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Meta-analysis

Efficacy and safety of first-line treatment for metastatic triple-negative breast cancer: A network meta-analysis

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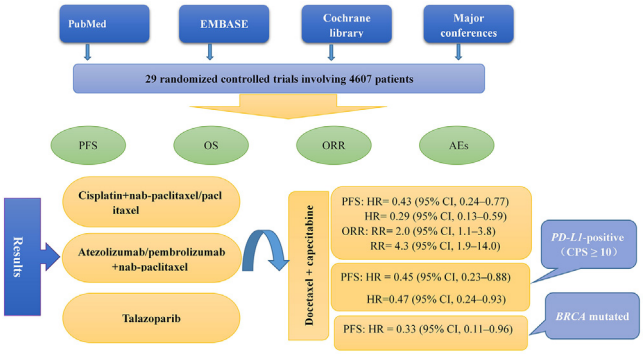
HIGHLIGHTS

- Efficacy and safety of first-line treatment for metastatic triple-negative breast cancer (mTNBC) first-line treatment
- A meta-analysis of 29 studies involving 4607 patients with mTNBC was conducted
- Cisplatin, nab-paclitaxel, and paclitaxel are the preferred first-line solutions
- Atezolizumab/pembrolizumab plus nab-paclitaxel and talazoparib was effective in programmed death-ligand 1 (PD-L1) positivity and breast cancer susceptibility gene (*BRCA)* mutations
- mTNBC treatment has made significant progress

GRAPHICAL ABSTRACT



In the first-line treatment of mTNBC, cisplatin combined with nab-paclitaxel or paclitaxel showed good efficacy in improving PFS and ORR. Based on different biomarkers, atezolizumab/pembrolizumab combined with nab-paclitaxel and talazoparib improved PFS in *PD-L1* positive and *BRCA*-mutated tumors, respectively. There was no significant difference in OS. Common severe adverse events were neutropenia, diarrhea, and fatigue. AEs: Adverse events; *BRCA*: Breast cancer susceptibility gene; CPS: Combined positive score; CI: Confidence intervals; HR: Hazard ratios; mTNBC: Metastatic triple-negative breast cancer; *PD-L1*: Programmed death-ligand 1; PFS: Progression-free survival; RR: Risk ratios; ORR: Objective response rate; OS: Overall survival.

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ABSTRACT

Background: Metastatic triple-negative breast cancer (mTNBC) is an aggressive histological subtype with poor prognosis. Several first-line treatments are currently available for mTNBC. This study conducted a network meta-analysis to compare these first-line regimens and to determine the regimen with the best efficacy.
Methods: A systematic search of PubMed, EMBASE, the Cochrane Central Register of Controlled Bases, and minutes of major conferences was performed. Progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) were analyzed via network meta-analysis using the R software (R Core Team, Vienna, Austria). The efficacy of the treatment regimens was compared using hazard ratios and 95% confidence intervals.
Results: A total of 29 randomized controlled trials involving 4607 patients were analyzed. The ranking was based on the surface under the cumulative ranking curve. Network meta-analysis results showed that cisplatin combined with nab-paclitaxel or paclitaxel was superior to docetaxel plus capecitabine in terms of PFS and ORR. For programmed death-ligand 1 (PD-L1) and breast cancer susceptibility gene (*BRCA)* mutation-positive tumors,

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atezolizumab/pembrolizumab combined with nab-paclitaxel and talazoparib was superior to docetaxel plus capecitabine. No significant difference was observed among the treatments in OS. Neutropenia, diarrhea, and fatigue were common serious adverse events.
Conclusion: Cisplatin combined with nab-paclitaxel or paclitaxel is the preferred first-line treatment for mTNBC. For PD-L1 and *BRCA* mutation-positive tumors, atezolizumab/pembrolizumab combined with nab-paclitaxel and talazoparib is an effective treatment option. Neutropenia, diarrhea, and fatigue are frequently occurring serious adverse events.

Introduction

Triple-negative breast cancer (TNBC) is characterized by a lack of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression.[1] This subtype accounts for approximately 15–20% of all breast cancers.[2] With advancements in medicine and the increased provision of personalized treatment, the curative effects of treatment modalities for breast cancer have continuously improved; however, TNBC is associated with an increased risk of early and distant recurrence, visceral metastasis, and death compared to other breast cancer subtypes.[3,4] Metastatic TNBC (mTNBC) is rapidly progressive and has a poor prognosis, with a median overall survival (OS) of approximately 12–18 months.[5]

Cytotoxic anticancer drugs are the mainstay of treatment for mTNBC.[6] Currently, taxanes and anthracyclines are the most commonly used drugs, in addition to platinum drugs, which are emerging as effective treatment options.[7] Immune-checkpoint inhibitors (ICIs), poly (ADP-ribose) polymerase inhibitors (PARPi), and platinum-based drugs have shown good efficacy in clinical trials evaluating first-line treatment modalities for mTNBC,[8,9] although drugs such as protein kinase B (AKT) inhibitors have demonstrated mixed results.

Currently, there are many options for first-line treatment of mTNBC. However, there is a scarcity of evidence on comparisons of the most effective regimens and further analysis of these therapeutic options is required. Network meta-analysis is a technique for comparing different treatment regimens to determine the efficacy of specific drugs. In this study, a network meta-analysis of the first-line treatments for mTNBC in clinical trials was conducted to analyze the efficacy of the different treatment regimens.

Materials and methods

Search strategy

A systematic search of the PubMed, EMBASE, and Cochrane Central Register of Controlled Trials databases, as well as the American Society of Clinical Oncology and European Society of Medical Oncology, was conducted. The search terms were as follows: “triple-negative breast cancer”, “breast tumor”, “breast neoplasms”, “breast cancer”, “breast tumor”, “breast tumor”, “randomized”, “randomized controlled trials”, and “randomized trials”. There were no language restrictions in the search. The retrieval period ranged from the establishment of each database until December 2022. References of relevant studies, reviews, and meta-analyses were manually screened to identify potentially eligible publications.

Selection criteria

All randomized controlled trials (RCTs) meeting the following eligibility criteria were included: (1) phase II or III RCTs; (2) RCTs including patients ≥18 years with histologically confirmed ER-negative and PR-negative mTNBC with no overexpression of HER2; (3) the results for first-line therapy for mTNBC were available; and (4) availability of study outcome indicators for progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and adverse events. The following exclusion criteria applied: (1) incomplete data on treatment and ER/PR/HER2 status; (2) non-RCT; (3) non-first-line treatment of patients with mTNBC; and (4) ongoing studies that did not provide or publish results at the time of the literature search.

Data extraction

Two independent reviewers extracted the data. The excluded studies and the reasons for their exclusion were documented and checked by a third reviewer. The following information was recorded for each eligible study: first author name, year of publication, study design, trial phase, line, hazard ratios (HR), 95% confidence interval (95% CI) of PFS and OS, adverse events, and ORR. The primary outcome was PFS and the secondary outcomes were OS, ORR, and adverse events. For multiple reports from the same trial, we used the first published primary endpoint to extract the PFS data from the intention-to-treat population. For OS, we used the report with the longest tracking time for analysis. For the subgroup analysis, we used publications that specifically reported the subgroup analysis, if available, or used the first published report. Notably, some studies included data on specific subtypes. Atezolizumab and pembrolizumab were granted approval by the United States Food and Drug Administration (FDA) for use in programmed death-ligand 1 (PD-L1)-positive tumors; therefore, we only included data pertaining to this specific population. In the three studies containing PARPi, all recruited patients had germline breast cancer susceptibility gene (*BRCA*) mutations, the included data were specific to this subtype. Finally, in three studies on the phosphatidylinositol 3-kinase/serine/threonine kinase 1 (PI3K/AKT1) signaling pathway, data from patients with PI3K alpha catalytic subunit (PIK3CA)/AKT1/Phosphatase and TENsin homolog deleted (PTEN) alterations were included.

Definition of treatment arms

The treatments were grouped according to drug regimens. The following drug name abbreviations were used: Atezolizumab = Atez, Pembrolizumab = Pemb, Trilaciclib = Tril, Nab-Paclitaxel = NabP, Capivasertib = Capi, Paclitaxel = P, Gemcitabine = G, Carboplatin = Cb, Iniparib = Inip, Sunitinib = Suni, Docetaxel = P, Cisplatin = Cis, Gemcitabine = G, Ipatasertib = Ipat, Bevacizumab = B, Sorafenib = Sora, Taxane/Anthracycline = P, Capecitabine = Cape, Veliparib = Veli, Vinorelbine = Vino, Ipatasertib = Ipat, Docetaxel = P, Talazoparib = Tala. From the two included studies, capecitabine was selected as the representative drug of choice for inclusion in the network. Neupane et al. selected paclitaxel as a representative drug in a doctor selection group.[10] In a study by Oravecz et al., taxane was used as the representative taxane/anthracycline drug.[11]

Risk-of-bias assessment

The risk of bias, including random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases was evaluated using the Cochrane Tool (version 6.3).

Statistical analysis

Network plots describing the geometries of all the comparisons were generated. Relative treatment effects were measured as HRs to compare PFS and OS among the different treatment regimens. The results from the

included trials were pooled using both a pairwise and frequentist network meta-analysis. Network meta-analysis involves the generalization of a pairwise meta-analysis that allows all evidence (both direct and indirect) to be considered in a single model. Direct evidence was extracted from head-to-head trials, whereas indirect evidence was extracted from trials using a common comparator arm. In a network meta-analysis, the final evidence for each pair of treatments comes from direct evidence only, indirect evidence only, or a combination of direct and indirect evidence, depending on the geometry of the network. A network meta-analysis was performed using mixed treatment comparisons Bayesian models based on both fixed and random effects.[12] If the difference between the deviance information criterion value was <5, a consistent model was used for the analysis.[13] A random or fixed model was selected based on the principle that a smaller deviance information criterion value is better. I^2 is an indicator of heterogeneity. I^2 <25% indicates low heterogeneity, while 25% ≤ I^2 ≤ 50% and I^2 >50% are considered as medium heterogeneity and high heterogeneity, respectively. If the heterogeneity was small, a consistency model was used for the analysis; otherwise, an inconsistency model was used.

R (v4.2.3, R Core Team, Vienna, Austria) and GEMTC software packages were used to compare the effects of different NIMM based on the network meta-analysis of the Markov chain Monte Carlo method. To fit the model, four chains were constructed using the Markov chain Monte Carlo model with 50,000 iterations and 20,000 burn-ins for each chain. Brooks–Gelman–Rubin plots were used to evaluate the model convergence.[14.] Stata (v14.2) software (Stata Corp, College Station, TX, USA) was used to draw funnel plots, sensitivity analysis plots, and Egger's test for publication bias.

In the network analysis, the regimens were sorted according to the posterior rank probability (indicating the probability that each regimen is the best regimen, second-best regimen, and so forth), and the surface under the cumulative rank curve (SUCRA) value.[15]

Treatment ranking and recommendation criteria

SUCRA has a value between 0 and 100% and is calculated based on the posterior rank probability (the greater the value, the more effective the treatment). We recommend a drug based on the ranking of SUCRA values and whether it has been approved by the FDA/Environmental Management Association or recommended by the National Comprehensive Cancer Network in the United States (as of December 2022).

Results

Of the 13,395 relevant records obtained from the electronic databases, the full texts of 453 potentially qualified studies were reviewed; 443 studies were excluded because of non-compliance with first-line treatment [Figure 1]. A total of 29 studies were included in the final analysis [Table 1].[11,16–43] Because of the disconnection of the network graph nodes, four studies on the first-line treatment of advanced breast cancer (including hormone receptor-positive patients with unknown HER2 status) were introduced to ensure the integrity of the network graph. In a study by Tan et al.,[16] some patients did not undergo first-line treatment. In the two PARPi-related studies[42,43] there was a lack of data on mTNBC; therefore, this study included the advanced breast cancer first-line data in the subgroup analysis. To visualize the results, the combined chemotherapy (docetaxel and capecitabine) was used, as recommended by the National Comprehensive Cancer Network guidelines as the reference arm to better compare the efficacy of each group. In the studies that lacked mTNBC data, the data of the overall intended population were used when grade 3-5 adverse events were included.

In all comparisons, the results showed low heterogeneity [Table 2]; therefore, a consistency model was selected for the analysis. Two researchers independently collected the data from the included studies and used the Cochrane Bias Risk Assessment Tool to assess the quality of the methodology. Most studies were assessed as having a low risk of bias, although nine studies were considered to be at high risk. The risk of bias for the studies included in this network meta-analysis is shown in Supplementary Figure 1.

Primary endpoint

Progression-free survival

Twenty-nine studies were included in the PFS analysis, comprising 4607 patients and 28 treatment regimens [Figure 2]. By adopting the fixed-effects model, treatment effectiveness was determined based on the SUCRA values from a mesh meta-analysis [Supplementary Figure 2A]. The results showed that the efficacy of the regimens approved by the FDA/Environmental Management Association or recommended by the National Comprehensive Cancer Network was better than docetaxel and capecitabine. The efficacy of cisplatin combined with nab-paclitaxel or paclitaxel was better than docetaxel and capecitabine, the HR values were 0.43 (95% CI, 0.24–0.77), and 0.29 (95% CI, 0.14–0.59) respectively. ICIs combined with chemotherapy groups and specifically, atezolizumab (HR = 0.45; 95% CI, 0.23–0.88) or pembrolizumab (HR = 0.47; 95% CI, 0.24–0.93) combined with nab-paclitaxel, showed advantages. Talazoparib is a poly (adenosine diphosphate–ribose) inhibitor, and the efficacy of single drug talazoparib seems to be better than that of docetaxel plus capecitabine (HR = 0.33; 95% CI, 0.11–0.96) [Figure 3].

Secondary endpoints

Overall survival

Twenty-one studies, including 3382 patients, reported OS (Supplementary Figure 3A). Using the random-effects model, the results showed no significant differences among the 20 protocols [Figure 4A]. There was no significant statistical difference in the efficacy between the 20 groups of regimens already used in clinical practice. This study found that docetaxel plus cisplatin, atezolizumab combined with nab-paclitaxel, carboplatin plus nab-paclitaxel have more advantages, according to the SUCRA ranking [Table 2, Supplementary Figure 2B].

Objective response rate

Eighteen studies, including 3094 patients, reported the ORR [Supplementary Figure 3B]. We used a random-effects model for the analysis. Cisplatin combined with nab-paclitaxel or paclitaxel was superior to docetaxel and capecitabine, the risk ratios values were 2.00 (95% CI, 1.10–3.80) and 4.30 (95% CI, 1.90–140) [Figure 4B and Supplementary Figure 2C].

Adverse events

Among grade 3–5 adverse events, the incidence of neutropenia, leukopenia, and anemia was high, whereas the incidence of nausea, vomiting, diarrhea, hypertension, and fatigue was low. The incidence of neutropenia was high in all included regimens, whereas the incidence of thrombocytopenia was high in the platinum-containing regimens and in patients treated with trilaciclib plus chemotherapy. The incidence of peripheral neuropathy in regimens containing taxanes was higher than that of other regiments [Supplementary Table 1].

Publication bias, and sensitivity analysis

Funnel plots and Egger's tests revealed no evidence of publication bias [Supplementary Figure 4]. The sensitivity analysis results showed that after sequentially excluding each study, the recalculated pooled results did not change significantly, indicating that no outlying study significantly influenced the overall results [Supplementary Figure 5].

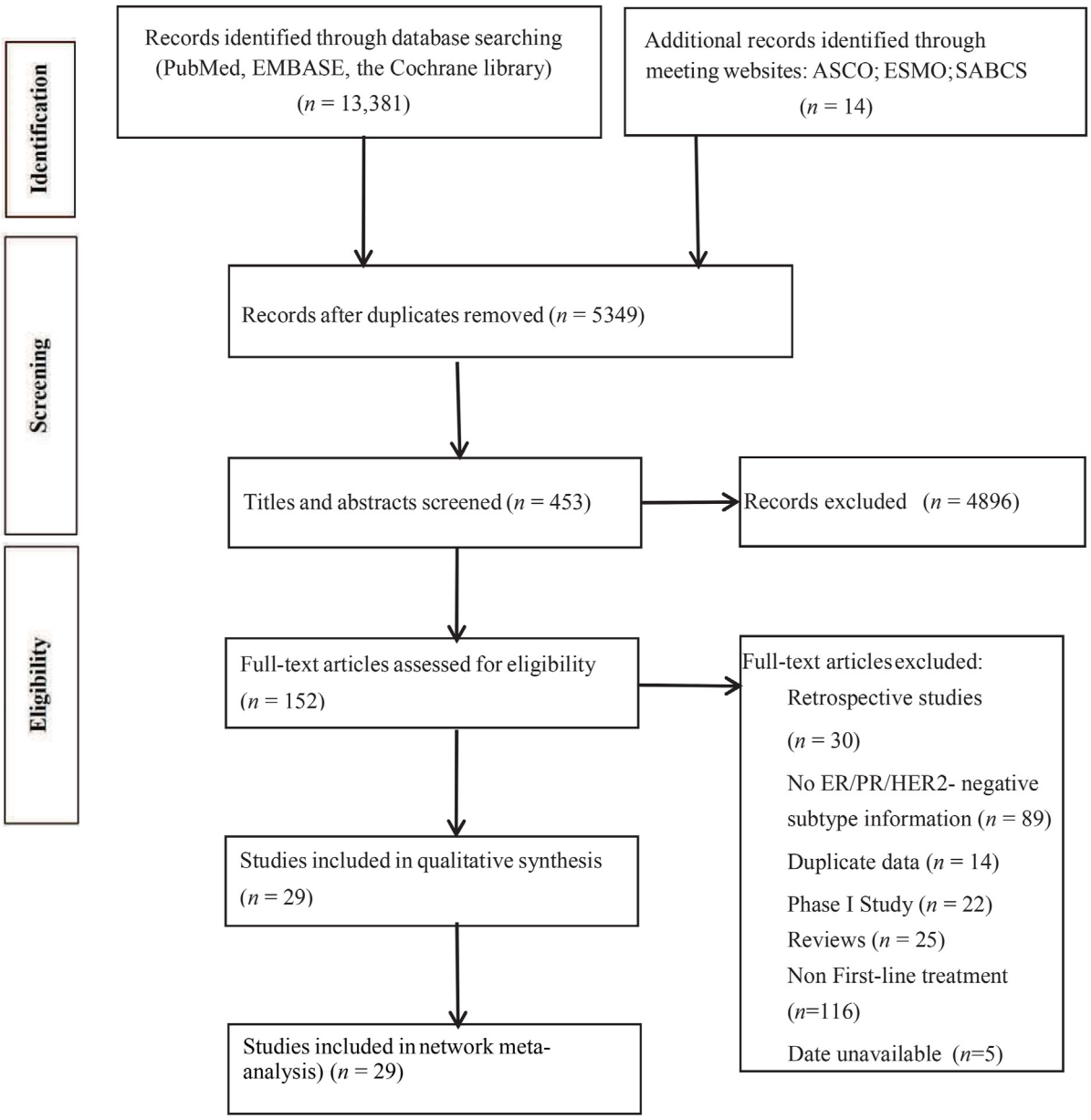

Figure 1. Search strings and flow charts for filtering and research selection. ASCO: American Society of Clinical Oncology; ER: Estrogen receptor; ESMO: European Society for Medical Oncology; HER2: Human epidermal growth factor receptor 2; PR: Progesterone receptor; SABCS: San Antonio Breast Cancer Symposium.

Discussion

In this network meta-analysis, we summarized the data obtained from 29 RCTs and compared the first-line treatment options for advanced TNBC through direct or indirect comparisons. The results showed that cisplatin combined with nab-paclitaxel or paclitaxel was superior to docetaxel plus capecitabine alone in terms of PFS and ORR. In PD-L1-positive mTNBC, atezolizumab or pembrolizumab combined with nab-paclitaxel has shown advantages. Talazoparib appears to be more effective than docetaxel plus capecitabine for patients with BRCA-mutated mTNBC. No significant differences were observed among the other treatment regimens. No significant differences in OS were observed. The incidence of neutropenia was very high in almost all regimens, whereas that of thrombocytopenia was very high in platinum-containing regimens and trilaciclib combined chemotherapy. Peripheral neuropathy was a common feature in taxane-containing regimens.

In the capecitabine plus bevacizumab plus vinorelbine regimen, PFS presented advantages over other regimens. A phase III study compared the efficacy of capecitabine plus bevacizumab combined with vinorelbine compared to capecitabine plus bevacizumab alone in HER2-negative breast cancer. Although there was no significant difference between the regimens in patients with HER2-negative metastatic or locally advanced breast cancer, improved PFS in mTNBC subgroup (HR = 0.33; 95% CI, 0.39–0.84, $P < 0.05$). However, the CARIN trial indicated that neurotoxicity caused by vinorelbine is more severe or protracted.[32] Furthermore, in regimens combining taxanes and capecitabine, the addition of bevacizumab also showed advantages in terms of PFS as a first-line treatment for mTNBC. Bevacizumab is prohibited by the FDA and was not recommended in the present study because clinical trial efficacy and safety data revealed that bevacizumab could only prolong PFS but could not improve OS, and resulted in an increase in serious adverse events.[16,26]

For efficacy analysis of ICIs combined with chemotherapy, this study included data from a PD-L1-positive population. PD-L1 is an immune-checkpoint protein that is highly expressed in activated T cells. ICIs act on PD-L1 to block the proximal signaling device of the TCR-CD28 system,[44,45] thereby inhibiting T cell activation. The results of the

Table 1
Characteristics of the outcomes of the studies included in this network meta-analysis.

Study	Journal	Center	Phase	Line	Regimens	No. of patients analyzed	PFS (HR, 95% CI)	OS (HR, 95% CI)	ORR, % (*n*/*N*)
Lück 2015[14]	Breast Cancer Research and Treatment	Multicenter	III	1	Taxanes + Bevacizumab + Capecitabine Taxanes + Bevacizumab	51	0.51 (0.27–0.96)	NA	NA
Cortes 2020[15]	Lancet	Multicenter	III	1	Pembrolizumab + Chemotherapy Placebo + Chemotherapy	323	0.66 (0.50–0.88)	0.73 (0.55–0.95)	52.7 (116/220) 40.8 (42/103)
Tan 2019[16]	Lancet Oncology	Multicenter	II	≥1	Trilaciclib + Gemcitabine + Carboplatin Gemcitabine + Carboplatin	64	0.63 (0.31–1.31)	0.46 (0.21–0.99)	43.3 (26/60) 33.3 (8/24)
Schmid 2020[17]	Lancet Oncology	Multicenter	III	1	Nab-Paclitaxel + Atezolizumab Nab-Paclitaxel	369	0.63 (0.50–0.80)	0.67 (0.53–0.86)	59.0 (109/185) 46.0 (85/185)
Schmid 2020[18]	Journal of Clinical Oncology	Multicenter	II	1	Paclitaxel + Capivasertib Paclitaxel	28	0.30 (0.11–0.79)	0.37 (0.12–1.12)	35.3 (6/17) 18.2 (2/11)
O'Shaughnessy 2014[19]	Journal of Clinical Oncology	Multicenter	III	1	Gemcitabine + Carboplatin + Iniparib Gemcitabine + Carboplatin	297	0.88 (0.67–1.17)	1.07 (0.80–1.41)	NA
Bergh 2012[20]	Journal of Clinical Oncology	Multicenter	III	1	Sunitinib + Docetaxel Docetaxel	127	1.03 (0.65–1.63)	NA	NA
Hu 2015[21]	Lancet Oncology	Multicenter	III	1	Cisplatin + Gemcitabine Paclitaxel + Gemcitabine	236	0.69 (0.52–0.92)	0.90 (0.60–1.34)	64.4 (76/118) 49.2 (58/118)
Kim 2017[22]	Lancet Oncology	Multicenter	III	1	Paclitaxe + Ipatasertib Paclitaxel	59	0.44 (0.20–0.99)	1.13 (0.52–2.47)	20.0 (13/26) 43.8 (7/16)
Wang 2022[23]	Nature Communications	Multicenter	III	1	Nab-Paclitaxel + Cisplatin Gemcitabine + Cisplatin	253	0.67 (0.50–0.88)	0.62 (0.44–0.90)	81.1 (103/127) 56.3 (71/126)
Gligorov 2014[24]	Lancet Oncology	Multicenter	III	1	Bevacizumab + Capecitabine Bevacizumab	46	0.57 (0.31–1.07)	0.44 (0.19–0.99)	NA
Gradishar 2013[25]	European Journal of Cancer	Multicenter	II	1	Sorafenib + Paclitaxel Paclitaxel	94	0.86 (0.50–1.45)	NA	NA
Miles 2017[26]	European Journal of Cancer	Multicenter	II	1	Paclitaxel + Bevacizumab Paclitaxel	78	0.64 (0.37–1.11)	0.81 (0.61–1.08)	NA
Robert 2011[27]	Journal of Clinical Oncology	Multicenter	III	1	Bevacizumab + Capecitabine Capecitabine Bevacizumab + Taxane/Anthracycline Taxane/Anthracycline	279	0.72 (0.49–1.06) 0.78 (0.53–1.15)	NA	NA
Miles 2021[28]	Annals of Oncology	Multicenter	III	1	Atezolizumab + Paclitaxe Placebo + Paclitaxe	292	0.86 (0.70–1.05)	0.87 (0.75–1.02)	62.8 (120/191) 55.4 (56/101)
Takashima 2016[29]	Lancet Oncology	Multicenter	III	1	S-1 Taxanes	147	NA	1.29 (0.88–1.89)	NA
Diéras 2020[30]	Lancet Oncology	Multicenter	III	≥1	Carboplatin + Paclitaxel + Veliparib Carboplatin + Paclitaxel	185	0.72 (0.50–1.04)	NA	NA
Welt 2016[31]	Breast Cancer Research and Treatment	Multicenter	III	1	Capecitabine + Bevacizumab + Vinorelbine Capecitabine + Bevacizumab	122	0.57 (0.39–0.84)	NA	NA
Zielinski 2016[32]	Lancet Oncology	Multicenter	III	1	Bevacizumab + Paclitaxel Bevacizumab + Capecitabine	130	1.37 (0.93–2.02)	1.33 (0.80–2.19)	NA
Fan 2013[33]	Annals of Oncology	Single center	II	1	Docetaxel + Cisplatin Docetaxel + Capecitabine	53	0.29 (0.14–0.57)	0.41 (0.18–0.92)	63.0 (17/27) 15.4 (4/26)
Mustafa 2019[34]	Egyptian Journal of Hospital Medicine	Single center	II	1	Cisplatin + Gemcitabine Paclitaxel + Gemcitabine	110	NA	NA	69.1 (38/55) 47.3 (26/55)
Yardley 2018[35]	Annals of Oncology	Multicenter	III	1	Nab-Paclitaxel + Carboplatin Nab-Paclitaxel + Gemcitabine/Gemcitabine + Carboplatin	191	0.59 (0.38–0.92) 0.58 (0.37–0.90)	0.73 (0.47–1.13) 0.80 (0.52–1.22)	70.1 (47/64) 39.3 (24/61) 44.0 (29/66)
Dent 2021[36]	Cancer Research	Multicenter	III	1	Ipatasertib + Paclitaxel Paclitaxel	255	1.02 (0.71–1.45)	NA	38.7 (65/168) 34.5 (30/87)
Xu 2011[37]	Breast Cancer	Multicenter	II	1	Gemcitabine + Carboplatin/Gemcitabine + Cisplatin Paclitaxel + Gemcitabine	147	1.46 (0.79–2.73) 1.25 (0.67–2.31)	0.81 (0.44–1.50) 1.49 (0.82–2.73)	17.1 (8/47) 26.5 (13/49) 15.7 (8/51)
Joensuu 2010[38]	Annals of Oncology	Multicenter	III	1		237	1.05 (0.79–1.41)	1.11 (0.75–1.64)	

(*continued on next page*)

Table 1 (*continued*)

Study	Journal	Center	Phase	Line	Regimens	No. of patients analyzed	PFS (HR, 95% CI)	OS (HR, 95% CI)	ORR, % (*n*/*N*)
					Docetaxel				60.0 (69/115)
					Docetaxel + Gemcitabine				59.8 (67/122)
Vici 2011[39]	Oncology	Multicenter	II	1	Docetaxel + Gemcitabine	72	0.84 (0.53–1.33)	1.11 (0.68–1.82)	41.7 (15/36)
					Docetaxel + Capecitabine				38.9 (14/36)
Tamura 2017[40]	Cancer Science	Multicenter	II	1	Nab-Paclitaxel	197	0.81 (0.59–1.10)	0.78 (0.54–1.14)	56.1 (55/98)
					Docetaxel				52.5 (52/99)
Robson 2017[41]	The New England Journal of Medicine	Multicenter	III	≥1	Olaparib	87	0.56 (0.34–0.98)	0.51 (0.29–0.90)	NA
					Chemotherapy				
Litton 2018[42]	The New England Journal of Medicine	Multicenter	III	≥1	Talazoparib	78	0.67 (0.35–1.27)	0.97 (0.53–1.77)	NA
					Chemotherapy				

Chemotherapy: group designated by the doctor, including taxane, anthracycline, platinum, capecitabine, eribulin, and vinorelbine. CI: Confidence interval; HR: Hazard ratio; NA: Not available; ORR: Objective response rate; OS: overall survival; PFS: Progression-free survival.

meta-analysis showed that the PFS of patients with PD-L1-positive tumors significantly improved after treatment with atezolizumab or pembrolizumab combined with nab-paclitaxel. Notably, in another study that adopted a similar design, a change to atezolizumab combined with paclitaxel resulted in no significant benefit in either PFS or OS. Follow-up studies attributed this finding to a decrease in $CXCL13^{+}$ T cells as a result of the paclitaxel regimen, which may affect the clinical outcome of TNBC treatment with atezolizumab, noting that the combined administration of steroids reduces the proliferation pathway of immune cells, making them less sensitive to the activation induced by atezolizumab.[46–48] Interestingly, in a study of advanced solid tumors, the combination of paclitaxel and steroids did not preclude the OS advantage of atezolizumab.[49] Further research needed to corroborates these findings. This study included a population with PD-L1 expression (combined positive score ≥10) from the KEYNOTE-355 trial in whom PFS was found to be significantly superior to chemotherapy with no significant increase in toxicity.[17] The above results indicated that the addition of immune agents to standard chemotherapy had an effect on the first-line treatment of mTNBC. Furthermore, immunotherapy combined with chemotherapy can be beneficial; however, further investigation of chemotherapy regimens is required to identify the best treatment effect.

For the efficacy analysis of the PARPi, we included data from patients with germline *BRCA* mutations. PARPi acts primarily by inhibiting PARylation, which induces trapping at the site of deoxyribonucleic acid (DNA) damage, activation of effector genes, and consequent interruption of the replication fork, leading to double-strand breaks responsible for the cytotoxic effect. The corresponding inhibition of PARP causes unpaired damage, leading to tumor cell death.[9,50,51] The results of our analysis showed that talazoparib significantly improved PFS in patients with *BRCA*-mutated mTNBC, whereas there was no significant change in OS. Similarly, a meta-analysis investigated the efficacy of PARPi in patients with metastatic breast cancer with *BRCA*1 or *BRCA*2 mutations. PARPi group significantly improved PFS (HR = 0.61, 95% CI: 0.47–0.80), while OS did not benefit (HR = 0.87, 95% CI: 0.76–1.00).[51] However, despite evidence on the efficacy of PARPi, approximately 50% of patients continued to progress during treatment. Drug resistance is more likely to occur during treatment with PARPi, which explains the progress in some patients.[51] A review suggested the need to investigate novel treatment regimens involving PARPi in combination with other drugs to achieve breakthroughs in the treatment of mTNBC.[9] Two studies exploring the combination of PARPi and ICIs have reported promising efficacy and safety results.[52,53]

The mechanism of action of platinum-based drugs involves direct binding of the drug with DNA, causing intra-strand or inter-chain crosslinking of DNA, leading to the dissociation of double-stranded DNA, triggering cell growth arrest, and sometimes inducing cell death.[54] Our results showed that cisplatin combined with paclitaxel or nab-paclitaxel significantly improved PFS compared with taxane-based chemotherapy. A previous study has shown that gemcitabine plus cisplatin was superior to gemcitabine plus paclitaxel as a first-line treatment for PFS in patients with mTNBC. Furthermore, a recent study comparing the efficacy and safety of nab-paclitaxel plus cisplatin or gemcitabine plus cisplatin as first-line treatment for advanced TNBC showed that nab-paclitaxel combined with cisplatin was associated with improvement in PFS and OS, suggesting that it is a good option as first-line treatment.[25] A study has shown that platinum-based chemotherapy can significantly improve the pathologic complete remission (PCR) rate and prognosis of patients with mTNBC, while chemotherapy regimens containing platinum compounds can significantly increase the incidence of adverse reactions such as thrombocytopenia and diarrhea.[55] Similarly, another study concluded that compared to non-platinum drugs, platinum drugs may cause more serious hematological adverse reactions in the treatment of TNBC.[56] Toxicity is clearly an important concern when using platinum-based drugs. In summary, a platinum-containing regimen may be used as a first-line treatment option when administered with a recombinant human granulocyte colony-stimulating factor to manage blood toxicity.

Table 2
Surface under the cumulative rank curve value of each treatment option for progression-free survival, overall survival, and objective response rate; value of I^2.

Treatments	SUCRA (PFS)	Rank	Treatments	SUCRA (OS)	Rank	Treatments	SUCRA (ORR)	Rank
VinoplusCapeplusB[a]	0.931	1	TrilplusCbplusG[a]	0.822	1	CisplusG	0.783	1
PplusBplusCape[a]	0.921	2	CisplusP	0.787	2	CisplusNabP	0.685	2
CapiplusP[a]	0.870	3	CapiplusP[a]	0.751	3	CapiplusP[a]	0.660	3
CisplusP	0.861	4	AtezplusNabP	0.661	4	PembplusNabP	0.597	4
CapeplusB[a]	0.751	5	CbplusNabP	0.640	5	AtezplusNabP	0.578	5
CisplusNabP	0.750	6	PembplusNabP	0.618	6	CbplusNabP	0.573	6
Tala	0.744	7	CapeplusB[a]	0.583	7	CisplusG	0.541	7
AtezplusNabP	0.725	8	CbplusG	0.542	8	AtezplusP[a]	0.519	8
PembplusNabP	0.670	9	CisplusNabP	0.525	9	TrilplusCbplusG	0.515	9
NabPplusB[a]	0.586	10	InipplusCbplusG[a]	0.497	10	IpatplusP[a]	0.470	10
PplusB[a]	0.568	11	NabPplusG	0.468	11	NabP	0.467	11
Cape	0.535	12	NabP	0.458	12	P	0.436	12
TrilplusCbplusG[a]	0.531	13	CapeplusP	0.430	13	CapeplusP	0.412	13
CisplusG	0.510	14	IpatplusP[a]	0.403	14	PplusG	0.411	14
VeliplusCbplusP	0.454	15	AtezplusP[a]	0.410	15	CbplusG	0.401	15
NabP	0.406	16	PplusG	0.371	16			
B[a]	0.394	17	P	0.315	17			
SoraplusP[a]	0.374	18	CisplusG	0.249	18			
AtezplusP[a]	0.365	19	B[a]	0.248	19			
IpatplusP[a]	0.335	20	S1[a]	0.221	20			
InipplusCbplusG[a]	0.317	21						
PplusG	0.279	22						
SuniplusP[a]	0.234	23						
P	0.223	24						
CbplusNabP	0.216	25						
CbplusG	0.210	26						
Olap	0.196	27						
CapeplusP	0.183	28						
NabPplusG	0.027	29						
	$I^2 = 16\%$			$I^2 = 4\%$			$I^2 = 5\%$	

[a] Treatment not recommended by the National Comprehensive Cancer Network and/or approved by the Food and Drug Administration/Environmental Management Association. Atez: Atezolizumab; B: Bevacizumab; Cape: Capecitabine; Capi: Capivasertib; Cb: Carboplatin; Cis: Cisplatin; G: Gemcitabine; Inip: Iniparib; Ipat: Ipatasertib; Ipat: Ipatasertib; NabP: Nab-paclitaxel; ORR: Objective response rate; OS: Overall survival; P: Docetaxel/docetaxel/taxane; Pemb: Pembrolizumab; PFS: Progression-free survival; S1: S-1; Sora: Sorafenib; SUCRA: Surface under the cumulative ranking curve; Suni: Sunitinib; Tril: Trilaciclib; Veli: Veliparib; Vino: Vinorelbine.

AKT is the central node of multiple signaling pathways that promote cell survival, growth, invasion, and migration.[57,58] Activation of the PI3K/AKT pathway is associated with a poor prognosis, and chemotherapy resistance can be an early compensatory mechanism that can be exploited to increase the efficacy of chemotherapy.[59] Capivasertib is a potent, highly selective, and active small-molecule kinase inhibitor with similar activity against the isoforms AKT1, AKT2, and AKT3.[60] Compared with docetaxel and capecitabine, capivasertib plus paclitaxel performed well in terms of the PFS of patients with mTNBC with PIK3CA/AKT1/PTEN-pathway alterations. In another study, the result showed no PFS improvement with the addition of ipatasertib to first-line in patients with PIK3CA/AKT1/PTEN-altered mTNBC.[37] Therefore, drugs targeting this pathway have not been approved for use in mTNBC, and their efficacy needs to be verified through clinical research.

Although all the drug regimens presented above have significant efficacy, few studies have provided a direct head-to-head comparison. This network meta-analysis addresses this gap in medical knowledge. Some drugs for the treatment of mTNBC are based on the expression of molecular markers. The discovery of novel molecular markers has improved our understanding of breast cancer. PD-L1 is expressed in breast cancer, particularly in mTNBC with an expression rate of approximately 40%. It is the main factor responsible for the significant effect of ICIs combined with chemotherapy in mTNBC. Similarly, the use of PARPi for the treatment of mTNBC is based on mutations in *BRCA*. The *BRCA* mutation rate in TNBC is approximately 15–27%. Therefore, patients harboring these mutations may have better treatment options. However, PARPi efficacy in biomarker-negative populations remains unclear. In studies on the PI3K/AKT pathway, no significant difference in OS was detected between controls and patients with PIK3CA/AKT1/PTEN-pathway alterations, although an advantage in PFS was found in the patients with the pathway alteration. Therefore, it is important to explore more targeted therapies. A phase 3 trial for advanced breast cancer is currently underway.

In terms of adverse events, neutropenia, diarrhea, and fatigue are common in combination chemotherapy with ICIs. Specifically, thrombocytopenia is more significant in regimens containing PARPi while neutropenia is more common in regimens containing platinum drugs. Anemia and nausea were the most common side effects of anthracycline or paclitaxel.

Currently, progress has been made in the treatment of mTNBC. In clinical practice, platinum-containing regimens, immunotherapy, and poly (ADP-ribose) PARPi have shown certain advantages. However, treatment methods based on biomarkers or mutant genes present various limitations and are not applicable to all patients with mTNBC. In recent years, research results on antibody–drug conjugates in the field of advanced breast cancer have been promising. Sacituzumab govitecan (SG) is an antibody–drug conjugate (ADC) composed of an antibody targeting the human trophoblast cell-surface antigen 2 (Trop-2), which is expressed in the majority of breast cancers, conjugated to SN-38 through a proprietary hydrolyzable linker.[61] This new antibody-based molecular platform enables the selective delivery of a potent cytotoxic payload to target cancer cells, resulting in improved efficacy. The ASCENT study was a phase 3 randomized controlled trial, including $\geq$2 patients with advanced TNBC with patients randomly assigned in a 1:1 ratio to receive either SG or chemotherapy. SG was found to be safe and achieve better survival outcomes than monotherapy chemotherapy, with improvement in patient quality of life. The excellent results of ADCs as non-first-line treatment of mTNBC introduce new treatment options. Therefore, it is important to explore the indications for ADCs as the first-line treatment of mTNBC. The DESTINY-Breast04 trial identified novel treatment

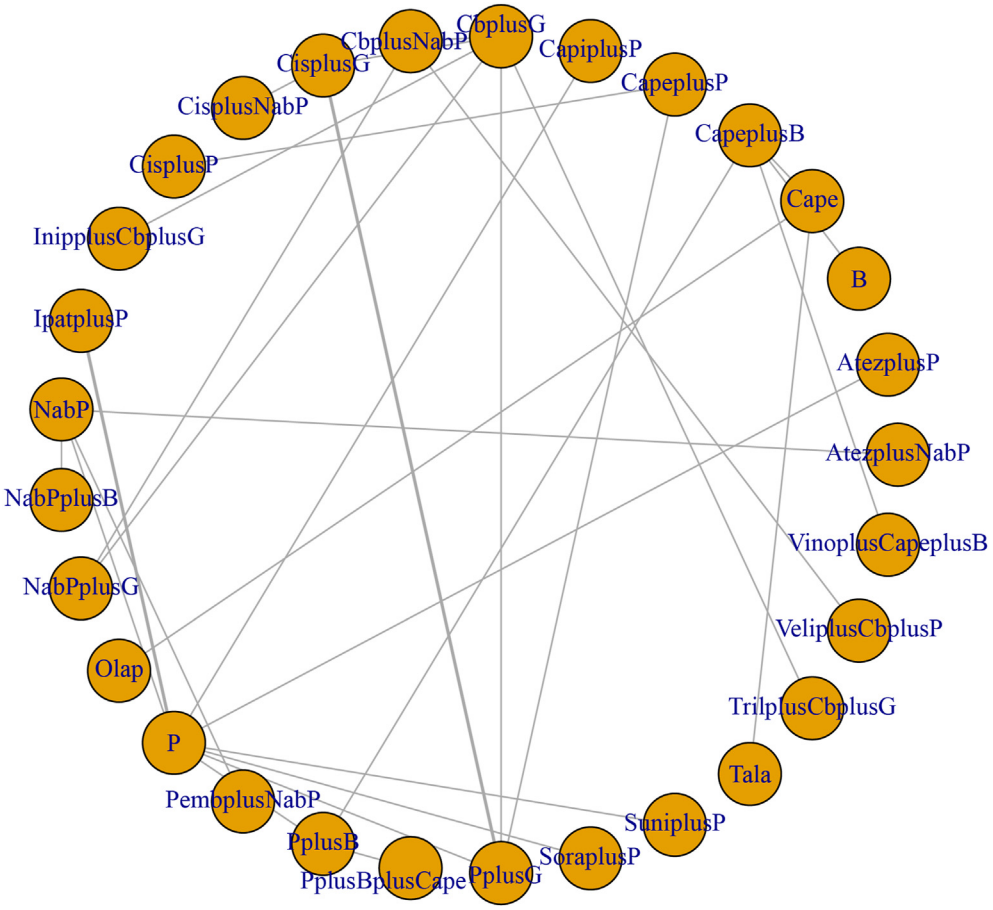

Figure 2. Network plot of progression-free survival for different first-line treatment regimens of metastatic triple-negative breast cancer. Atez: Atezolizumab; B: Bevacizumab; Cape: Capecitabine; Capi: Capivasertib; Cb: Carboplatin; Cis: Cisplatin; G: Gemcitabine; Inip: Iniparib; Ipat: Ipatasertib; NabP: Nab-Paclitaxel; Olap: Olaparib; P: Docetaxel/Docetaxel/Taxane; Pemb: Pembrolizumab; Suni: Sunitinib; Sora: Sorafenib; Tala: Talazoparib; Tril: Trilaciclib; Veli: Veliparib; Vino: Vinorelbine.

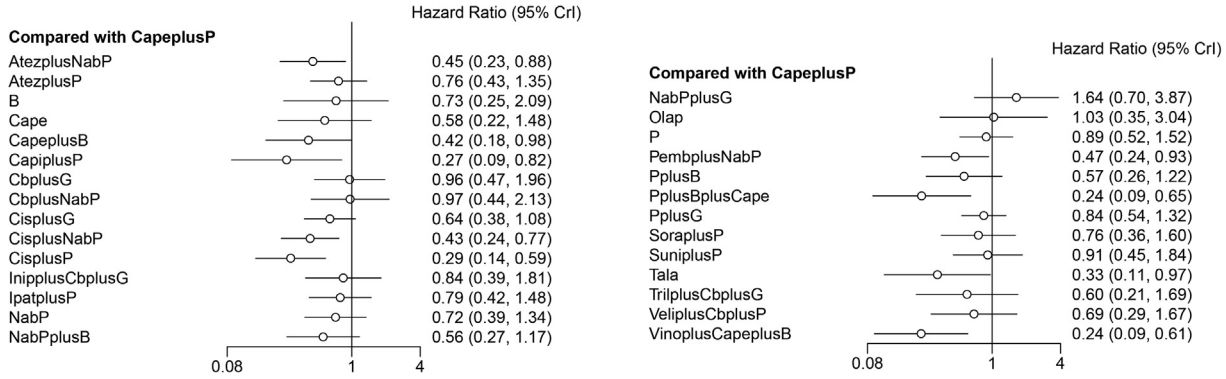

Figure 3. Forest plot of progression-free survival for different first-line treatment regimens of metastatic triple-negative breast cancer. Atez: Atezolizumab; B: Bevacizumab; Cape: Capecitabine; Capi: Capivasertib; Cb: Carboplatin; Cis: Cisplatin; G: Gemcitabine; Inip: Iniparib; Ipat: Ipatasertib; NabP: Nab-Paclitaxel; Olap: Olaparib; P: Docetaxel/Docetaxel/Taxane; Pemb: Pembrolizumab; Suni: Sunitinib; Sora: Sorafenib; Tala: Talazoparib; Tril: Trilaciclib; Veli: Veliparib; Vino: Vinorelbine.

strategies for mTNBC. In the subgroups with low HER2 expression and negative hormone receptors, trastuzumab deruxtecan significantly improved median PFS and median OS compared to the chemotherapy group[62] It should be noted that the population included in the DESTINY-Breast04 trial includes patients who have previously undergone one or two rounds of chemotherapy.

This network meta-analysis has several limitations. First, the number of studies included was relatively small. Second, some of the results are based on specific biomarkers and are not applicable to the entire maTNBC population. Furthermore, in the analysis of adverse events, the side effects data of some of the included studies were the data of the entire study population. Nonetheless, this network meta-analysis is a comprehensive network meta-analysis of RCTs on mTNBC and presents a systematic comparison of the efficacy of current clinical or approved experimental protocols.

In conclusion, there has been significant progress in the treatment of mTNBC. Cisplatin combined with nab-paclitaxel or paclitaxel showed good efficacy in improving PFS and ORR and is a promising first-line treatment for mTNBC. Based on different biomarkers, atezolizumab/pembrolizumab combined with nab-paclitaxel and talazoparib are first-

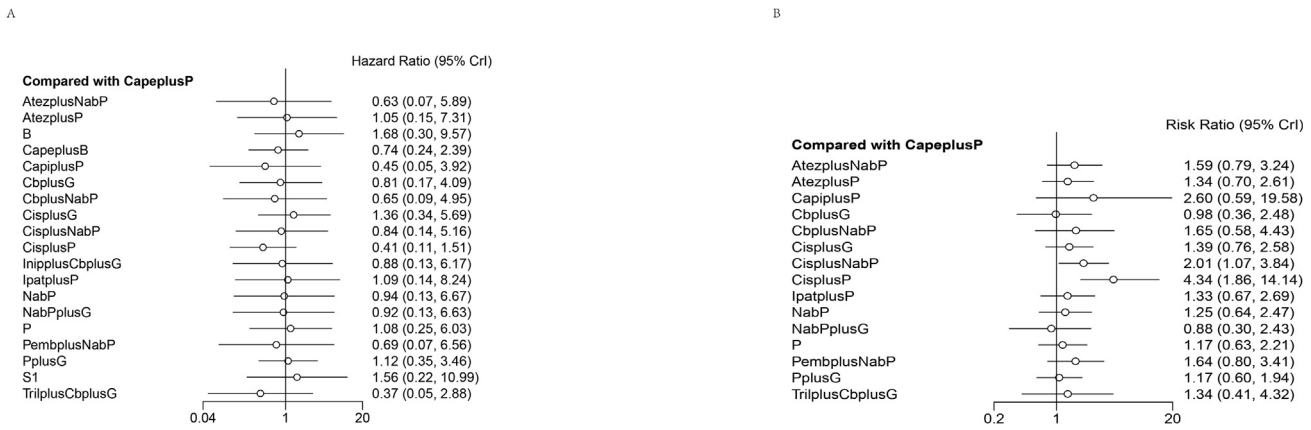

Figure 4. Forest plots of overall survival and objective response rate for different first-line treatment regimens of metastatic triple-negative breast cancer (A) Forest plots of overall survival (B) Forest plots of objective response rate. Atez: Atezolizumab; B: Bevacizumab; Cape: Capecitabine; Capi: Capivasertib; Cb: Carboplatin; Cis: Cisplatin; G: Gemcitabine; Inip: Iniparib; Ipat: Ipatasertib; NabP: Nab-Paclitaxel; Olap: Olaparib; P: Docetaxel/Docetaxel/Taxane; Pemb: Pembrolizumab; Suni: Sunitinib; Sora: Sorafenib; Tala: Talazoparib; Tril: Trilaciclib; Veli: Veliparib; Vino: Vinorelbine.

line treatment options for PD-L1 positive and *BRCA*-mutated populations, respectively. Neutrophils, diarrhea, and fatigue are common and serious adverse reactions.

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Authors contribution

Mingqiang Shi: Methodology, formal analysis, data curation, and writing - original draft; Zhoujuan Li: Methodology, formal analysis, data curation, and writing–original draft; Guoshuang Shen: Methodology, writing - original draft; Tianzhuo Wang: Data curation; Jinming Li: Data curation; Miaozhou Wang: Data curation; Zhen Liu: Writing - review & editing; Fuxing Zhao: Writing - review & editing; Dengfeng Ren: Writing, reviewing, and editing; Jiuda Zhao: Conceptualization, writing, review, editing, and supervision. All authors critically revised the successive drafts of the manuscript and approved the final version. The corresponding author attests that all listed authors meet the authorship criteria and that no other persons meeting these criteria have been omitted.

Ethics statement

None.

Data availability statement

The datasets used in the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpt.2023.06.002.

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