Long-term survival after neoadjuvant therapy for triple-negative breast cancer under different treatment regimens: a systematic review and network meta-analysis

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Abstract

Background Triple-negative breast cancer (TNBC) is a life-threatening subtype of breast cancer with limited treatment options. Therefore, this network meta-analysis (NMA) aimed to evaluate and compare the effect of various neoadjuvant chemotherapy (NCT) options on the long-term survival of patients with TNBC.

Methods PubMed, Embase, Medline, Cochrane Library, Web of Science, and major international conference databases were systematically searched for randomized controlled trials (RCTs) on the efficacy of various NCT options in patients with TNBC. Searches were performed from January 2000 to June 2023. Study heterogeneity was assessed using the I^2 statistic. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to evaluate disease-free survival (DFS) and overall survival (OS). Odds ratios (ORs) and 95% CIs were used to evaluate the pathologic complete response (pCR). The primary outcome was DFS.

Results We conducted an NMA of 21 RCTs involving 8873 patients with TNBC. Our study defined the combination of anthracyclines and taxanes as the preferred treatment option. On this basis, the addition of any of the following new drugs is considered a new treatment option: bevacizumab (B), platinum (P), poly-ADP-ribose polymerase inhibitors (PARPi), and immune checkpoint inhibitor (ICI). Based on the surface under the cumulative ranking curve (SUCRA) values, the top three SUCRA area values of DFS were taxanes, anthracycline, and cyclophosphamide (TAC; 89.23%); CT (84.53%); and B (81.06%). The top three SUCRA area values of OS were CT (83.70%), TAC (62.02%), and B-containing regimens (60.06%). The top three SUCRA area values of pCR were B + P-containing regimens (82.7%), ICI + P-containing regimens (80.2%), and ICI-containing regimens (61.8%).

Conclusions This NMA showed that standard chemotherapy is a good choice with respect to long-term survival. Moreover, B associated with P-containing regimens is likely to be the optimal treatment option for neoadjuvant TNBC in terms of pCR.

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Introduction

The latest global cancer burden data released by the World Health Organization International Agency for Research on Cancer in 2020 indicated that the number of new breast cancer cases reached 2.26 million worldwide, exceeding the total number (2.2 million) of lung cancer cases [1]. Breast cancer has replaced lung cancer to become the world's most prevalent cancer [2]. It poses a great threat to the physical and mental health of patients worldwide. Breast cancer treatment is a very long and complex process, and the cost is also very high, and even some patients give up treatment because they cannot afford the treatment cost, and further worsen the condition. Triple-negative breast cancer (TNBC) is a subtype of breast cancer characterized by the lack of receptor-estrogen and progesterone expression and amplification of human epidermal growth factor receptor 2 [3, 4]. Clinically, TNBC is one of the most aggressive subtypes of breast cancer, accounting for approximately 15%–20% of all breast cancers [5]. Endocrine therapy with hormone receptor and targeted therapy to block human epidermal growth factor receptor 2 (HER-2) have proven ineffective for patients with TNBC [6]. The clinical course of TNBC is aggressive, with a high probability of visceral and brain metastases, and its prognosis is the worst among the breast cancer subtypes [7, 8]. The BRCA 1/2 gene is particularly strongly associated with triple-negative breast cancer. In the Chinese population, the BRCA 1/2 mutation rate is less than 1% in the general population and about 3% in all breast cancer patients, and up to 17.3% in triple-negative breast cancer. From another perspective, approximately 60%-80% of breast cancer patients carrying the BRCA 1 mutation are triple-negative breast cancer, while approximately 25% of breast cancer patients carrying the BRCA 2 mutation have triple-negative breast cancer [9, 10].

Anthracyclines, cyclophosphamides, and taxanes are the preferred neoadjuvant chemotherapy (NCT) for TNBC [11, 12]. NCT can reduce the micrometastasis, shrink the tumor, reduce the stage, and increase the chance of breast preservation treatment, which improve the radical cure and breast preservation rate and obtain the drug sensitivity information [13, 14]. Studies confirm that achieving pathological complete response (pCR) after a neoadjuvant treatment with TNBC has a good predictive value for long-term survival benefits [15]. Currently, platinum (P) and poly-ADP-ribose polymerase inhibitors (PARPi) play important antitumor roles in NCT for TNBC, and their efficacy is significant in young patients, especially with BRCA gene mutations. As a DNA cross-linking agent, P cross-connects with the DNA after entering the tumor cells, which interferes with DNA replication of the tumor cells, leading to double-strand DNA breaks of the tumor cells, and then killing the tumor cells. Several single-arm or randomized controlled clinical studies including GeparSixto, CALGB40603, BrighTNess, NeoCART have confirmed the efficacy and safety of P-containing chemotherapy regimens for the treatment of TNBC [16–19].

Immune checkpoint inhibitor (ICI) therapy is directed against the interaction between the programmed death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) [20, 21]. PD-1 is a co-inhibitory molecule expressed by activated T cells when antigen-presenting cells or tumor cells are combined with PD-L1, which further lead to inhibiting the T-cell activation and suppressing the body's antitumor immune response. Moreover, the view of PD-1/PD-L1 ICI can improve the suppressed antitumor immune response to relieve the body's immune response inhibition state, further realizing the antitumor effects [22, 23]. ICI may enhance the endogenous anticancer immunity after increasing the release of tumor-specific antigens through chemotherapy. Most current studies show that ICI treatment has a better therapeutic effect and lesser toxicity in TNBC [24, 25]. Moreover, the vascular endothelial growth factor (VEGF) is an important regulator of tumor angiogenesis and metastasis [26, 27]. Bevacizumab (B) is a recombinant human monoclonal antibody against VEGF that plays various roles in the tumor blood vessels by specifically binding to VEGF and blocking its interaction with receptors [28]. Relevant studies have reported that adding B based on chemotherapeutic drugs can improve the pCR. Antivascular therapy combined with immunotherapy showed an excellent antitumor activity of different cancers [29, 30]. Liu et al. showed that antiangiogenic therapy can improve the sensitivity of PD-L1 expression and the infiltration of PD-1/PD-L1 immunotherapy, playing a synergistic sensitization effect and improving the disease-free survival (DFS) and overall survival (OS) of patients with TNBC [31, 32].

Although numerous NCT regimens are currently being used for TNBC, the clinical efficacy of different treatment regimens, especially in terms of long-term survival, remains unclear. Therefore, we conducted a Bayesian meta-analysis of randomized controlled trials

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(RCTs) to evaluate the effectiveness of different treatment regimens (long-term survival and pCR), thereby providing evidence-based medical information on NCT for TNBC in clinical practice.

Methods

Search strategy

This network meta-analysis (NMA) was performed according to the preferred reporting items for systematic reviews and meta-analyses statement [33]. PubMed, EMBASE, Medline, Cochrane Library, Web of Science, main oncology conference of American Society of Clinical Oncology, the European Society of Medical Oncology, and San Antonio Breast Cancer Symposium databases were searched for high-quality RCTs from January 2000 to June 2023. The search was performed using the following keywords without any restrictions: (triple-negative breast cancer OR triple negative breast neoplasm OR er-negative pr-negative her2-negative breast cancer OR TNBC) AND (neoadjuvant therapy OR neoadjuvant treatment OR neoadjuvant chemotherapy OR neoadjuvant chemotherapy treatment) AND (DFS OR disease free survival) AND (OS OR overall survival) AND (pCR OR pathological complete response). The reference lists of relevant studies, reviews, and meta-analyses were manually screened for potentially eligible publications.

Selection criteria

Eligible trials included those that prospectively compared at least two arms of different neoadjuvant chemotherapeutic regimens in patients with TNBC. Inclusion criteria were as follows: patients with pathologically confirmed TNBC; those with clinical stages of II and III (T1c, N1-2 or T2-4, and N0-2); and those who did not receive surgical NCT. The study end-points included event-free survival (EFS) or DFS, OS, and pCR. The exclusion criteria were as follows: studies involving patients with metastatic TNBC; non-RCTs; articles not written in English; and studies with no data regarding EFS or DFS, OS, and pCR. If several publications from the same trial were identified, only the most recent or complete publications were included.

Data extraction

Eight reviewers were divided into four groups to independently screen the articles (ZL and JL, FZ and QX, DR and ZL, and YC and SH), perform data extraction (ZL and JL and LZ and ZY), and assess the risk of bias (ZL and JL and LZ and MW). Disagreements were resolved by discussion, with assistance from a third party (GS or JZ) if necessary. The following information was recorded: study, author–year, journal, country, arms, medicine,

clinical stage, trial phase, TNBC definition, sample size, and study outcomes (EFS or DFS, OS, and pCR).

Explanation of treatment regimens and outcome definitions

Currently, the standard treatment options for TNBC are not yet established, and NCT with anthracycline and purple line represents the cornerstone historical standard for TNBC treatment [34]. Our study defined the combination of anthracyclines and taxanes as the preferred treatment option. On this basis, any addition of other therapeutic drugs is a new treatment option.

Statistical analysis

Hazards ratio (HR) and odds ratio (OR) were used to estimate pooling effect sizes. For pairwise meta-analysis, the Cochrane Q statistic and the I^2 test were used to calculate heterogeneity. Statistical heterogeneity was defined as P of < 0.1 and/or I^2 of $> 50\%$. A pairwise meta-analysis was performed using a random-effects model or a fixed-effect model depending on the presence of statistical heterogeneity. All pairwise meta-analyses were performed using the Review Manager version 5.3. Results are reported as HR, OR, and corresponding 95% confidence intervals (CIs). All *P*-values were two sided, and differences with *P* < 0.05 were considered statistically significant. A Bayesian NMA was performed using the Aggregate Data Drug Information System version 1.16.6 (http://www.drugis.org). Node splitting analyses were performed to verify the consistency between direct and indirect evidence. If no significant inconsistency was detected, a consistency model was used to analyze the relative effects of the interventions. Otherwise, an inconsistency model was applied. The "gemtc" package of the R (v14.1) software was used for sorting chats and analyze the data. The NMA results are presented as HR and its corresponding 95% CIs. The "network" packages of the Stata (v14.2) software were used for sorting chats and data analysis. The NMA results are presented as OR and corresponding 95% CIs. The rank probability for each treatment was calculated to determine the treatment ranking. When assessing the merit of the drug efficacy, the surface under the cumulative ranking curve (SUCRA) values was used. It has a value of 0 to 1, and higher SUCRA values indicate better efficacy of the agent.

Results

Study selection and characteristics of the included studies

Figure 1 illustrates the study retrieval process. A total of 10,000 results were obtained from the database, and 1500 studies were automatically removed by Zotero. Based on titles and abstracts, 120 suitable full-text studies were screened, and 31 studies were excluded due to the lack of
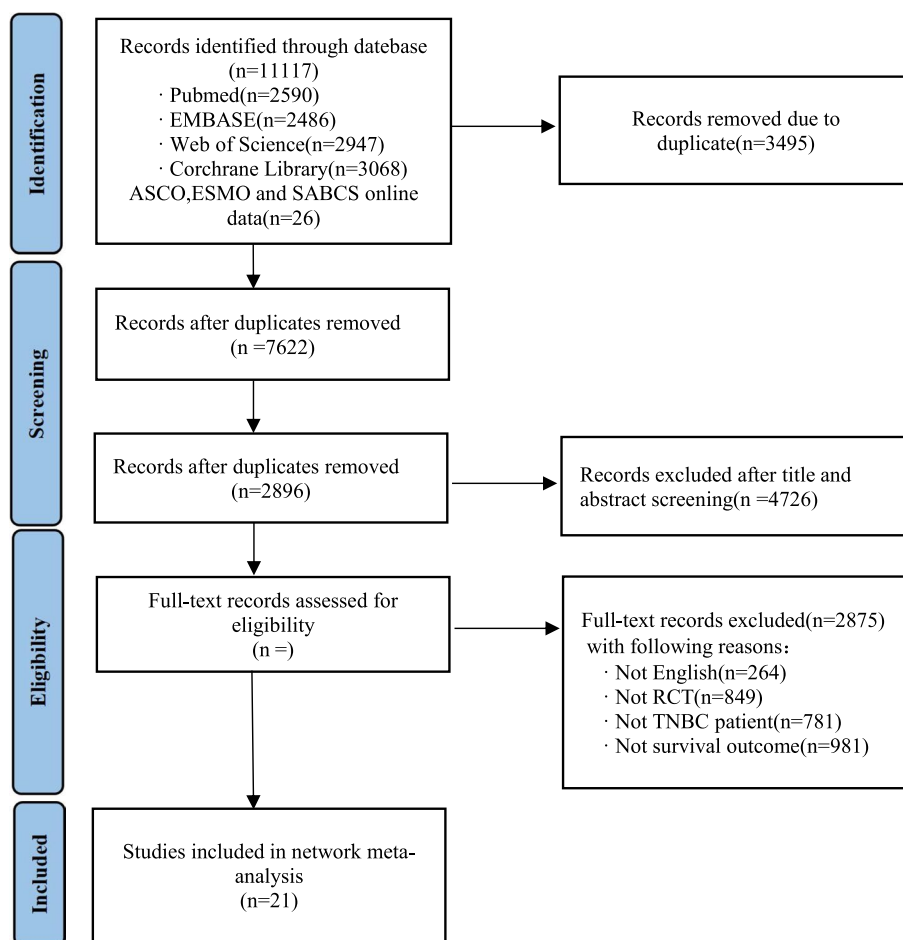
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Fig. 1 A flowchart of the study selection process

assessment results. Ultimately, 21 studies involving 8873 patients were included in our reticulated meta-analysis [16–19, 25, 34–49]. Table 1 summarizes the characteristics of the included RCTs. A total of 18 phase III trials and 3 phase II trials were identified. This study evaluated nine treatment regimens in the form of network maps: standard chemotherapeutic agents, TAC (taxanes, anthracycline, and cyclophosphamide), TC (taxanes and cyclophosphamide), B, P, B + P, P + PARPi, ICI, and ICI + P (Fig. 2).

DFS

Of the 21 studies, 20 reported data on DFS, with 3 studies including standard chemotherapy, 8 studies including P-containing regimen, 1 study including B + P-containing regimen, 4 studies including B-containing regimen, 1 study including P + PARPi-containing regimen, 2 studies including ICI-containing regimen, and 1 study including ICI + P-containing regimen, all of which were NCTs. Results showed that CT compared with P (HR, 0.8; 95% CI, 0.68–0.94), B + ICI (HR, 0.29; 95% CI, 0.12–0.73),

and B + P (HR, 0.43; 95% CI, 0.23–0.8) had a significant benefit of DFS. Figure 3A summarizes the results of DFS analysis.

A cumulative ranking of the nine treatment regimens was also analyzed. The results showed that TAC (89.23%), CT (84.53%), B (81.06%), and P (55,30%) ranked first to forth, while ICI (37.86%), ICI + P (30.94%), B + P (15.48%), and B + ICI (5.58%) ranked fifth to eighth (Fig. 3B).

OS

Of the 21 studies, 17 reported data on OS, with 3 studies including B-containing regimen, 3 studies including standard chemotherapy, 8 studies including P-containing regimen, 2 studies including ICI-containing regimen, and 1 study including PARPi + P-containing regimen, all of which were NCTs. Results showed that PARPi + P-containing regimen compared with B (HR, 0.24; 95% CI, 0.06–0.99), P (HR, 0.24; 95% CI, 0.07–0.89), and standard chemotherapy (HR, 0.21; 95% CI, 0.05–0.8) had a significant benefit of OS. Figure 4A summarizes the results of OS analysis.

Table 1 Main characteristics of the included clinical studies

Study ID	Author-year	Journal	Masking	RCT	Arms	Medicine	Clinical stage	TNBC definition	Endpoints	Total numbers	pCR (%)	HR for DFS	P value	HR for OS	P value
NATT trial	Xiaosong Chen-2013	Breast Cancer Res Treat	Open-label	RCT	2	TAC vs TC	IIB—IIIC	ER < 1% PR < 1% Her2(0−2+FISH-)	pCR EFS DFS OS	26 23	15.40% 4.30%	DFS 0.33(0.12−0.95)	0.004	0.52(0.06−0.46)	0.045
PREPARE trial(NCT00544232)	M. Untch-2011	Annals of Oncology	Open-label	RCT	2	ddE-ddT-CMF vs EC-T	IIB—IIIC	ER < 1% PR < 1% Her2(0−2+FISH-)	pCR EFS DFS OS	363 370	18.70% 13.20%	1.14(0.85−1.52)	0.37	1.26(0.86−1.85)	0.237
NeoSTOP(NCT02413320)	Priyanka Sharma-2021	Clin Cancer Res	Open-label	RCT	2	CbP-AC vs CbD	I—III	ER < 10% PR < 10% Her2(-)	pCR EFS OS	48 52	54.00% 54.00%	EFS → DFS 2.85(0.34−23.60)	> 0.05	1.83(0.28−11.76)	> 0.05
NeoCART (NCT03154749)	Liulu Zhang-2021	Int J Cancer	Open-label	RCT	2	DCb vs EC-D	II-III	ER < 1% PR < 1% Her2(0−2+FISH-)	pCR EFS OS	44 44	61.40% 38.60%	EFS → DFS 0.76(0.2−2.84)	0.683	0.96(0.19−4.76)	0.959
(UMIN000003355)	Madoka Iwase-2020	Breast Cancer Research and Treatment	Open-label	RCT	2	CbP-CEF vs P-CEF	II-III	ER(-) PR(-) Her2(0−2+FISH-)	DFS OS pCR	37 38	61.20% 26.30%	0.22(0.06−0.82)	0.015	0.12(0.01−0.96)	0.046
GeparOcto (NCT02125344)	Andreas Schneeweiss-2022	European Journal of Cancer	Open-label	RCT	2	PMCb vs iddEPC	II	ER(-) PR(-) Her2(0−2+FISH-)	pCR iDFS OS	203 200	48.00% 48.30%	0.73(0.047−1.13)	0.1562	0.66(0.38−1.15)	0.1442
WSG-ADAPT-TN (NCT01815242)	Oleg Gluz-2022	European Journal of Cancer	Open-label	RCT	2	nab-pac + Cb vs nab-pac + G	I-III	ER < 1% PR < 1% Her2(0−2+FISH-)	pCR i/dDFS OS	182 154	44.00% 28.00%	1.21(0.76−1.94)	0.424	1.06(0.63−1.78)	0.836
GeparSixto (NCT01426880)	Eric Hahnen-2017	JAMA Oncol	Open-label	RCT	2	PMBevCb vs PMBev	II-III	ER < 1% PR < 1% Her2(0−2+FISH-)	pCR DFS	158 157	53.20% 36.90%	0.53(0.29−0.96)	0.04	NA	NA
(NCT01276769)	Pin Zhang-2016	Oncotarget	Open-label	RCT	2	pac + Cb vs pacE	II-III	ER < 10% PR < 10% Her2(0−2+FISH-)	pCR RFS OS	47 44	38.60% 14.00%	(RFS → DFS) 0.35(0.13−0.96)	0.043	1.20(0.37−3.87)	0.350
CALGB 40603 (NCT00861705)	William M.Sikov-2022	J Clin Oncol	Open-label	RCT	2	pac + Cb + AC vs pac + AC	II-III	ER < 10% PR < 10% Her2(-)	pCR EFS OS	221 212	54% 41%	(EFS → DFS) 0.94(0.67−1.32)	0.7210	OS 1.12(0.77−1.61)	0.5585
(ChiCTR-TRC-14005019)	Wenting Yan-2022	Ther Adv Med Oncol	Open-label	RCT	2	TEL vs TE	I-III	ER < 10% PR < 10% Her2(0−2+FISH-)	tpCR DFS OS	99 101	41.40% 17.80%	0.44(0.21−0.90)	0.028	0.44(0.18−1.02)	0.061
Kun Wang (SABCS)	Kun Wang-2022	SABCS	Open-label	RCT	2	wPCb-AC vs wP-AC	II	NA	DFS OS pCR	365 355	55.20% 41.50%	0.79(0.61−1.02)	0.073	0.75(0.57−0.98)	0.034
I-SPY2 Trial(NCT01042379)	Nanda, R-2020	JAMA Oncol	Open-label	RCT	2	P+pac+AC vs PBO+pac+AC	I-III	ER(-) PR(-) Her2(-)	pCR EFS	29 85 168	60.00% 22.00% 41.1%	EFS → DFS 0.6(0.36−3.81)	> 0.05	NA	NA

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Table 1 (continued)

Study ID	Auther-year	Journal	Masking	RCT	Arms	Medicine	Clinical stage	TNBC definition	Endpoints	Total numbers	pCR (%)	HR for DFS	P value	HR for OS	P value
KEYNOTE-173 (NCT02622074)	P. Schmid-2020	Annals of Oncology	Open-label	RCT	6	P+Nab-pac+AC vs P+Nab-pac+Cb+AC vs P+Nab-pac+Cb+AC vs P+pac+Cb+AC vs P+pac+Cb+AC	I-III	ER <1% PR <1% Her2(0-2+FISH-)	pCR EFS OS	10 10 10 10 10 10	60% 80% 80% 60% 30% 50%	EFS→DFS NA	NA	NA	NA
KEYNOTE-522(NCT03036488)	P. Schmid-2020	New England Journal of Medicine	Open-label	RCT	2	P+pac+Cb+A/EC vs pbo+pac+Cb+A/EC	II-III	ER(-) PR(-) Her2(0-2+FISH-)	pCR EFS	784 390	64.80% 51.20%	EFS→DFS 0.63(0.48-0.82)	P <0.001	NA	NA
GeparNuevo (NCT02685059)	S. Loibl-2022	Annals of Oncology	Open-label	RCT	2	Dur+nab-pac vs PBO+nab-pac	I-III	NA	pCR iDFS DDFS OS	88 86	NA NA	DDFS→DFS 0.31(0.13-0.74)	0.005	0.24(0.08-0.72)	0.006
BrighTNess (NCT02032277)	Sibylle Loibl-2022	Annals of Oncology	Open-label	RCT	3	Paclitaxel+carboplatin+veliparib vs Paclitaxel+carboplatin+veliparib placebo vs Paclitaxel+carboplatin placebo+veliparib placebo	I-III	ER <1% PR <1% Her2(0 or 1+)	pCR EFS OS breast-conservation surgery	316 160 158	53.00% 58.00% 31.00%	EFS→DFS 1.12(0.72-1.72) (1 vs 2) 0.56(0.34-0.93) (2 vs 3)	0.62(1 vs 2) 0.02(2 vs 3)	1.25 (0.70-2.24) (1 vs 2) 0.63 (0.33-1.21) (2 vs 3)	0.46 (1 vs 2) 0.17 (2 vs 3)
NSABP-B40(NCT00408408)	Harry D Bear-2015	Lancet Oncol	Open-label	RCT	2	Bev+ vs Non-Bev	I-III	ER(-) PR(-) Her2(-)	pCR EFS	592 594	51.10% 47.10%	0.8(0.63-1.01)	0.06	0.65(0.49-0.88)	0.004
GeparQuinto(NCT00567554)	G. von Minckwitz-2014	Annals of Oncology	Open-label	RCT	2	ECB-DB vs EC-D	II-III	ER (<10%) PR (<10%) Her2(0-2+FISH-)	pCR DFS OS	323 340	39.30% 27.90%	1.03(0.84-1.25)	0.784	0.97(0.75-1.26)	0.842
SWOG S0800(NCT00856492)	Z. A. Nahleh-2016	Breast Cancer Res Treat	Open-label	RCT	2	Bev+nab-pac+ddAC vs Non-Bev-based	IIB—IIIC	ER(-) PR(-) Her2(-)	pCR DFS OS	98 113	59.40% 28.60%	EFS→DFS 0.46(0.2-1.05)	0.06	0.49(0.19-1.29)	0.14
ARTemis(NCT01093235)	H.M. Earl-2017	Annals of Oncology	Open-label	RCT	2	Bev+D-FEC vs D-FEC	NA	(ER) status as negative when Allred score was 0-2/8; ER weakly positive was 3-5/8; and ER strongly positive was 6-8/8 Her2(0-2+FISH-)	pCR DFS OS	388 393	22.00% 17.00%	1.18(0.89-1.57)	0.25	1.26(0.9-1.76)	0.19
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Kun Wang (SABCS)	Kun Wang-2022	SABCS	Open-label	RCT	2	**wPCb-AC vs wP-AC**	II	NA	DFS OS pCR	365 355	55.20% 41.50%	0.79(0.61–1.02)	0.073	0.75(0.57–0.98)	0.034
I-SPY2 Trial(NCT01042379)	Nanda, R-2020	JAMA Oncol	Open-label	RCT	2	P+pac+AC vs PBO+pac+AC	II-III	ER(-) PR(-) Her2(-)	pCR EFS	29 85 168	60.00% 22.00% 41.1%	EFS→DFS 0.6(0.36–3.81)	> 0.05	NA	NA
KEYNOTE-173 (NCT02622074)	P. Schmid-2020	Annals of Oncology	Open-label	RCT	6	P+Nab-pac+AC vs P+Nab-pac+Cb+AC vs P+Nab-pac+Cb+AC vs P+Nab-pac+Cb+AC vs P+pac+Cb+AC vs P+pac+Cb+AC	I-III	ER < 1% PR < 1% Her2(0-2 + FISH-)	pCR EFS OS	10 10 10 10 10 10	60% 80% 80% 60% 30% 50%	EFS→DFS NA	NA	NA	NA
KEYNOTE-522(NCT03036488)	P. Schmid-2020	New England Journal of Medicine	Open-label	RCT	2	P+pac+Cb+A/EC vs pbo+pac+Cb+A/EC	II-III	ER(-) PR(-) Her2(0-2 + FISH-)	pCR EFS	784 390	64.80% 51.20%	EFS→DFS 0.63(0.48–0.82)	P < 0.001	NA	NA

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Table 1 (continued)

Study ID	Author-year	Journal	Masking	RCT	Arms	Medicine	Clinical stage	TNBC definition	Endpoints	Total numbers	pCR (%)	HR for DFS	P value	HR for OS	P value
GeparNuevo (NCT02685059)	S. Loibl-2022	Annals of Oncology	Open-label	RCT	2	Dur+nab-pac vs PBO+nab-pac	I–III	NA	pCR iDFS DDFS OS	88 86	NA NA	DDFS→DFS 0.31(0.13–0.74)	0.005	0.24(0.08–0.72)	0.006
BrighTNess (NCT02032277)	Sibylle Loibl-2022	Annals of Oncology	Open-label	RCT	3	Paclitaxel+carboplatin+veliparib vs Paclitaxel+carboplatin+veliparib placebo vs Paclitaxel+carboplatin placebo+veliparib placebo	I–III	ER<1% PR<1% Her2(0 or 1+)	pCR EFS OS breast-conservation surgery	316 160 158	53.00% 58.00% 31.00%	EFS→DFS 1.12(0.72–1.72) (1 vs 2) 0.56(0.34–0.93) (2 vs 3)	0.62(1 vs 2) 0.02(2 vs 3)	1.25 (0.70–2.24) (1 vs 2) 0.63(0.33–1.21) (2 vs 3)	0.46 (1 vs 2) 0.17 (2 vs 3)
NSABP-B40(NCT00408408)	Harry D Bear-2015	Lancet Oncol	Open-label	RCT	2	Bev+ vs Non-Bev	I–III	ER(-) PR(-) Her2(-)	pCR EFS	592 594	51.10% 47.10%	0.8(0.63–1.01)	0.06	0.65(0.49–0.88)	0.004
GeparQuinto(NCT00567554)	G. von Minckwitz-2014	Annals of Oncology	Open-label	RCT	2	ECB-DB vs EC-D	II-III	ER (<10%) PR (<10%) Her2(0-2+FISH-)	pCR DFS OS	323 340	39.30% 27.90%	1.03(0.84–1.25)	0.784	0.97(0.75–1.26)	0.842
SWOG S0800(NCT00856492)	Z. A. Nahleh-2016	Breast Cancer Res Treat	Open-label	RCT	2	Bev+nab-pac+ddAC vs Non-Bev-based	IIB—IIIC	ER(-) PR(-) Her2(-)	pCR DFS OS	98 113	59.40% 28.60%	EFS→DFS 0.46(0.2–1.05)	0.06	0.49(0.19–1.29)	0.14
ARTemis(NCT01093235)	H.M. Earl-2017	Annals of Oncology	Open-label	RCT	2	Bev+D-FEC vs D-FEC	NA	(ER) status as negative when Allred score was 0–2/8; ER weakly positive was 3–5/8; and ER strongly positive was 6–8/8 Her2(0-2+FISH-)	pCR DFS OS	388 393	22.00% 17.00%	1.18(0.89–1.57)	0.25	1.26(0.9–1.76)	0.19
Study ID	Author-year	Journal	Masking	RCT	Arms	Medicine	Clinical stage	TNBC definition	Endpoints	Total numbers	pCR (%)	HR for DFS	P value	HR for OS	P value
NATT trial	Xiaosong Chen-2013	Breast Cancer Res Treat	Open-label	RCT	2	TAC vs TC	IIB—IIIC	ER<1% PR<1% Her2(0-2+FISH-)	pCR EFS DFS OS	26 23	15.40% 4.30%	DFS 0.33(0.12–0.95)	0.004	0.52(0.06–0.46)	0.045
PREPARE trial(NCT00544232)	M. Untch-2011	Annals of Oncology	Open-label	RCT	2	ddE-ddT-CMF vs EC-T	IIB—IIIC	ER<1% PR<1% Her2(0-2+FISH-)	pCR EFS DFS OS	363 370	18.70% 13.20%	1.14(0.85–1.52)	0.37	1.26(0.86–1.85)	0.237
NeoSTOP(NCT02413320)	Priyanka Sharma-2021	Clin Cancer Res	Open-label	RCT	2	CbP-AC vs CbD	I—III	ER<10% PR<10% Her2(-)	pCR EFS OS	48 52	54.00% 54.00%	EFS→DFS 2.85(0.34–23.60)	>0.05	1.83(0.28–11.76)	>0.05
NeoCART (NCT03154749)	Liulu Zhang-2021	Int J Cancer	Open-label	RCT	2	DCb vs EC-D	II-III	ER<1% PR<1% Her2(0-2+FISH-)	pCR EFS OS	44 44	61.40% 38.60%	EFS→DFS 0.76(0.2–2.84)	0.683	0.96(0.19–4.76)	0.959
(UMIN000003355)	Maddoka Iwase-2020	Breast Cancer Research and Treatment	Open-label	RCT	2	CbP-CEF vs P-CEF	II-III	ER(-) PR(-) Her2(0-2+FISH-)	DFS OS pCR	37 38	61.20% 26.30%	0.22(0.06–082)	0.015	0.12(0.01–0.96)	0.046

Table 1 (continued)

Study ID	Auther-year	Journal	Masking	RCT	Arms	Medicine	Clinical stage	TNBC definition	Endpoints	Total numbers	pCR (%)	HR for DFS	P value	HR for OS	P value
GeparOcto (NCT02125344)	Andreas Schneeweiss-2022	European Journal of Cancer	Open-label	RCT	2	PMCb vs iddEPC	II	ER(-) PR(-) Her2(0-2+FISH-)	pCR iDFS OS	203 200	48.00% 48.30%	0.73(0.47-1.13)	0.1562	0.66(0.38-1.15)	0.1442
WSG-ADAPT-TN (NCT01815242)	Oleg Gluz-2022	European Journal of Cancer	Open-label	RCT	2	nab-pac+Cb vs nab-pac+G	I-III	ER<1% PR<1% Her2(0-2+FISH-)	pCR i/dDFS OS	182 154	44.00% 28.00%	1.21(0.76-1.94)	0.424	1.06(0.63-1.78)	0.836
GeparSixto (NCT01426880)	Eric Hahnen-2017	JAMA Oncol	Open-label	RCT	2	PMBevCb vs PMBev	II-III	ER<1% PR<1% Her2(0-2+FISH-)	pCR DFS	158 157	53.20% 36.90%	0.53(0.29-0.96)	0.04	NA	NA
(NCT01276769)	Pin Zhang-2016	Oncotarget	Open-label	RCT	2	pac+Cb vs pacE	II-III	ER<10% PR<10% Her2(0-2+FISH-)	pCR RFS DFS	47 44	38.60% 14.00%	(RFS→DFS) 0.35(0.13-0.96)	0.043	1.20(0.37-3.87)	0.350
CALGB 40603 (NCT00861705)	William M.Sikov-2022	J Clin Oncol	Open-label	RCT	2	pac+Cb+AC vs pac+AC	II-III	ER<10% PR<10% Her2(-)	pCR EFS OS	221 212	54% 41%	(EFS→DFS) 0.94(0.67-1.32)	0.7210	OS 1.12(0.77-1.61)	0.5585
(ChiCTR-TRC-14005019)	Wenting Yan-2022	Ther Adv Med Oncol	Open-label	RCT	2	TEL vs TE	I-III	ER<10% PR<10% Her2(0-2+FISH-)	tpCR DFS OS	99 101	41.40% 17.80%	0.44(0.21-0.90)	0.028	0.44(0.18-1.02)	0.061
Kun Wang (SABCS)	Kun Wang-2022	SABCS	Open-label	RCT	2	wPCb-AC vs wP-AC	II	NA	DFS OS pCR	365 355	55.20% 41.50%	0.79(0.61-1.02)	0.073	0.75(0.57-0.98)	0.034
I-SPY2 Trial(NCT01042379)	Nanda, R-2020	JAMA Oncol	Open-label	RCT	2	P+pac+AC vs PBO+pac+AC	II-III	ER(-) PR(-) Her2(-)	pCR EFS	29 85 168	60.00% 22.00% 41.1%	EFS→DFS 0.6(0.36-3.81)	>0.05	NA	NA
KEYNOTE-173(NCT02622074)	P. Schmid-2020	Annals of Oncology	Open-label	RCT	6	P+Nab-pac+AC vs P+Nab-pac+Cb+AC vs P+Nab-pac+Cb+AC vs P+Nab-pac+Cb+AC vs P+pac+Cb+AC vs P+pac+Cb+AC	II-III	ER<1% PR<1% Her2(0-2+FISH-)	pCR EFS OS	10 10 10 10 10 10	60% 80% 80% 60% 30% 50%	EFS→DFS NA	NA	NA	NA
KEYNOTE-522(NCT03036488)	P. Schmid-2020	New England Journal of Medicine	Open-label	RCT	2	P+pac+Cb+A/EC vs pbo+pac+Cb+A/EC	II-III	ER(-) PR(-) Her2(0-2+FISH-)	pCR EFS	784 390	64.80% 51.20%	EFS→DFS 0.63(0.48-0.82)	P<0.001	NA	
GepanNuevo (NCT02685059)	S. Loibl-2022	Annals of Oncology	Open-label	RCT	2	Dur+nab-pac vs PBO+nab-pac	I-III	NA	pCR iDFS DDFS OS	88 86	NA NA	DDFS→DFS 0.31(0.13-0.74)	0.005	0.24(0.08-0.72)	0.006
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Table 1 (continued)

Study ID	Author-year	Journal	Masking	RCT	Arms	Medicine	Clinical stage	TNBC definition	Endpoints	Total numbers	pCR (%)	HR for DFS	P value	HR for OS	P value
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GeparQuinto(NCT00567554)	G. von Minckwitz-2014	Annals of Oncology	Open-label	RCT	2	ECB-DB vs EC-D	II–III	ER (< 10%) PR (< 10%) Her2(0–2 + FISH-)	pCR DFS OS	323 340	39.30% 27.90%	1.03(0.84–1.25)	0.784	0.97(0.75–1.26)	0.842
SWOG S0800(NCT00856492)	Z. A. Nahleh-2016	Breast Cancer Res Treat	Open-label	RCT	2	Bev + nab-pac + ddAC vs Non-Bev-based	IIB—IIIC	ER(-) PR(-) Her2(-)	pCR DFS OS	98 113	59.40% 28.60%	EFS→DFS 0.46(0.2–1.05)	0.06	0.49(0.19–1.29)	0.14
ARTemis(NCT01093235)	H.M. Earl-2017	Annals of Oncology	Open-label	RCT	2	Bev + D-FEC vs D-FEC	NA	(ER) status as negative when Allred score was 0–2/8; ER weakly positive was 3–5/8; and ER strongly positive was 6–8/8 Her2(0–2 + FISH-)	pCR DFS OS	388 393	22.00% 17.00%	1.18(0.89–1.57)	0.25	1.26(0.9–1.76)	0.19

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Fig. 2 Network plots for eligible comparisons were included in the network meta-analysis. **A** Network diagram of the disease-free survival (DFS). **B** Network diagram of the overall survival (OS). **C** Network diagram of the pathological complete response (pCR)

A cumulative ranking of the nine treatment regimens was also analyzed. The results showed that CT (83.70%), TAC (62.02%), and B-containing regimens (60.06%) ranked first to third, while P-containing regimens (58.89%), ICI-containing regimens (31.48%), and PARPi + P-containing regimens (3.85%) ranked forth to sixth (Fig. 4B).

pCR

All 21 included trials reported pCR, with 3 studies including standard chemotherapy, 8 studies including P-containing regimen, 1study including B + P-containing regimen, 4 studies including B-containing regimen, 1 study including P + PARPi-containing regimen, 2 studies including ICI-containing regimen, and 2 studies including ICI + P-containing regimen, all of which were NCTs. The incidence of pCR in the PARPi + P-containing regimen (OR, 0.43; 95% CI, − 0.02 to 0.89), P-containing regimen (OR, 0.43; 95% CI, 0.24–0.62), and B-containing regimen (OR, 0.34; 95% CI, 0.06–0.63) was significantly higher than that of standard chemotherapeutic agents. Figure 5A summarizes the results of pCR analysis.

A cumulative ranking of the nine treatment regimens was also analyzed. The results showed that B + P-containing regimens (82.7%), ICI + P-containing regimens (80.2%), ICI-containing regimens (61.8%), and P-containing regimens (55.0%) ranked first to forth, while PARPi + P-containing regimens (53.5%), B-containing regimens (44.4%), CT (20.5%), TAC (1.8%), and TC (1.5%) ranked fifth to ninth (Fig. 5B).

Discussion

Currently, the combination of P, B, PARPi, and ICI based on anthracyclines, cyclophosphamides, and taxanes has paved a new avenue for TNBC treatment [50–54]. However, the long-term survival after neoadjuvant treatment in patients with TNBC under different treatment regimens remains unclear. Therefore, we conducted a Bayesian meta-analysis of RCTs to evaluate the effectiveness of different treatment regimens (long-term survival and pCR) and provide evidence-based medical information on NCT for TNBC in clinical practice. The results showed that, based on SUCRA values, standard chemotherapy is still a better choice for long-term survival consideration compared with NCT for TNBC, and the B + P-containing regimen is most likely the optimal NCT option for TNBC based on pCR results.

In 2022, Li et al [53]. published an NMA evaluating eight neoadjuvant treatment options for TNBC. The treatment regimen included the combination of P, B, PARPi, and ICI. In this previous study, the observation indicator was pCR; our study added survival indicators to determine the efficacy ranking of several treatment options for TNBC.

This study included 21 RCTs involving 8873 patients with TNBC. Of these, 20 RCTs reported data on DFS; however, only 7 RCTs reported statistical significance for DFS, with 2 studies using standard chemotherapies,
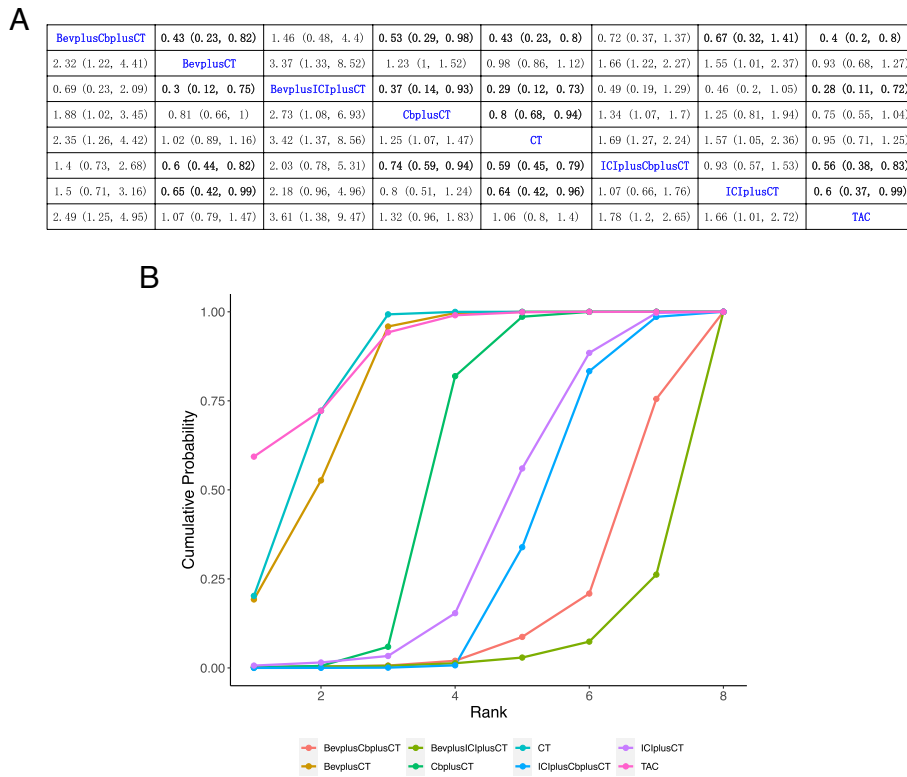
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A

BevplusCbplusCT	0.43 (0.23, 0.82)	1.46 (0.48, 4.4)	0.53 (0.29, 0.98)	0.43 (0.23, 0.8)	0.72 (0.37, 1.37)	0.67 (0.32, 1.41)	0.4 (0.2, 0.8)
2.32 (1.22, 4.41)	BevplusCT	3.37 (1.33, 8.52)	1.23 (1, 1.52)	0.98 (0.86, 1.12)	1.66 (1.22, 2.27)	1.55 (1.01, 2.37)	0.93 (0.68, 1.27)
0.69 (0.23, 2.09)	0.3 (0.12, 0.75)	BevplusICIplusCT	0.37 (0.14, 0.93)	0.29 (0.12, 0.73)	0.49 (0.19, 1.29)	0.46 (0.2, 1.05)	0.28 (0.11, 0.72)
1.88 (1.02, 3.45)	0.81 (0.66, 1)	2.73 (1.08, 6.93)	CbplusCT	0.8 (0.68, 0.94)	1.34 (1.07, 1.7)	1.25 (0.81, 1.94)	0.75 (0.55, 1.04)
2.35 (1.26, 4.42)	1.02 (0.89, 1.16)	3.42 (1.37, 8.56)	1.25 (1.07, 1.47)	CT	1.69 (1.27, 2.24)	1.57 (1.05, 2.36)	0.95 (0.71, 1.25)
1.4 (0.73, 2.68)	0.6 (0.44, 0.82)	2.03 (0.78, 5.31)	0.74 (0.59, 0.94)	0.59 (0.45, 0.79)	ICIplusCbplusCT	0.93 (0.57, 1.53)	0.56 (0.38, 0.83)
1.5 (0.71, 3.16)	0.65 (0.42, 0.99)	2.18 (0.96, 4.96)	0.8 (0.51, 1.24)	0.64 (0.42, 0.96)	1.07 (0.66, 1.76)	ICIplusCT	0.6 (0.37, 0.99)
2.49 (1.25, 4.95)	1.07 (0.79, 1.47)	3.61 (1.38, 9.47)	1.32 (0.96, 1.83)	1.06 (0.8, 1.4)	1.78 (1.2, 2.65)	1.66 (1.01, 2.72)	TAC

Fig. 3 Bayesian network meta-analysis for disease-free survival (DFS). **A** League comparison table. Data are expressed as hazards ratio (HR) and 95% confidence interval (CI). HR of < 1 supports column definition processing, whereas HR of > 1 supports row definition processing. **B** Plot of sequencing probabilities for nine DFS schemes. The larger the area of the curve and the X-axis, the higher the recommended treatment

A

BevplusCT	1.01 (0.57, 1.75)	0.87 (0.55, 1.29)	1.54 (0.54, 4.28)	4.18 (1.01, 17.01)	0.99 (0.51, 2.03)
0.99 (0.57, 1.76)	CbplusCT	0.86 (0.58, 1.24)	1.53 (0.55, 4.21)	4.14 (1.12, 15.23)	0.98 (0.52, 1.99)
1.15 (0.78, 1.8)	1.16 (0.81, 1.72)	CT	1.78 (0.69, 4.59)	4.82 (1.25, 18.81)	1.15 (0.68, 2.09)
0.65 (0.23, 1.86)	0.65 (0.24, 1.83)	0.56 (0.22, 1.45)	ICIplusCT	2.7 (0.52, 14.32)	0.64 (0.22, 2.03)
0.24 (0.06, 0.99)	0.24 (0.07, 0.89)	0.21 (0.05, 0.8)	0.37 (0.07, 1.91)	PARPiplusCbplusCT	0.24 (0.06, 1.05)
1.01 (0.49, 1.96)	1.02 (0.5, 1.93)	0.87 (0.48, 1.47)	1.56 (0.49, 4.49)	4.19 (0.95, 17.68)	TAC
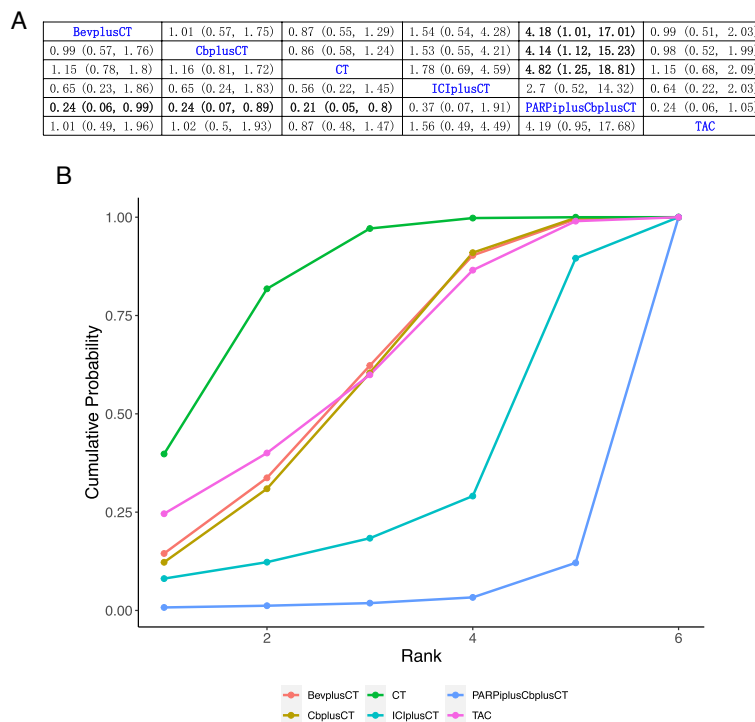
Fig. 4 Bayesian network meta-analysis of the overall survival (OS). **A** League comparison table. Data are expressed as hazards ratio (HR) and 95% confidence interval (CI). HR of < 1 supports the column definition processing, whereas HR of > 1 supports the row definition processing. **B** Plot of sequencing probabilities for nine OS schemes. The larger the area of the curve and the X-axis, the higher the recommended treatment

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A

TC	1.26 (-0.91,3.43)	2.04 (-0.25,4.33)	2.30 (0.02,4.58)	2.19 (-0.10,4.47)	2.04 (-0.21,4.29)	1.61 (-0.64,3.86)	2.35 (0.07,4.63)	1.95 (-0.31,4.22)
-1.26 (-3.43,0.91)	TAC	0.78 (0.04,1.51)	1.04 (0.35,1.73)	0.92 (0.20,1.64)	0.77 (0.17,1.38)	0.35 (-0.23,0.92)	1.09 (0.38,1.80)	0.69 (0.04,1.34)
-2.04 (-4.33,0.25)	-0.78 (-1.51,-0.04)	PARPi+Cb+CT	0.26 (-0.31,0.83)	0.14 (-0.46,0.75)	-0.00 (-0.45,0.44)	-0.43 (-0.89,0.02)	0.31 (-0.29,0.90)	-0.09 (-0.62,0.44)
-2.30 (-4.58,-0.02)	-1.04 (-1.73,-0.35)	-0.26 (-0.83,0.31)	ICI+CT	-0.11 (-0.61,0.38)	-0.26 (-0.63,0.10)	-0.69 (-1.07,-0.31)	0.05 (-0.49,0.58)	-0.35 (-0.81,0.12)
-2.19 (-4.47,0.10)	-0.92 (-1.64,-0.20)	-0.14 (-0.75,0.46)	0.11 (-0.38,0.61)	ICI+Cb+CT	-0.15 (-0.58,0.29)	-0.58 (-1.00,-0.15)	0.16 (-0.41,0.74)	-0.23 (-0.74,0.27)
-2.04 (-4.29,0.21)	-0.77 (-1.38,-0.17)	0.00 (-0.44,0.45)	0.26 (-0.10,0.63)	0.15 (-0.29,0.58)	Cb+CT	-0.43 (-0.62,-0.24)	0.31 (-0.09,0.71)	-0.09 (-0.41,0.24)
-1.61 (-3.86,0.64)	-0.35 (-0.92,0.23)	0.43 (-0.02,0.89)	0.69 (0.31,1.07)	0.58 (0.15,1.00)	0.43 (0.24,0.62)	CT	0.74 (0.33,1.15)	0.34 (0.06,0.63)
-2.35 (-4.63,-0.07)	-1.09 (-1.80,-0.38)	-0.31 (-0.90,0.29)	-0.05 (-0.58,0.49)	-0.16 (-0.74,0.41)	-0.31 (-0.71,0.09)	-0.74 (-1.15,-0.33)	Bev+Cb+CT	-0.40 (-0.80,0.01)
-1.95 (-4.22,0.31)	-0.69 (-1.34,-0.04)	0.09 (-0.44,0.62)	0.35 (-0.12,0.81)	0.23 (-0.27,0.74)	0.09 (-0.24,0.41)	-0.34 (-0.63,-0.06)	0.40 (-0.01,0.80)	Bev+CT

B
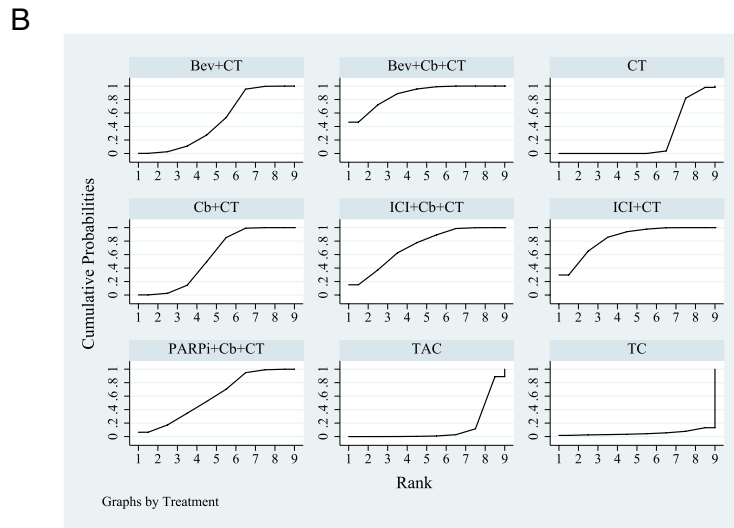
Fig. 5 Bayesian network meta-analysis of pathological complete response (pCR). **A** The league table of comparisons. Data are presented as odds radio (OR) and 95% confidence intervals (CI). An OR of > 1 favors the column-defining treatment, and an OR of < 1 favors the row-defining treatment. **B** Cumulative sequence diagram of nine pCR schemes. The higher the SUCRA value, the higher the ranking

3 studies using P-containing regimens, 1 using ICI-containing regimens, and 1 trial using B + P-containing regimens. Longer survival was also reported in the remaining 13 trials without significant statistical significance. Due to limited DFS data, we treated data regarding EFS, relapse-free survival, and distant DFS reported in these studies as DFS data; however, the significant DFS data remained somewhat unsatisfactory. It may be related to the small number of patients included in the study or the lack of relevant data. When we summarized 20 studies based on SUCRA values, the proportion of studies using standard chemotherapy was relatively high, and the top three treatment options were standard chemotherapy (89.23%), B-containing regimens (81.06%), and P-containing regimens (55.30%).

In our NMA, 17 of 21 trials reported data on OS, but only 5 of them reported statistical significance for OS, which included 1 study using standard chemotherapy, 2 studies using P-containing regimens, 1 study using ICI-containing regimens, and 1 study using B-containing regimens. Longer survival was also reported in the remaining 12 trials, but without significant statistical significance. This may be related to the small number of patients included in the study or the short follow-up time; however, the addition of P, B, and ICI to the standard

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chemotherapy can partly prolong the OS of patients with TNBC [55–59]. Further large-scale clinical trials are warranted to confirm their efficacy in the future. In terms of OS, when we summarized 17 studies based on SUCRA values, a high proportion of studies were based on standard chemotherapy, and the top three treatment options were standard chemotherapy (83.70%), B-containing regimens (60.06%), and P-containing regimens (58.89%).

All 21 trials reported pCR data, which were shown to be statistically significant. Compared with standard chemotherapeutic agents alone, P-containing regimens, PARPi-containing regimens, or neoadjuvant regimens based on B or ICI showed significant associations with better pCR. Moreover, a recent paired meta-analysis revealed that NCT based on the above regimens significantly improved pCR in patients with TNBC compared with standard chemotherapy [53], which is consistent with our findings. The results of reticulation analysis based on SUCRA values suggested that B + P-containing regimens are most likely the optimal NCT option for TNBC. The subsequent regimens were ICI + P (80.2%) and ICI (61.8%), and the final recommendation was standard chemotherapy.

This study has some limitations. First, the small number of clinical patients included in these studies or insufficient follow-up time may have caused a bias on the study results. Second, the RCTs included in this study were mainly based on standard chemotherapy, and the proportion of pairs among nine neoadjuvant regimens was small, which may have led to missing indirect contrast data, resulting in inaccurate estimation of the optimal treatment regimen. Third, although we included survival indicators, survival data of different treatment regimens remained insufficient. However, we believe that the use of our carefully pooled data and statistical methods can overcome these limitations of reticulation analysis.

Conclusions

This NMA demonstrated that standard chemotherapy is a good choice with respect to long-term survival, and B-containing regimens are associated with significantly higher pCR rates among patients with neoadjuvant TNBC. Future research should focus on evaluating larger clinical studies to obtain further survival data to help optimize personalized treatment for patients with TNBC.

Abbreviations

TNBC	Triple-negative breast cancer
NMA	Network meta-analysis
NCT	Neoadjuvant chemotherapy
RCTs	Randomized controlled trials
HR	Hazard ratio
CI	Confidence interval
DFS	Disease-free survival
OS	Overall survival
ORs	Odds ratios
pCR	Pathologic complete response
B	Bevacizumab
P	Platinum
PARPi	Poly-ADP-ribose polymerase inhibitors
ICI	Immune checkpoint inhibitor
SUCRA	Surface under the cumulative ranking curve
PD-1	Programmed death protein 1
PD-L1	Programmed death ligand 1
VEGF	Vascular endothelial growth factor
EFS	Event-free survival

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