Third-line Treatment for Metastatic Triple-negative Breast Cancer

A Systematic Review and Network Meta-analysis

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Objective: Metastatic triple-negative breast cancer (mTNBC) is an invasive histologic subtype with a poor prognosis and rapid progression. Currently, there is no standard therapy for the third-line treatment of mTNBC. In this study, we conducted a network meta-analysis to compare regimens and determine treatment outcomes.

Methods: We performed a systematic search of PubMed, EMBASE, the Cochrane Central Register of Controlled Bases, and the minutes of major conferences. Progression-free survival, overall survival, and objective response rate were analyzed through network meta-analysis using the R software (R Core Team). The efficacy of the treatment regimens was compared using hazard ratios, odds ratios, and 95% CIs.

Results: We evaluated 15 randomized controlled trials involving 6,010 patients. Compared with the physician's choice treatment, sacituzumab govitecan showed significant advantages in progression-free survival and overall survival, with hazard ratio values of 0.41 (95% CI: 0.32-0.52) and 0.48 (95% CI, 0.39-0.60). In terms of objective response rate, sacituzumab govitecan is the best-performing therapy (odds ratio: 10.82; 95% CI: 5.58-20.97). Adverse events among grades 3 to 5 adverse reactions, the incidence of neutropenia and leukopenia in each regimen was higher, whereas the incidence of fever, headache, hypertension, and rash was lower.

Conclusion: Compared with the treatment of the physician's choice, sacituzumab govitecan appears more efficacious and is the preferred third-line treatment for mTNBC.

Key Words: metastatic triple-negative breast cancer, antibody-drug conjugates (ADC), chemotherapy

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Triple-negative breast cancer (TNBC) is a breast cancer subtype defined by the lack of estrogen receptor (ER) and progesterone receptor (PR) expression and the absence of human epidermal growth factor receptor 2 (HER2) overexpression.[1,2] TNBC accounts for 15% to 20% of breast cancers and is characterized by its heterogeneity, treatment difficulty, and rapid progression.[3,4] Patients with TNBC who relapse often do so within the first 3 years after diagnosis and frequently develop visceral metastases, with a minority not surviving beyond 2 years.[5] In addition, repeated exposure to chemotherapy regimens may lead to cumulative toxicity and a decreased quality of life (QoL). Therefore, the treatment of advanced TNBC after second-line treatment should be carefully considered.

Cytotoxic chemotherapy remains the primary treatment method for metastatic TNBC (mTNBC).[6] New treatment methods have recently been developed.[7] Clinical studies on drugs, such as antibody-drug conjugates (ADCs) and poly-adenosine diphosphate ribose polymerase inhibitors have been conducted.[8,9] Studies in hormone receptor-negative breast cancer populations with low HER2 expression have also been conducted and have shown promising results.[10] The treatment of mTNBC is diverse, based on the expression of different receptors or gene mutations.

Currently, there is no standard treatment for mTNBC, and there is a lack of direct comparisons among different treatments. Therefore, we conducted a network meta-analysis (NMA) to address the lack of standardized third-line therapies. This study provides strong evidence for clinicians and researchers by systematically comparing the efficacy of different treatments.

METHODS

Search Strategy

We searched PubMed, Embase, and Cochrane Library databases. We also conducted further searches of the European Society for Medical Oncology Meeting, the American Society of Clinical Oncology Meeting, and the San Antonio Breast Cancer Symposium. The search was conducted from the date of creation of the database to March 1, 2023. References of relevant studies, reviews, and meta-analyses were manually screened to identify potentially eligible publications. The search keywords included "breast cancer," "breast neoplasms," "breast tumor," "triple-negative breast cancer," and "advanced" or "metastatic." The search was limited to studies published in English.

Selection Criteria

Eligible randomized controlled trials (RCTs) were included using the following criteria: (1) phase 2 or 3 RCT, comparing at least two different treatment regimens for patients with mTNBC, (2) patients (>18 y) with mTNBC histologically confirmed as ER-negative, PR-negative, and with

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no overexpression of HER2, (3) more than 2 previous standard chemotherapy schemes (no upper limit) for patients with recurrent or refractory mTNBC, and (4) patients who had study outcome indicators available for progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and grades 3 to 5 adverse effects. The exclusion criteria were as follows: (1) incomplete treatment data and ER/PR/HER2 status, (2) non-RCT, (3) patients who received systematic treatment for metastatic breast cancer no more than twice, and (4) ongoing studies that did not provide or publish results at the time of the literature search.

Data Extraction

Data extracted from each study included the name of the first author, year of publication, study design, trial phase, line of treatment, hazard ratios (HRs), 95% credible interval (95% CI) of PFS and OS, adverse events (grades 3 to 5), and ORR. For multiple reports of the same trial, only the most recent outcomes were used.

Statistical Analyses

NMA was performed using R (version 4.2.3, R Core Team) and Netmeta software packages. Based on frequentist point estimates and standard errors, the *P* score was used to rank the different topical treatments. Higher scores indicated better treatment.[11] Data from the included studies were extracted and inputted into specialized data collection tables for analysis.

NMA 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 NMA, 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 network geometry.

Heterogeneity between the studies was assessed using Cochran *Q*-statistics and the I^2-measure from the Netmeta statistical package. I^2 values of 25% to 49% indicate low, 50% to 74% indicate moderate, and $\geq$75% indicate high levels of heterogeneity. A fixed-effect model was used when I^2 was <50%; otherwise, a random-effect model was used.[12] The decomp design function was used to assess the global inconsistency in each model. A *P* value of <0.05 was considered suggestive of significant inconsistency. We used a net heat plot, a graphical tool for locating inconsistencies in NMA. The stronger the intensity of the color, the greater the inconsistency between the specific direct evidence in the entire network. When the network graph did not form a closed loop, we specified using a random-effect model and did not apply consistency testing or a net heat plot.[13]

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).

RESULTS

Of the 7,043 records obtained from the electronic databases, the full texts of 5,496 potentially qualifying studies were reviewed, and 4,844 studies were excluded because of noncompliance with third-line treatment (Fig. 1). A total of 15 studies were included in the final analysis (Table 1).[14–28] Of note, when the number of treatment lines in the included studies was not limited to third-line treatment and contained data on non-mTNBC, we included such literature for systematic analysis. In 9 studies, the control group used the physician's choice (treatment of the physician's choice [TPC]) treatment group, and the specific content is shown in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/AJCO/A505). Three studies expressed specific biomarkers or targets, and Winer et al[26] studied the effect of the immune checkpoint inhibitor pembrolizumab on programmed death-ligand 1 (PD-L1) targets. Therefore, the included population was the PD-L1 positive population (combined positive score $\geq$1) with relevant data. The 2 studies on polyadenosine-diphosphate-ribose polymerase (PARP) inhibitors, olaparib and talazoparib, were based on *BRCA* mutation, and all included populations had *BRCA* mutations.[21,25] "DESTINY-Breast04" is a study on a breast cancer population with low HER2 expression (low expression of HER2 was defined as a score of 1+ on immunohistochemical [IHC] analysis or as an IHC score of 2+ and negative results on in situ hybridization [ISH]), and we included data from the hormone receptor-negative group.[24]

We used a random-effect model for NMA. Two researchers independently collected 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 7 were considered medium risk. The risk of bias in the included studies is shown in Supplemental Figure 1 (Supplemental Digital Content 2, http://links.lww.com/AJCO/A506).

Primary Endpoint

Progression-free Survival

Fifteen RCTs and 6,010 patients were included in the PFS analysis (Fig. 2). The results showed that compared with TPC, sacituzumab govitecan (HR: 0.41; 95% CI: 0.32-0.52) and trastuzumab deruxtecan (HR: 0.46; 95% CI: 0.24-0.88) showed significant advantages in PFS and the *P* scores were 0.96 and 0.83. Talazoparib (HR: 0.54; 95% CI: 0.41-0.71; *P* score = 0.77) and olaparib (HR: 0.58; 95% CI: 0.43-0.80; *P* score = 0.69) showed significant differences in the *BRCA* mutation population. In addition, the efficacies of ixabepilone plus capecitabine, etoposide plus cisplatin, vinorelbine plus gemcitabine, vinflunine plus capecitabine, capecitabine, and eribulin were superior to that of TPC (Fig. 3A). The efficacy of pembrolizumab did not show advantages (HR: 1.35; 95% CI: 1.09-1.67; *P* score = 0.02; Fig. 3A).

Overall Survival

Fifteen RCTs, which included 6,010 patients, reported OS (Supplemental Fig. 2A, Supplemental Digital Content 2, http://links.lww.com/AJCO/A506). The results of the NMA showed that compared with TPC, sacituzumab govitecan and trastuzumab deruxtecan showed significant advantages; the HR values were 0.48 (95% CI: 0.39-0.60; *P* score = 0.99) and 0.64 (95% CI: 0.48-0.84; *P* score = 0.87), respectively. In addition, eribulin had significant therapeutic effects compared with TPC (HR: 0.81; 95% CI: 0.68-0.97; *P* score = 0.67; Fig. 3B).

Objective Response Rate

Fifteen studies comprising 6,010 patients were included in the ORR analysis (Supplemental Fig. 2B, Supplemental Digital Content 2, http://links.lww.com/AJCO/A506). Compared with TPC, sacituzumab govitecan showed statistical differences and had the best therapeutic effect (*P* score = 0.93), and the odds

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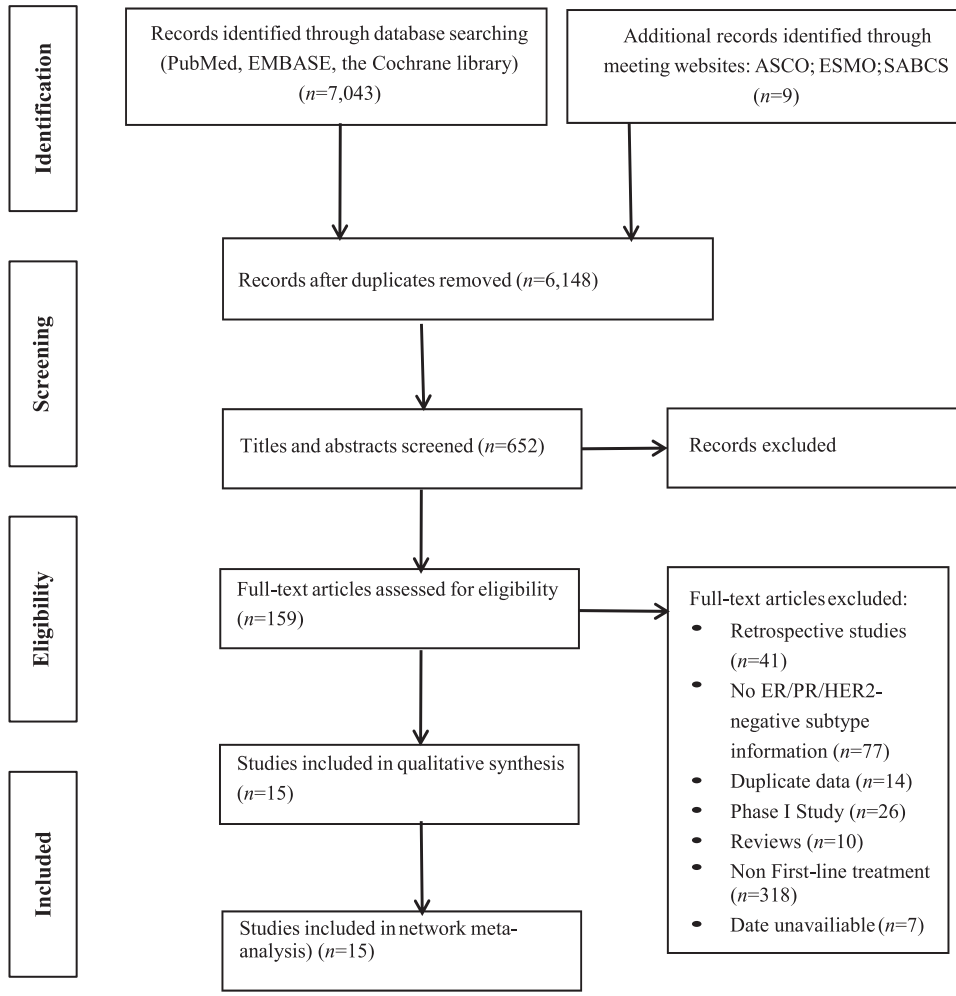

FIGURE 1. Search strings and flowcharts for filtering and research selection. ER indicates estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

ratio (OR) value was 10.82 (95% CI: 5.58-20.97). The efficacy of ixabepilone plus capecitabine was second only to sacituzumab govitecan, with an OR value of 5.22 (95% CI: 2.27-12.00). The therapeutic effect of trastuzumab deruxtecan is also better than TPC; the OR was 5.00 (95% CI: 1.25-19.99). In the *BRCA* mutation population, talazoparib and olaparib showed statistically significant efficacy. The OR values were 4.47 (95% CI: 2.73-7.34) and 3.75 (95% CI: 2.20-6.40), respectively. Vinflunine plus gemcitabine, sunitinib plus capecitabine, eribulin, capecitabine, and etoposide plus cisplatin showed significant therapeutic effects, with OR values of 3.43 (95% CI: 1.46-8.03), 2.94 (95% CI: 1.17-7.38), 2.83 (95% CI: 1.42-5.66), 2.76 (95% CI: 1.26-6.07), and 1.98 (95% CI: 1.04-3.78; Fig. 4).

Adverse Events

For grades 3 to 5 adverse reactions, the incidence of neutropenia and leukopenia was high, whereas the incidence of pyrexia, headache, hypertension, and rash was low. The incidence of anemia with olaparib and talazoparib was relatively high at 16.1% and 40.2%, respectively. The incidence of hand-foot syndrome was significantly higher in the scheme containing capecitabine than in the other schemes (4% to 24%). In the scheme with eribulin, the incidence of peripheral neuropathy was significantly higher than in other schemes (5% to 8%; Supplemental Table 2, Supplemental Digital Content 1, http://links.lww.com/AJCO/A505).

Publication Bias, Consistency, Net Heat Plot

The funnel plot and Egger test showed no evidence of publication bias (Supplemental Fig. 3, Supplemental Digital Content 2, http://links.lww.com/AJCO/A506). No closed loop in the network diagram exists, suitable for consistency evaluation and not for net heat plots.

DISCUSSION

In this NMA, we aimed to evaluate the efficacy of treatment methods for mTNBC above third-line treatment through direct or indirect comparisons to facilitate clinical decision-making. Our results showed that sacituzumab govitecan exhibited the best performance in terms of PFS, OS, and ORR. Therefore, it appears that sacituzumab govitecan was the best third-line treatment drug. Trastuzumab deruxtecan also showed significant therapeutic effects and performed well in terms of PFS, OS, and ORR. Notably, trastuzumab deruxtecan is suitable for patients negative for hormone receptors and low HER2 expression. Eribulin showed significant efficacy in PFS, OS, and ORR and can be a treatment option.

TABLE 1. Characteristics of 15 Studies Included in This NMA

Study	Journal	Center	Phase	Line	Regimens	No. patients analyzed	PFS (HR, 95% CI)	OS (HR, 95% CI)	ORR, %
Bardia[14]	New England Journal of Medicine	Multicenter	III	≥ 3	Sacituzumab Govitecan TPC	468	0.41 (0.32-0.52)	0.48 (0.38-0.59)	35 (82/235) 5 (11/233)
Clemons[15]	Journal of Clinical Oncology	Multicenter	II	≥ 3	Enzastaurin + Capecitabine Capecitabine	85	1.73 (1.00-2.97)	1.77 (0.89-3.53)	12 (5/42) 12 (5/43)
Crots[16]	Lancet Oncology	Multicenter	III	≥ 3	Eribulin TPC	675	0.79 (0.64-0.96)	0.81 (0.67-0.96)	12 (57/459) 5 (10/216)
Crown[17]	Journal of Clinical Oncology	Multicenter	III	123	Sunitinib + Capecitabine Capecitabine	442	1.22 (0.95-1.58)	0.99 (0.76-1.30)	19 (40/221) 17 (36/221)
Decker[18]	BMC Cancer	Multicenter	II	23	Paclitaxel Sorafenib + Paclitaxel	60	1.80 (1.02-3.20)	2.01 (1.11-3.64)	43 (13/30) 40 (12/30)
Icli[19]	British Journal of Cancer	Multicenter	III	123	Etoposide + Cisplatin Paclitaxel	185	0.60 (0.45-0.79)	0.84 (0.61-1.15)	36 (33/91) 22 (21/94)
Kaufman[20]	Journal of Clinical Oncology	Multicenter	III	123	Eribulin Capecitabine	1102	1.08 (0.93-1.25)	0.88 (0.77-1.00)	11 (61/554) 11 (63/548)
Litton[21]	New England Journal of Medicine	Multicenter	III	≥ 1	Talazoparib TPC	333	0.54 (0.41-0.71)	0.76 (0.55-1.06)	63 (137/219) 27 (31/114)
Martin[22]	Lancet Oncology	Multicenter	III	123	Gemcitabine + Vinorelbine Vinorelbine	251	0.66 (0.50-0.88)	1.04 (0.78-1.39)	36 (45/125) 26 (33/126)
Martin[23]	Annals of Oncology	Multicenter	III	≥ 1	Vinflunine + capecitabine Capecitabine	770	0.84 (0.71-0.99)	0.98 (0.83-1.15)	27 (104/384) 23 (89/386)
Modi[24]	New England Journal of Medicine	Multicenter	III	≥ 2	Trastuzumab Deruxtecan TPC	58	0.46 (0.24-0.89)	0.48 (0.24-0.95)	50 (20/40) 17 (3/18)
Robson[25]	New England Journal of Medicine	Multicenter	III	≥ 1	Olaparib TPC	302	0.58 (0.43-0.80)	0.90 (0.66-1.23)	60 (123/205) 29 (28/97)
Winer[26]	Lancet Oncology	Multicenter	III	≥ 2	Pembrolizumab Chemotherapy	405	1.35 (1.08-1.68)	0.86 (0·69-1·06)	12 (24/203) 9 (18/202)
Yardley[27]	Clinical Breast Cancer	Multicenter	II	≥ 3	Ramucirumab + Eribulin Eribulin	122	0.83 (0.56-1.23)	0.91 (0.59-1.41)	21 (13/62) 28 (17/60)
Thomas[28]	Journal of Clinical Oncology	Multicenter	III	123	Ixabepilone + Capecitabine Capecitabine	752	0.79 (0.69-0.90)	0.90 (0.77-1.05)	35 (130/375) 14 (54/377)

HR indicates hazard ratio; NMA, network meta-analysis; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TPC, treatment of the physician's choice.

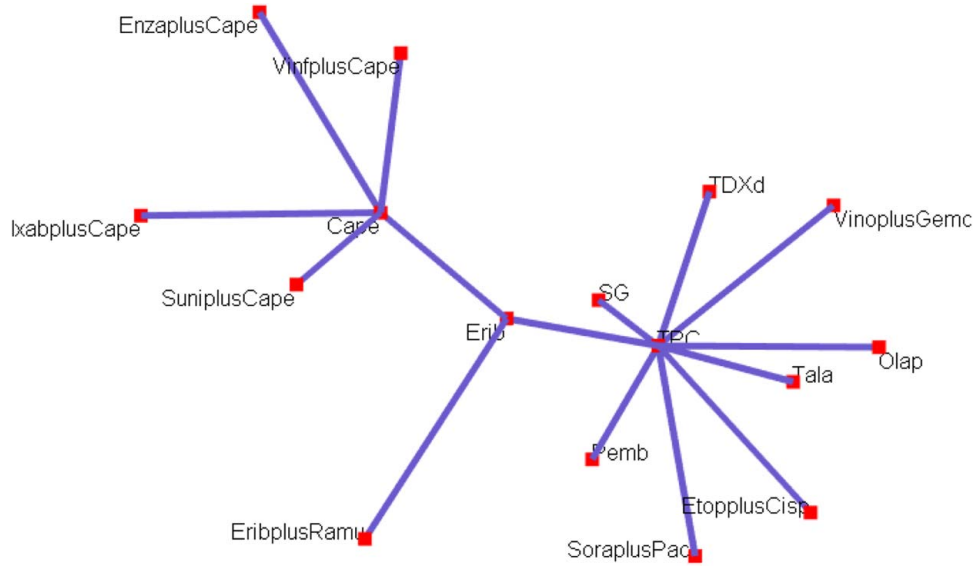

FIGURE 2. Network plot of PFS for different treatments of mTNBC. Cape indicates capecitabine; EnzaplusCape, enzastaurin plus capecitabine; Erib, eribulin; EribplusRamu, eribulin plus ramucirumab; EtopplusCisp, etoposide plus cisplatin; IxabplusCape, ixabepilone plus capecitabine; mTNBC, metastatic triple-negative breast cancer; Olap, olaparib; Pemb, pembrolizumab; PFS, progression-free survival; SG, sacituzumab govitecan; SoraplusPacl, sorafenib plus paclitaxel; SuniplusCape, sunitinib plus capecitabine; Tala, talazoparib; TDXd, trastuzumab deruxtecan; TPC, treatment physician's choice; VinfplusCape, vinflunine plus capecitabine; VinoplusGemc, vinorelbine plus gemcitabine. full color online

Sacituzumab govitecan Sacituzumab govitecan is an ADC composed of an antitrophoblast cell surface antigen 2 (Trop-2) immunoglobulin 1 kappa antibody coupled to SN-38, an active metabolite of irinotecan and a topoisomerase 1 inhibitor through a proprietary hydrolyzable linker.[29–31] Trop-2 is a transmembrane calcium signal sensor highly expressed in breast cancer and other tumor types. Anti–Trop-2 monoclonal antibodies bind to Trop-2 expressed on the surface of tumor cells and allow the targeted delivery of SN-38 to tumor cells to exert their effects.[32] Our results showed that sacituzumab govitecan exhibited the best therapeutic effects on PFS, OS, and ORR. The PFS and OS of patients receiving sacituzumab govitecan were significantly longer than those receiving chemotherapy twice or more. Overall, sacituzumab govitecan was associated with greater improvements in health-related QoL. Compared with TPC, physical and emotional functioning, global health status/QoL, and delayed worsening of QoL.[33] From the existing research results, ADC drugs have significant applications in further-line breast cancer treatment.

In TNBC, the proportion of low HER2 is ~35%, defined as a score of 1+ on IHC analysis or an IHC score of 2+ and negative results on ISH.[34] A key consideration of the DESTINY-Breast04 trial is the use of traditional HER2-IHC testing (as well as the applicable HER2-ISH testing) to identify cancers

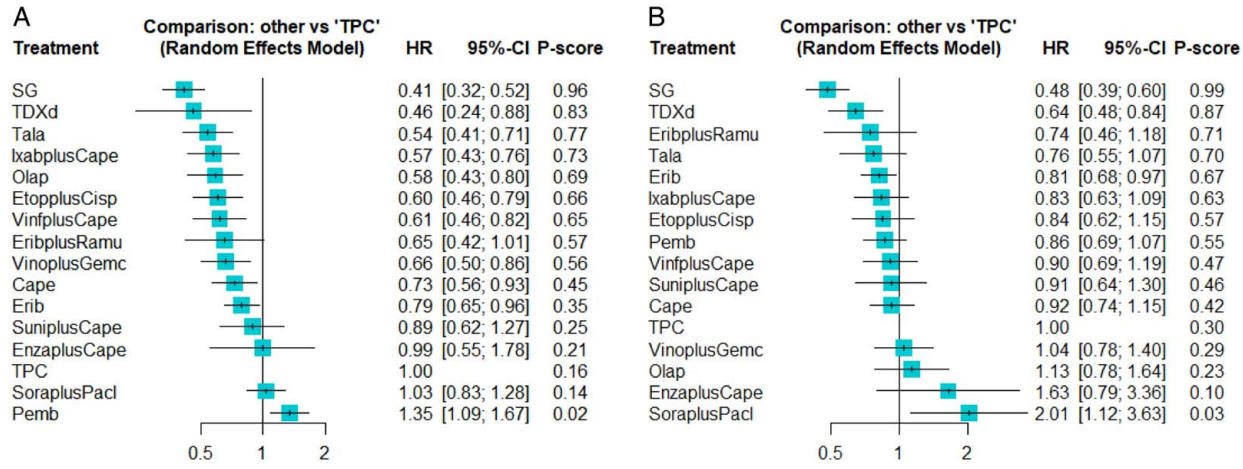

FIGURE 3. Forest plots of PFS and OS for different treatments of mTNBC. A, Forest plots of PFS. B, Forest plots of OS. Cape indicates capecitabine; EnzaplusCape, enzastaurin plus capecitabine; Erib, eribulin; EribplusRamu, eribulin plus ramucirumab; EtopplusCisp, etoposide plus cisplatin; IxabplusCape, ixabepilone plus capecitabine; mTNBC, metastatic triple-negative breast cancer; OS, overall survival; Olap, olaparib; Pemb, pembrolizumab; PFS, progression-free survival; SG, sacituzumab govitecan; SoraplusPacl, sorafenib plus paclitaxel; SuniplusCape, sunitinib plus capecitabine; Tala, talazoparib; TDXd, trastuzumab deruxtecan; TPC, treatment physician's choice; VinfplusCape, vinflunine plus capecitabine; VinoplusGemc, vinorelbine plus gemcitabine. full color online

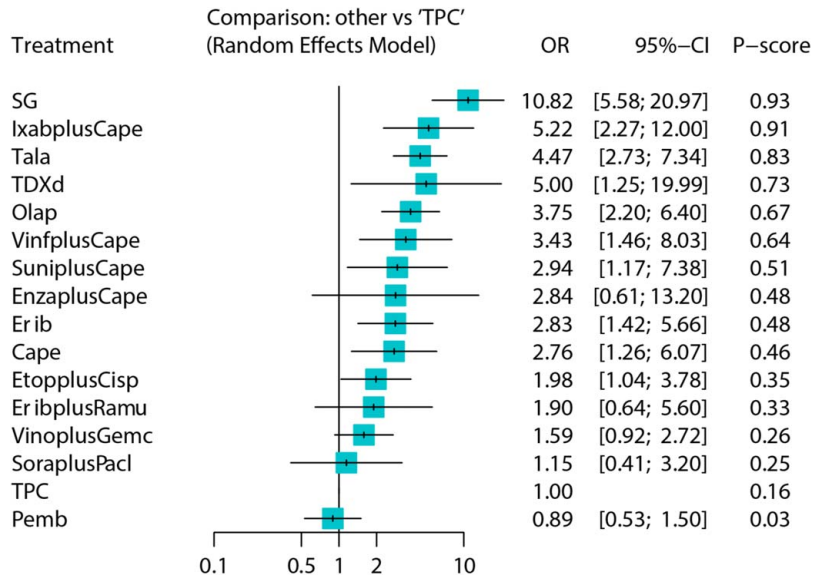

FIGURE 4. Forest plots of objective response rate for different treatments of mTNBC. Cape indicates capecitabine; EnzaplusCape, enzastaurin plus capecitabine; Erib, eribulin; EribplusRamu, eribulin plus ramucirumab; EtopplusCisp, etoposide plus cisplatin; IxabplusCape, ixabepilone plus capecitabine; mTNBC, metastatic triple-negative breast cancer; Olap, olaparib; Pemb, pembrolizumab; SG, sacituzumab govitecan; SoraplusPacl, sorafenib plus paclitaxel; SuniplusCape, sunitinib plus capecitabine; Tala, talazoparib; TDXd, trastuzumab deruxtecan; TPC, treatment physician's choice; VinfplusCape, vinflunine plus capecitabine; VinoplusGemc, vinorelbine plus gemcitabine. full color online

with low HER2 status. Therefore, patients with negative hormone receptors and low HER2 expression can be considered patients with TNBC. In this study, data from this section were included in the analysis, and the results showed that trastuzumab deruxtecan had a better ORR than chemotherapy. In addition, the proportion of three or more adverse events in the population receiving trastuzumab deruximab was lower than in the chemotherapy group.[24] Therefore, trastuzumab deruxtecan has a definite therapeutic effect on mTNBC. However, the use of trastuzumab deruxtecan was based on the premise of low expression of HER2.

Eribulin mesilate (E7389) is a non-taxane inhibitor of microtubule dynamics and belongs to the halichondrin class of antineoplastic drugs.[35] Eribulin mesilate inhibits microtubule aggregation and formation, thereby inhibiting the division and proliferation of tumor cells.[36] Eribulin has been approved for use in patients with advanced breast cancer who have received at least 2 chemotherapy regimens (the previous chemotherapy scheme should include one anthracene and one taxane drug). Our results showed that eribulin has significant therapeutic effects. Another study showed that eribulin has good therapeutic effects and controllable toxicity.[37] Therefore, eribulin was considered in the mTNBC population that had previously used anthracycline and taxane drugs.

Olaparib and talazoparib are suitable for populations with *BRCA* mutation and show statistically significant differences in PFS and ORR. Cancer cells with deleterious mutations in breast cancer susceptibility genes 1 or 2 (*BRCA1*/2) are deficient in the repair mechanism for DNA double-strand breaks, leaving these tumors highly dependent on the repair pathway for single-strand breaks. PARP regulates this pathway.[38] In cells with *BRCA1*/2 mutations, PARP inhibition causes cell death due to the accumulation of irreparable DNA damage.[39] The OlympiAD study showed the efficacy of olaparib, and it is now regarded as the standard choice for patients with metastatic *BRCA* mutation breast cancer.[25] These patients progress after first or second-line chemotherapy. Olaparib has been approved by the US Food and Drug Administration and was used in this case. In this study, we included a population of patients who had previously received treatment at or above second-line therapy, and the results confirmed its positive effect.

In the KEYNOTE-119 trial, pembrolizumab, a single drug, was compared with chemotherapy.[26] Pembrolizumab is a highly selective, humanized monoclonal anti–programmed death-protein 1 (PD-1) antibody designed to block the interaction of the receptor with PD-L1 and PD-L2, activating an antitumor response. PD-L1 is not detected in normal breast tissue but is expressed in approximately half of all breast cancers and up to 30% of TNBCs.[40] Our results show that pembrolizumab does not improve the survival rate of mTNBC-expressing PD-L1 receptors (combined positive score ≥ 1). Interestingly, pembrolizumab has demonstrated significant efficacy.[41] This may be related to the combination of pembrolizumab with chemotherapy drugs.[42,43] Further research is required to elucidate the underlying mechanisms. In addition, ixabepilone plus capecitabine, etoposide plus cisplatin, and capecitabine showed significant advantages in terms of PFS and ORR. However, they have not shown any advantages in terms of OS; therefore, it is necessary to choose the previously mentioned options carefully.

Currently, there is no standard treatment for mTBNC with multiple relapses or metastases. With the emergence of new treatment models, there has been a turnaround in the treatment of mTNBC. In particular, the success of clinical trials on ADC drugs has greatly changed the dilemma of mTNBC treatment options. Sacituzumab govitecan is a targeted therapeutic agent that reduces systemic toxicity. Compared with the limitations caused by immunotherapy targeting the expression of PD-L1 or PD-1, Sacituzumab govitecan directly targets and kills TNBC cells regardless of their immune reactivity, making it a more promising treatment option. Similarly, compared with PARP inhibitors, sacituzumab govitecan can be applied to a broader population of patients with mTNBC and is not limited to

patients with specific gene mutations (*BRCA* mutation). Furthermore, traditional chemotherapeutic drugs are highly destructive, causing significant damage to the body, and have no targeted selectivity towards tumor cells. Therefore, ADCs with targeted killing properties are preferred. Ongoing research on ADC drugs in combination with PARP, PD-L1 inhibitors, and other related drugs is also worth considering.[44]

In addition, the proposal for low HER2 expression has expanded the indications for trastuzumab deruxtecan. With the positive conclusion of the DESTINY-Breast04 study, trastuzumab deruxtecan was approved by the US Food and Drug Administration for use in cases of low HER2 expression hormone receptor-negative populations. In summary, third-line treatment methods for mTNBC are constantly evolving, multiple clinical studies are underway, and personalized treatment of mTNBC is becoming a trend.

This NMA has several limitations. First, the study included non–third-line treatments and non-TNBC populations. This may have led to a decrease in the specificity of this study for the TNBC subtype. Second, some of the research findings were based on specific biomarkers or gene mutations, making the conclusions of this section not universally applicable. Third, in the included studies, there were relatively diverse chemotherapy regimens, which may have led to differences in patient responsiveness to subsequent treatment. However, this was unavoidable because we did not have sufficient detailed data to conduct a subgroup analysis.

CONCLUSIONS

This NMA showed that sacituzumab govitecan significantly improved PFS, OS, and ORR and had the highest *P* score, deeming it an efficacious third-line treatment for mTNBC. In addition, based on different biological characteristics, we provided corresponding treatment options for selection. In terms of safety, the incidence of neutropenia and leukopenia was high, whereas the incidence of pyrexia, headache, hypertension, and rash was low. Fortunately, the survival rate of patients with mTNBC has continued to improve.

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