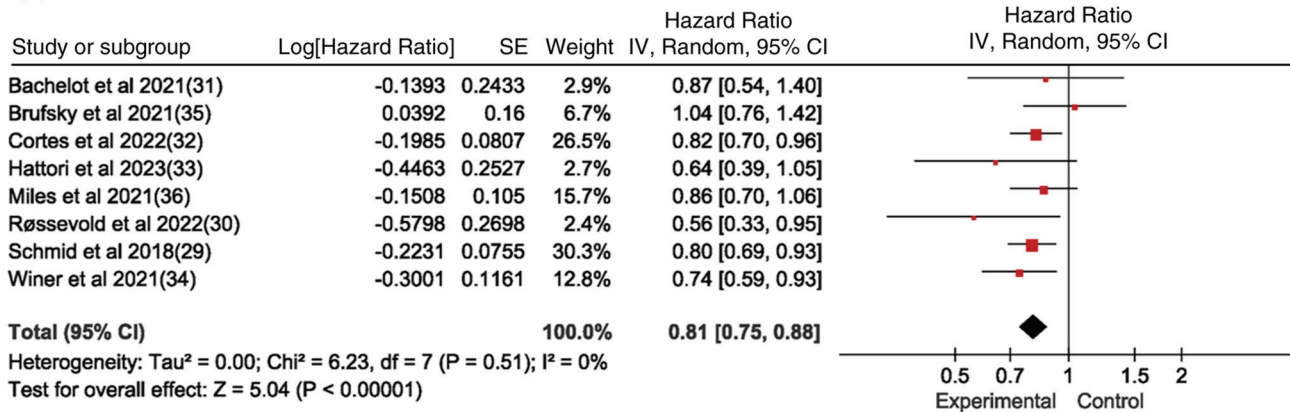
is important to inform patients of such events when choosing PD-1/PD-L1 therapy for patients with TNBC, and clinicians must remain vigilant in recognizing and intervening in the prevention of serious complications such as hypothyroidism, pneumonia and neutropenia (42,43).

Compared with chemotherapy alone, treatment with PD-1/PD-L1 and CLTA-4 ICIs significantly increased the occurrence of irAEs, including severe pneumonia, hypothyroidism and hypoadrenocorticism, in patients with TNBC. However, the incidence of irAEs was relatively low. Serious immune-related adverse events included thyroid dysfunction (hypothyroidism and hyperthyroidism), severe skin events, colitis and pneumonia (43). Although the aetiological mechanism of TNBC that leads to serious immune-related adverse events is unclear, the pathophysiology of immune-associated thyroid dysfunction has been described for thyroiditis with concomitant thyroid destruction, which is mediated by T-cell toxicity, natural killer cells and PD-1/PD-L1 expression in thyroid cells (44). Severe skin events are also due to the blockade of PD-1/PD-L1 inhibitors, which may lead

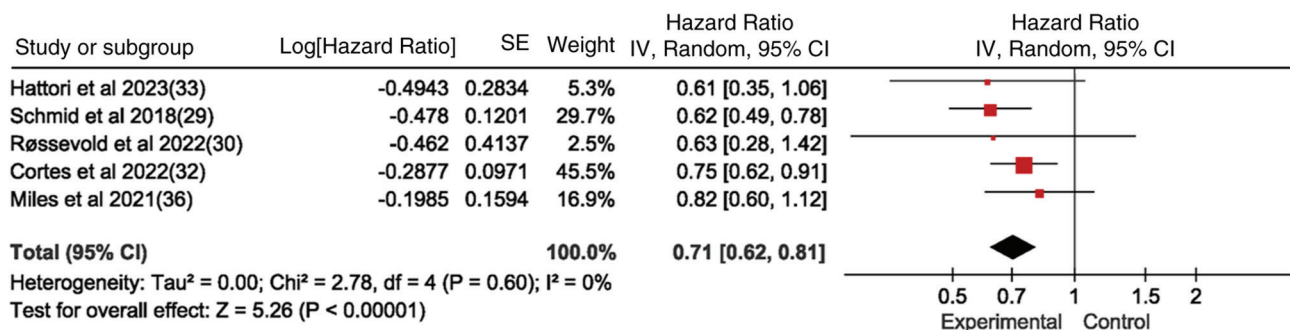
to the activation of nonspecific T lymphocytes that target antigen-carrying keratinocytes and other skin cells, resulting in skin toxicities such as rashes, purpura and other skin disorders (45). For pneumonia, it has been suggested that alveolar macrophages become overactivated in patients receiving PD-1 inhibitors; this hypothesis is supported by the fact that interstitial macrophages and alveolar cells express repulsive guidance molecule B on their surfaces, which may be a ligand for PD-L2 (46).

Data for the current meta-analysis were collected up to July 19, 2023, thus including more data than similar meta-analyses. In the meta-analysis by Zhang *et al* (47), data for the analysis were collected up to October 2021, and the results showed that immunotherapy based on PD-1/PD-L1 inhibitors had no effect on OS in the ITT population (HR=0.90; 95% CI=0.78-1.04; $P=0.144$; $I^2=24.0\%$) versus the PD-L1(+) population, and was not associated with PD-L1 status. However, the PFS in the ITT population (HR=0.82; 95% CI=0.76-1.14; $P<0.001$; $I^2=0\%$) and in the PD-L1(+) population (HR=0.68; 95% CI=0.6-0.76; $P<0.001$) was significantly prolonged in the ITT and PD-L1(+)

A



B



C

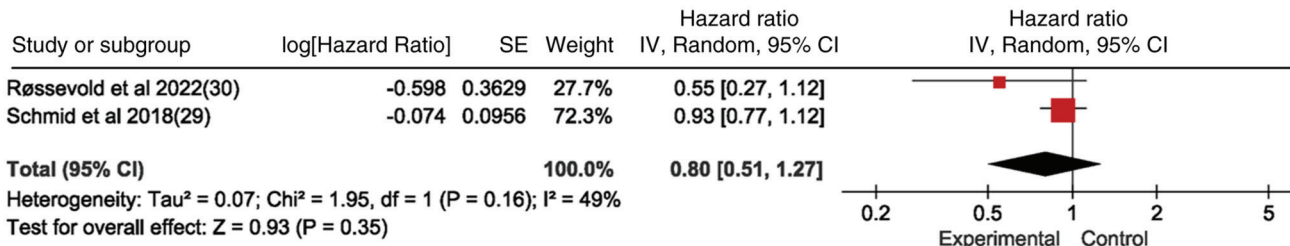
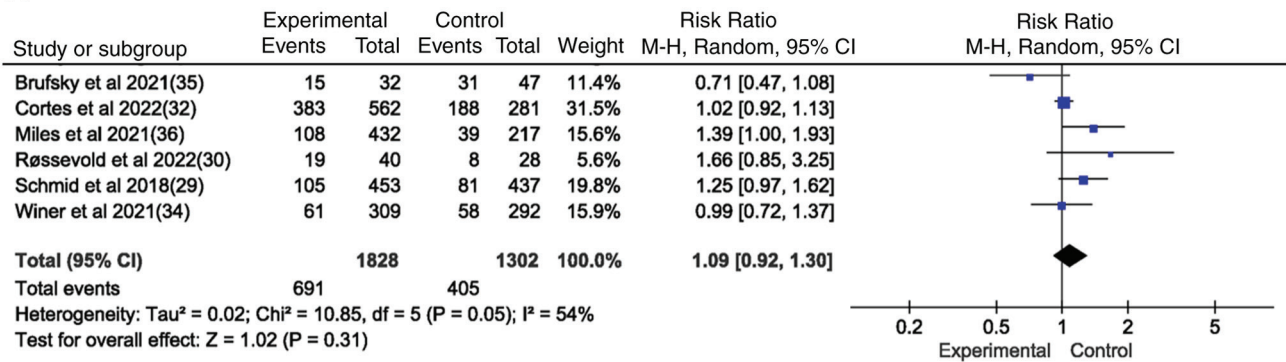


Figure 4. Forest plot of PFS in patients with locally advanced or metastatic triple-negative breast cancer receiving immunotherapy with immune checkpoint inhibitors versus other therapies. (A) PFS in the intention-to-treat population: $P < 0.00001$. (B) PD-L1(+) PFS: $P < 0.00001$. (C) PD-L1(-) PFS: $P = 0.35$ PFS, progression-free survival; PD-L1, programmed death ligand 1; SE, standard error; CI, confidence interval; df, degrees of freedom.

populations. Wang (48) collected data through August 30, 2021 for treatments targeting early to mid- and late-stage TNBC, and the analysis showed that, regarding the PFS and OS of all subjects treated with or without PD-1/PD-L1 inhibitors, there was no significant effect on PD-L1 subgroup status, while the results of PD-L1 subgroup status showed that treatment of the PD-L1(+) TNBC population with PD-1/PD-L1 inhibitors significantly improved their PFS and OS ($P < 0.05$); the safety analysis was the same as in the present analysis, with a significant effect on SAEs and immune adverse events. The study by Yu *et al* (49) was a meta-analysis focused on immunotherapy for metastatic TNBC, excluding data on locally advanced unresectable TNBC, and the results showed that there was a significant difference in PFS between the ITT population and the PD-L1(+) group, which was similar to the results of the present meta-analysis, whereas the OS of the ITT population was not significantly different, which is

in disagreement with the present analysis that may be due to the addition of OS data for the intention-to-treat population with locally advanced unresectable TNBC (33), and the OS of the PD-L1(+) group was significantly different from that of the ITT population, which is similar to the present results. The novelty of the present meta-analysis is the significant effect of time and trial size on PFS and OS in the ITT and PD-L1(+) populations receiving PD-1/PD-L1-based immunotherapy, which differs from similar previous analyses in that immunotherapy had a significant effect on the OS of ITT patients with locally advanced unresectable and metastatic TNBC receiving PD-1/PD-L1-based immunotherapy. Therefore, it may be hypothesized that the incorporation of supplementary clinical data pertaining to immunosuppressive therapy in patients diagnosed with metastatic and locally advanced unresectable TNBC has the potential to impact OS within the targeted treatment population.

A



B

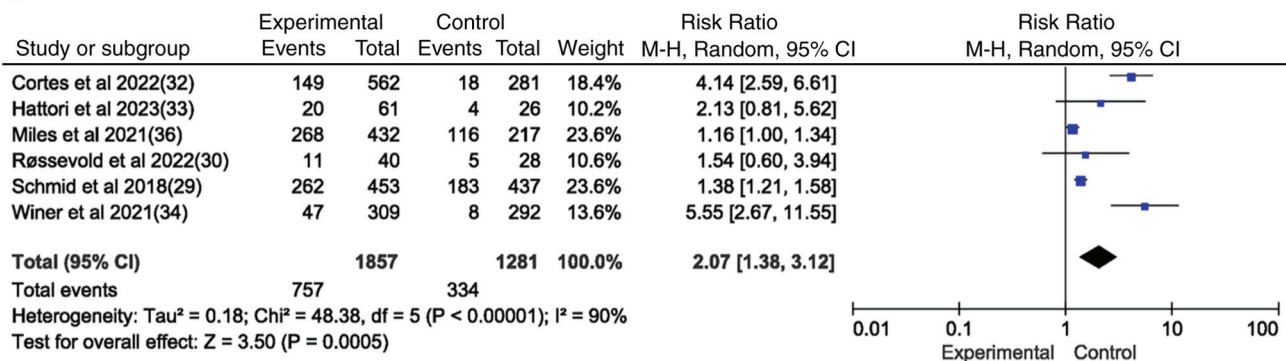


Figure 5. Forest plot of adverse events from immunotherapy with immune checkpoint inhibitors versus other therapies for locally recurrent or metastatic triple-negative breast cancer. (A) Serious adverse events: $P=0.31$. (B) Immune-related adverse events: $P=0.0005$.

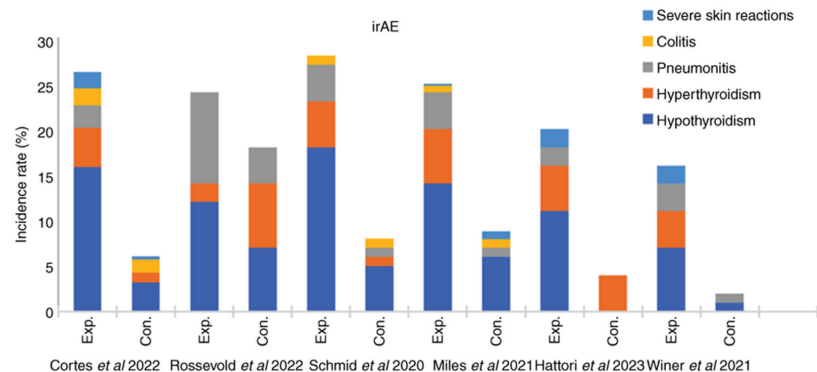


Figure 6. irAE stacking diagram. irAE, immune-related adverse event. Con, control; Exp, experimental group.

The present meta-analysis has several limitations. First, only eight studies were included, and some of the clinical trials did not report long-term survival outcomes, such as KEYNOTE-522, which did not report patient OS. Second, some studies did not stratify PFS or OS analyses based on PD-L1 subgroup status, which may have affected the data results and potentially contributed to the inability to determine the benefits of ICIs for the treatment of locally advanced or metastatic TNBC. In addition, the multiple dosing regimens and delivery modes of treatment included in the present meta-analysis complicated the determination of the optimal treatment regimen. Therefore, it is necessary to conduct numerous RCTs of relevant treatment regimens and to obtain clinical treatment data in the future in order to

refine the use of other therapies combined with ICI immunotherapy for TNBC.

In conclusion, the present meta-analysis revealed that treatment with ICIs in combination with other therapies prolonged PFS in patients with locally advanced or metastatic TNBC compared with other therapies, and that immunotherapies also significantly prolonged OS and PFS in patients with TNBC in the PD-L1(+) subgroup and in the ITT population (OS), but not in the PD-L1(-) subgroup (OS and PFS). The main adverse reaction of any grade arising from the use of ICIs was hypothyroidism. Additionally, hyperthyroidism accounted for a relatively high proportion of adverse events, but this adverse effect was generally manageable.

In summary, the present study has illustrated that PD-1/PD-L1 inhibitors are effective in the treatment of TNBC, although a significant association with PD-L1 subgroup status was observed. Targeting the adverse effects associated with immunotherapy may affect patient selection and clinical application, but may have a relatively significant efficacy in OS and PFS in the ITT and PD-L1(+) population. Future studies should focus on PD-L1 expression status, as this parameter may help to optimize personalized treatment for patients.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YC, LS, WY, HX and CL contributed to the conception and development of the present study. YC edited the entire manuscript and contributed to data visualization; WY proposed the direction and purpose of the study, and guided and reviewed the article. LS and YC reviewed and collected a large quantity of literature and data, participated in literature screening, and discussed the article's inclusion criteria. LS and YC confirm the authenticity of all the raw data. CL guided the overall framework of the article and provided comments on the article's structure. HX and WY reviewed the final draft of the manuscript and provided comments on the revisions. All the authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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