The Breast 66 (2022) 126–135

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

Neoadjuvant therapy in triple-negative breast cancer: A systematic review and network meta-analysis

Ying-Yi Lin [a,b,1], Hong-Fei Gao [b,1], Xin Yang [a,c,1], Teng Zhu [b], Xing-xing Zheng [b,d], Fei Ji [b], Liu-Lu Zhang [b], Ci-Qiu Yang [b], Mei Yang [b], Jie-Qing Li [b], Min-Yi Cheng [b], Kun Wang [a,b,*]

[a] Shantou University Medical College, Shantou, 515041, Guangdong, China
[b] Department of Breast Cancer, Cancer Center, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, 510080, Guangdong, China
[c] Department of Anesthesiology, the First Affiliated Hospital of Shantou University Medical College, 57 Changping Road, Shantou, 515041, Guangdong, China
[d] Southern Medical University, Guangzhou, 510515, Guangdong, China

ARTICLE INFO

Keywords:
Neoadjuvant therapy
Triple-negative breast cancer
Network meta-analysis

ABSTRACT

Background: Evidence for the preferred neoadjuvant therapy regimen in triple-negative breast cancer (TNBC) is not yet established.

Methods: Literature search was conducted from inception to February 12, 2022. Phase 2 and 3 randomized controlled trials (RCTs) investigating neoadjuvant therapy for TNBC were eligible. The primary outcome was pathologic complete response (pCR); the secondary outcomes were all-cause treatment discontinuation, disease-free survival or event-free survival (DFS/EFS), and overall survival. Odd ratios (OR) with 95% credible intervals (CrI) were used to estimate binary outcomes; hazard ratios (HR) with 95% CrI were used to estimate time-to-event outcomes. Bayesian network meta-analysis was implemented for each endpoint. Sensitivity analysis and network meta-regression were done.

Results: 41 RCTs (N = 7109 TNBC patients) were eligible. Compared with anthracycline- and taxane-based chemotherapy (ChT), PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT was associated with a significant increased pCR rate (OR 3.95; 95% CrI 1.81–9.44) and a higher risk of premature treatment discontinuation (3.25; 1.26–8.29). Compared with dose-dense anthracycline- and taxane-based ChT, the combined treatment was not associated with significantly improved pCR (OR 2.57; 95% CrI 0.69–9.92). In terms of time-to-event outcomes, PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT was associated with significantly improved DFS/EFS (HR 0.42; 95% CrI 0.19–0.81).

Conclusions: PD-1 inhibitor plus platinum and anthracycline- and taxane-based ChT was currently the most efficacious regimen for pCR and DFS/EFS improvement in TNBC. The choice of chemotherapy backbone, optimization of patient selection with close follow-up and proactive symptomatic managements are essential to the antitumor activity of PD-1 inhibitor.

1. Introduction

Breast cancer is the most commonly diagnosed cancer worldwide and is the fifth leading cause of cancer mortality globally and the top cause of cancer death in women [1]. Triple-negative breast cancer (TNBC), defined by the absence of estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor-2 (HER2) expression, accounts for approximately 15–20% of all breast cancer cases and remains a challenge for clinicians due to its aggressive nature and scarcity of effective treatment options comparable to endocrine therapy for ER-positive and anti-HER2 agents for HER2-positive breast cancer [2–4].

Neoadjuvant chemotherapy (ChT) has been widely accepted as the standard-of-care for early TNBC to preemptively predict tumor response and to give adequate adjuvant treatments [5]. Pathologic complete response (pCR) of TNBC after neoadjuvant ChT was shown to predict

* Corresponding author. Department of Breast Cancer, Cancer Center, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, 510080, China.
E-mail address: gzwangkun@126.com (K. Wang).
[1] These authors have contributed equally to this work and share first authorship.

https://doi.org/10.1016/j.breast.2022.08.006
Received 7 April 2022; Received in revised form 5 August 2022; Accepted 15 August 2022
Available online 20 August 2022
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long-term clinical benefits [6,7], and can serve as an intermediate for improved survival [8]. Conventional neoadjuvant ChT regimen consisting of anthracycline, cyclophosphamide, and taxane resulted in a pCR rate of 35–45% [9]. Considerable effort has been undertaken to explore neoadjuvant therapy combinations that can yield higher pCR rates in TNBC patients. However, there are concerns about the balance of clinical benefits and harms regarding combination cancer therapy, and conclusive evidence of the optimal neoadjuvant treatment option for TNBC is still insufficient. To better inform clinical practice, we performed a systematic review and network meta-analysis of randomized controlled trials (RCTs) to estimate the comparative efficacy and acceptability of existing neoadjuvant regimens in early TNBC.

2. Methods

This network meta-analysis (PROSPERO CRD42021264094) was conducted following the PRISMA extension statement for network meta-analysis (eTable 1).

2.1. Data sources and search strategy

A literature search in PubMed, Embase, Web of Science, and Cochrane Central Register of Clinical trials as well as online archives of American Society of Clinical Oncology, European Society of Medical Oncology, and San Antonio Breast Cancer Symposium was conducted from inception to April 28, 2021. A repeated literature search was conducted from inception to February 12, 2022, to identify any updated publications. Citation lists of relevant literature were also reviewed for eligible studies. Only English publications were included. The complete list of search terms is provided in Appendix 1.

2.2. Study selection

Studies identification was performed by two investigators (YYL and HFG) independently, and disagreements were resolved by consensus. Only the most recent and informative publications were included the analysis in the case of duplicate studies. Phase 2 and 3 RCTs investigating neoadjuvant ChT with or without targeted therapies or immunotherapies in TNBC were identified. Inclusion criteria were: (1) trials enrolling patients with histologically confirmed, clinical stage I-III, primary TNBC; (2) trials reporting pCR rates, and hazard ratios (HR) with 95% confidence intervals (CI) for disease-free survival (DFS), event-free survival (EFS), or overall survival (OS) in TNBC. Studies not adhering to the predetermined criteria were excluded. Other exclusion criteria were: (1) other types of publication including review, meta-analysis, and trial protocol; (2) studies comparing drug dose, dosage form, sequencing, route of administration or treatment schedule; (3) studies evaluating treatment strategies adjunct to antitumor therapies; (4) studies investigating post-neoadjuvant treatment strategies.

2.3. Data extraction and risk of bias assessment

Two investigators (YYL and XY) independently extracted data from eligible studies on the following information: study design, treatment regimens, patient characteristics, number of TNBC patients, total number of patients, number of TNBC patients achieving pCR, number of patients discontinuing study treatment prematurely, HR with 95% CI for DFS, EFS, or OS, and proportions of patients with grade 3-4 adverse events (AEs). GetData Graph Digitizer (http://www.getdata-graph-digitizer.com/) and HR calculation spreadsheet [10] were used to compute HR with 95% CI when required. Data not retrievable or computable from the original publications were searched for in relevant reviews. Discrepancies were resolved by consultation of a third investigator (HFG). The Cochrane Collaboration's tool [11] was used to assess the risk of bias of individual studies from the seven following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Studies were considered at high risk of bias when high in $\geq$1 of the first four domains or unclear in $\geq$4 of the first four domains.

2.4. Statistical analysis

2.4.1. Effect size measure and data handling

Odd ratios (OR) and HR with 95% credible intervals (CrI) was used to estimate effect sizes of binary and time-to-event outcomes, respectively. The primary outcome was pCR defined as the absence of residual invasive disease in the resected breast and lymph nodes. The secondary outcomes were all-cause premature treatment discontinuation; DFS/EFS defined as the time from randomization to disease recurrence, development of secondary malignancy, or death from any cause; and OS defined as the time from randomization to death from any cause. In the case of trial with a zero cell in sparse networks, 0.5 was added to the numerator and 1 was added to the denominator for model convergence and treatment estimation [12,13]. A descriptive analysis of the proportions of patients developing grade 3–4 AEs was also performed.

2.4.2. Frequentist pairwise meta-analysis

Conventional pairwise meta-analysis was conducted for all direct treatment comparisons using Mantel-Haenszel method for binary outcomes, and inverse-variance-weighted method for time-to-event outcomes. Statistical heterogeneity was assessed by the Cochran Q test and Higgins I^2 statistic [14]. A fixed-effects model was used unless substantial heterogeneity was observed (I^2 >50%). A two-sided $P < 0.05$ was considered statistically significant. Pair-wise analyses were carried out using Review Manager 5.4 (Cochrane Tech, London, UK).

2.4.3. Bayesian network meta-analysis

Network transitivity was analyzed with descriptive statistics of study design and patient characteristics [15,16]. Network plots were produced for each endpoint to visualize network geometry using the "network" package [17] in Stata MP 16.0. Bayesian network meta-analyses were implemented for each endpoint with non-informative prior using Markov Chain Monte Carlo methods with Gibbs sampling. Both fixed and random effects model was applied to assess the model fitness by computing the Deviance Information Criterion (DIC) [13,18]. The model with a lower DIC was considered a significantly better fit to the data when the difference in DIC was greater than 5. For pCR and premature treatment discontinuation, three chains were run for 500,000 iterations, with 250,000 iterations discarded as burn-in, at a thinning interval of 10, leaving 25,000 iterations per chain for estimation and inference. For time-to-event outcomes, 200,000 iterations were generated for three chains with 100,000 burn-ins at a thinning interval of 10. Convergence of chains was assessed by Gelman and Rubin diagnostic [19]. Effect sizes of all treatment comparisons were presented in forest plots and league tables. Probability values of ranking were reported as surface under the cumulative ranking curve (SUCRA) [20]. A larger SUCRA value indicated a better treatment. The homogeneity assumption was assessed by the Higgins I^2 statistic [16]. Global inconsistency was checked by comparing the model fit of consistency and inconsistency models; local inconsistency was examined using the node splitting approach [21,22]. Publication bias was evaluated by visual inspection of comparison-adjusted funnel plots [23]. The main analysis was conducted on all eligible trials, and in the subgroup excluding small-sized trials (25% of the smallest trials) given the stronger effect estimates seen in smaller studies [24]. The network meta-analysis was performed in R (4.1.0) with "gemtc" and "R2OpenBUGS" packages interfacing to OpenBUGS (3.2.3) [25,26].

2.4.4. Sensitivity analyses and network meta-regression

Sensitivity analysis and network meta-regression were done to assess the robustness of results. The first analysis excluded trials enrolling

Table 1
Study characteristics.

Study	Year	Phase	Design	Treatment arm	No. of TNBC pts	No. of ITT pts	Median age, y (range)	Clinical stage	Primary endpoint
Ando et al.	2014	II	Multicenter, open-label, randomized (1:1)	Carboplatin + paclitaxel→ FEC	37	91	47 (30–69)	II-III	ypT0/is pN0
				Paclitaxel→ FEC	38	88	47 (30–70)		
GeparOcto	2019	III	Multicenter, open-label, randomized (1:1)	Paclitaxel + doxorubicin→ carboplatin	203	475	48 (21–76)	I-III	ypT0/is pN0
				Epirubicin→ paclitaxel→ cyclophosphamide	200	470	48 (23–76)		
Zhang et al.	2016	II	Multicenter, open-label, randomized (1:1)	Carboplatin + paclitaxel	44	44	48 (24–73)	II-III	ypT0/is pN0
				Epirubicin + paclitaxel	43	43	46 (24–65)		
NeoCART	2020	II	Multicenter, open-label, randomized (1:1)	Carboplatin + docetaxel	44	44	50 (38–59)	II-III	ypT0/is pN0
				EC→ docetaxel	44	44	49 (40–56)		
NeoSTOP	2021	II	Multicenter, open-label, randomized (1:1)	Carboplatin + docetaxel	52	52	54 (29–70)	I-III	ypT0/is pN0
				Carboplatin + paclitaxel→ AC	48	48	51 (32–69)		
Aguilar Martinez et al.	2015	II	Single-center, randomized (1:1)	Cisplatin + paclitaxel→ cisplatin + doxorubicin	30	30	NR	NR	ypT0/is pN0
				Paclitaxel→ FAC	31	31			
TBCRC 030	2020	II	Multicenter, open-label, randomized (1:1)	Cisplatin	72	72	53 (28–82)	I-III	ypT0/is pN0
				Paclitaxel	67	67			
INFORM	2020	II	Multicenter, open-label, randomized (1:1)	Cisplatin	44	60	40 (31–49)*	I-III	ypT0/is pN0
				AC	38	58	44 (34–54)*		
Neo-tAnGo	2014	III	Multicenter, open-label, randomized (1:1:1:1)	EC→ Paclitaxel	73	404	NR	II-III	ypT0/is pN0
				Paclitaxel→ EC					
				EC→ Paclitaxel + gemcitabine	84	408			
				Paclitaxel + gemcitabine→ EC					
WSG-ADAPT-TN	2018	II	Multicenter, open-label, randomized (1:1)	Carboplatin + nab-paclitaxel	146	146	NR	I-III	ypT0/is pN0
				Gemcitabine + nab-paclitaxel	178	178			
TBCRC 008	2015	II	Multicenter, double-blind, randomized (1:1)	Vorinostat + carboplatin + nab-paclitaxel	12	30	48 (31–68)	II-III	ypT0/is pN0
				Carboplatin + nab-paclitaxel	12	31	48 (24–72)		
JBCRG-22	2021	II	Multicenter, randomized (1:1:1:1)	Carboplatin + eribulin→ FEC or AC	22	22	47.5 (26–63)*	I-III	ypT0/is pN0
				Carboplatin + paclitaxel→ FEC or AC	23	23	44 (28–64)*		
				Eribulin + capecitabine→ FEC or AC	27	27	60 (37–70)*		
				Eribulin + cyclophosphamide→ FEC or AC	27	27	59 (35–70)*		
Jiang et al.	2021	II	Single-center, open-label, randomized (1:1)	Vinorelbine + epirubicin	19	45	48 (26–66)	II-III	ypT0/is pN0
				Paclitaxel + epirubicin	17	46	50 (30–68)		
MDACC	2011	III	Multicenter, open-label, randomized (1:1)	Capecitabine + docetaxel→ FEC	30	300	49 (42–57)	II-III	Relapse-free survival
				Paclitaxel→ FEC	28	301	47 (40–55)		
Wu et al.	2018	II	Single-center, open-label, randomized (1:1)	Lobaplatin→ docetaxel + epirubicin	62	62	47 (33–70)	I-III	ypT0/is pN0
				Docetaxel + epirubicin	63	63			
KBOG 1101	2019	II	Multicenter, open-label, randomized (1:1)	FEC→ docetaxel + AC or EC	33	53	54.1 (12.4)**	II-III	ypT0 pN0
				Docetaxel + cyclophosphamide	33	50	53.6 (10.4)**		
NATT	2013	III	Multicenter, open-label, randomized (1:1)	Docetaxel + AC or EC	26	51	47.2 (26–62)*	II-III	ypT0/is pN0
				Docetaxel + cyclophosphamide	23	45	48 (25–69)*		
NSABP FB-9	2015	II	Multicenter, open-label, randomized (1:2)	Paclitaxel→ AC	8	19	48 (34–67)	II-III	ypT0/is pN0
				Eribulin→ AC	9	30	50 (28–70)		
Yardley et al.	2018	II	Multicenter, open-label, randomized (2:1)	Eribulin + cyclophosphamide	19	54	53 (23–77)	II-III	ypT0/is pN0
				Docetaxel + cyclophosphamide	6	22	51 (38–73)		
Saura et al.	2013	II	Multicenter, open-label, randomized (1:1)	AC→ ixabepilone	73	148	48 (25–79)	II-III	ypT0/is pN0
				AC→ paclitaxel	71	147	46 (26–74)		
SWOG S0800	2016	II	Multicenter, open-label, randomized (2:1:1)	Bevacizumab + nab-paclitaxel→ AC	32	98	51.7 (22–71)	II-III	ypT0/is pN0
				Nab-paclitaxel→ AC, or AC→ nab-paclitaxel	35	113	51.3 (31–75)		
ARTemis	2015	III	Multicenter, open-label, randomized (1:1)	Bevacizumab + docetaxel→ FEC	119	388	NR	II-III	ypT0/is pN0
				Docetaxel→ FEC	122	393			
GeparQuinto	2012	III	Multicenter, open-label, randomized (1:1)	Bevacizumab + EC→ docetaxel	323	956	49 (21–75)	I-III	ypT0 pN0
				EC→ docetaxel	340	969	48 (24–78)		

(*continued on next page*)

Table 1 (*continued*)

Study	Year	Phase	Design	Treatment arm	No. of TNBC pts	No. of ITT pts	Median age, y (range)	Clinical stage	Primary endpoint
GeparSixto	2014	II	Multicenter, open-label, randomized (1:1)	Bevacizumab + carboplatin + paclitaxel + doxorubicin	158	295	48 (21–75)	II-III	ypT0 pN0
				Bevacizumab + paclitaxel + doxorubicin	157	293	47 (21–78)		
CALGB 40603	2015	II	Multicenter, open-label, randomized (2:2)	Carboplatin + paclitaxel→ AC	111	113	NR	II-III	ypT0/is
				Bevacizumab + paclitaxel→ AC	105	110			
				Bevacizumab + carboplatin + paclitaxel→ AC	110	112			
				Paclitaxel→ AC	107	108			
BrighTNess	2018	III	Multicenter, double-blind, randomized (2:1:1)	Veliparib + carboplatin + paclitaxel→ AC	316	316	50 (41–59)	II-III	ypT0/is pN0
				Carboplatin + paclitaxel→ AC	160	160			
				Paclitaxel→ AC	158	158			
GeparOLA	2020	II	Multicenter, open-label, randomized (2:1)	Olaparib + paclitaxel→ EC	50	69	48 (25–71)	I-III	ypT0/is pN0
				Carboplatin + paclitaxel→ EC	27	37	45 (26–67)		
Rugo et al.	2016	II	Multicenter, open-label, randomized (2:1)	Veliparib + carboplatin + paclitaxel→ AC	72	72	48.5 (27–70)	II-III	ypT0/is pN0
				Paclitaxel→ AC	44	44	47.5 (24–71)		
SOLTI NeoPARP	2015	II	Multicenter, open-label, randomized (1:1:1)	Iniparib 11.2 mg/kg + paclitaxel	46	46	49 (27–78)	II-III	ypT0/is
				Iniparib 5.6 mg/kg + paclitaxel	48	48	49 (30–75)		
				Paclitaxel	47	47	50 (29–73)		
KEYNOTE-522	2020	III	Multicenter, double-blind, randomized (2:1)	Pembrolizumab + carboplatin + paclitaxel→ pembrolizumab + AC or EC	401	784	49 (22–80)	II-III	ypT0/is pN0
				Carboplatin + paclitaxel→ AC or EC	201	390	48 (24–79)		
Nanda et al.	2020	II	Multicenter, open-label, adaptively randomized	Pembrolizumab + paclitaxel→ AC	29	69	50 (27–71)	II-III	ypT0/is pN0
				Paclitaxel→ AC	85	181	47 (24–77)		
Pusztai et al.	2020	II	Multicenter, open-label, adaptively randomized	Durvalumab + olaparib + paclitaxel→ AC	21	73	46 (28–71)	II-III	ypT0/is pN0
				Paclitaxel→ AC	142	299	48 (24–80)		
NeoTRIPaPDL1	2020	III	Multicenter, open-label, randomized (1:1)	Atezolizumab + carboplatin + nab-paclitaxel	138	138	50 (24–79)	II-III	5-year event free survival
				Carboplatin + nab-paclitaxel	142	142			
IMpassion031	2020	III	Multicenter, double-blind, randomized (1:1)	Atezolizumab + nab-paclitaxel→ atezolizumab + AC	165	165	51 (22–76)	II-III	ypT0/is pN0
				Nab-paclitaxel→ AC	168	168	51 (26–78)		
GeparNuevo	2019	II	Multicenter, double-blind, randomized (1:1)	Durvalumab + nab-paclitaxel→ durvalumab + EC	88	88	49.5 (25–74)	I-III	ypT0 pN0
				Nab-paclitaxel→ EC	86	86	49.5 (23–76)		
FAIRLANE	2019	II	Multicenter, double-blind, randomized (1:1)	Ipatasertib + paclitaxel	76	76	51 (29–78)	I-III	ypT0/is pN0
				Paclitaxel	75	75	54 (31–78)		
Jo Chien et al.	2020	II	Multicenter, open-label, adaptively randomized	MK-2206 + paclitaxel→ AC	32	94	53 (25–73)	II-III	ypT0/is pN0
				Paclitaxel→ AC	24	57	46 (28–71)		
Gonzalez-Angulo et al.	2014	II	Single-center, open-label, randomized (1:1)	Everolimus + paclitaxel→ FEC	23	23	46 (32–75)	II-III	mTOR pathway inhibition
				Paclitaxel→ FEC	27	27	52 (30–65)		
Jovanovic et al.	2017	II	Multicenter, double-blind, randomized (2:1)	Everolimus + cisplatin + paclitaxel	96	96	52 (43–57.25)	II-III	ypT0/is pN0
				Cisplatin + paclitaxel	49	49	52 (43–58)		
Holmes et al.	2015	II	Multicenter, open-label, randomized (2:1)	MM-121 + paclitaxel→ AC	56	56	NR	II-III	ypT0 pN0
				Paclitaxel→ AC	29	29			
Bardia et al.	2018	II	Multicenter, open-label, randomized (1:1)	LCL-161 + paclitaxel	105	105	NR	II-III	>7.5% increase in ypT0 rate
				Paclitaxel	102	102			

→ = followed by. EC = epirubicin plus cyclophosphamide. FEC = 5-fluorouracil plus epirubicin plus cyclophosphamide. AC = doxorubicin plus cyclophosphamide. FAC = 5-fluorouracil plus doxorubicin plus cyclophosphamide. NR = not reported. * Mean age (range). ** Mean age (standard deviation).

patients with clinical stage I tumor. The second analysis excluded trials not specifically designed for TNBC. The third analysis excluded trials exclusively enrolling patients with prespecified genetic mutations. The fourth analysis excluded trials at high risk of bias. Network meta-regression was applied to evaluate if different cut-off values for ER negativity affected the magnitude of effect sizes in the network. A binary coding scheme was used, in which 1 referred to less than 1% stained cells by immunohistochemistry, and 0 to other definitions of ER negativity.

3. Results

A total of 1306 records were retrieved, of which 45 publications for 41 RCTs (N = 7109 TNBC patients) were eligible (eFig. 1). The latest data from 9 updated publications were also included. Characteristics of included trials are summaries in Table 1 and Appendix 2. Of the 41 RCTs, 17 exclusively enrolled TNBC patients; 37 were multicenter trials; 10 were phase III trials. The demographics and clinical features of the included patients represented typical early TNBC population, and the transitivity assumption was accepted. 12 trials were considered at high

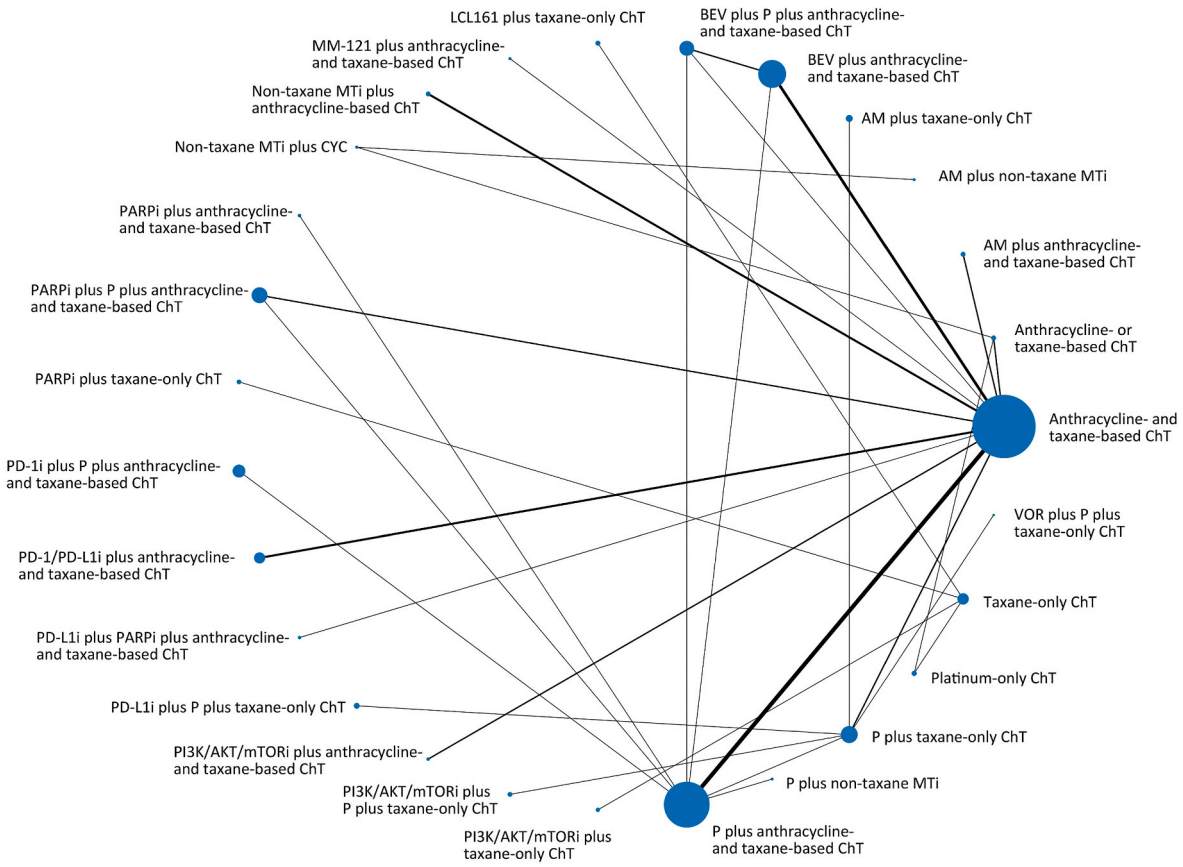

Fig. 1. Network meta-analysis of the proportion of patients achieving pathologic complete response (a 2-column fitting image). AM = antimetabolite. MTi = microtubule inhibitor. T = taxane. BEV = bevacizumab. P = platinum. A = anthracycline. CYC = cyclophosphamide. PARPi = PARP inhibitor. PD-1i = PD-1 inhibitor. PD-L1i = PD-L1 inhibitor. PD-1/PD-L1i = PD-1/PD-L1 inhibitor. PI3K/AKT/mTORi = PI3K/AKT/mTOR inhibitor. VOR = vorinostat.

risk of bias (eFig. 2). 27 combinations of neoadjuvant treatment regimen were investigated in these RCTs (Appendix 2).

3.1. Primary outcome

10 head-to-head comparisons were identified (Appendix 3). Network meta-analysis of pCR included all 27 neoadjuvant regimens (Fig. 1). A random-effects, consistency model was applied as it provided a better fit to the data. All treatments were compared with anthracycline- and taxane-based ChT, and 8 treatments were associated with significantly higher pCR rates (Fig. 2), including PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT (OR 3.95; 95% CrI 1.81–9.44), bevacizumab plus platinum plus anthracycline- and taxane-based ChT (3.35; 1.89–6.13), and PARP inhibitor plus platinum plus anthracycline- and taxane-based ChT (2.39; 1.40–4.37). Complete results of indirect comparisons for pCR are presented in eTable 2. The Bayesian ranking results were consistent with the pooled analysis, with PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT yielding the highest probability of being the most efficacious neoadjuvant treatment for TNBC (SUCRA = 0.90) (Fig. 3, eTable 3). Substantial heterogeneity was observed in two comparisons; no inconsistency between direct and indirect estimates was identified (Appendix 4). There was no strong evidence of publication bias (eFig. 3).

When small-sized trials were excluded, the network meta-analysis involved 22 regimens (eFig. 4a). PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT remained significantly associated with pCR improvement (OR 4.06; 95% CrI 1.57–11.51) (eFig. 4b). Complete results of indirect comparisons are presented in eTable 4. The SUCRA and probability of ranking followed a similar pattern (eTable 5). Additional analyses were conducted to explore the impact of treatment dose density on pCR. Treatments with dose-dense anthracycline- and taxane-based ChT were associated with overall better outcomes. When compared with dose-dense anthracycline- and taxane-based ChT, there was no longer a statistically significant association of PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT with improved pCR (OR 2.57; 95% CrI 0.69–9.92) (eFig. 5).

3.2. Secondary outcomes

8 direct comparisons were identified for premature treatment discontinuation (Appendix 3). The comparative analysis involved 24 regimens from 33 RCTs (N = 9489, TNBC and non-TNBC combined) (eFig. 6a). Compared with anthracycline- and taxane-based ChT, PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT significantly increased the incidence of all-cause premature treatment discontinuation (OR 3.25; 95% CrI 1.26–8.29) (eFig. 6). Indirect comparisons between all included treatment appear in eTable 6. The ranking results were consistent with the pooled analysis (eTable 7). Significant heterogeneity was observed in two comparisons (Appendix 4). There was no significant inconsistency (Appendix 4), nor strong evidence of small study effects (eFig. 3d). When excluding trials with 25% of the smallest sample size, 19 interventions were studies, and PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT remained associated with increased premature treatment discontinuation (OR 3.12; CrI 1.12–8.29; SUCRA = 0.25) (eFig. 7; eTable 8-9).

Data for DFS/EFS was retrievable from 18 RCTs (N = 5247). 10 neoadjuvant treatments were included (eFig. 8a). Compared with anthracycline- and taxane-based ChT, PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT (HR 0.42; 95% CrI 0.19–0.81), and platinum plus anthracycline- and taxane-based ChT (0.67; 0.44–0.92)

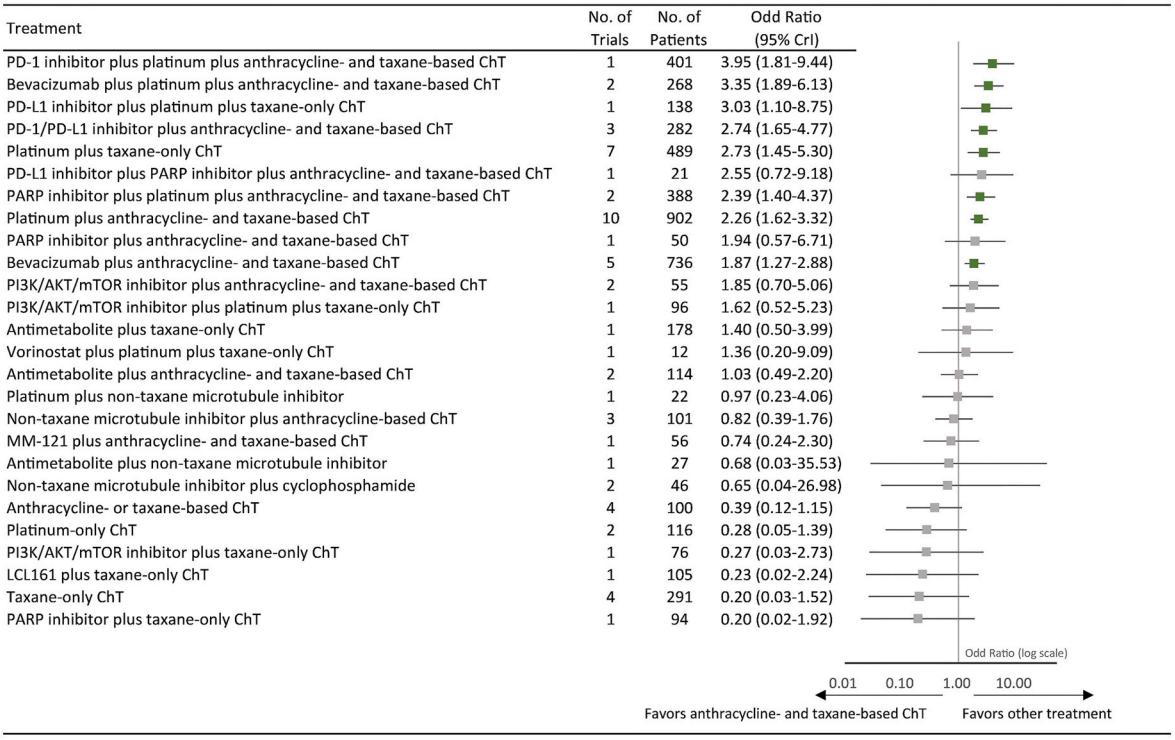

Fig. 2. Forest plot for the estimates of pathologic complete response improvement of different treatments using anthracycline- and taxane-based chemotherapy as a reference treatment (a 2-column fitting image). Green box indicates significantly in favor of the compared treatment. Grey box indicates non-significant result. CrI = credible interval. ChT = chemotherapy. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

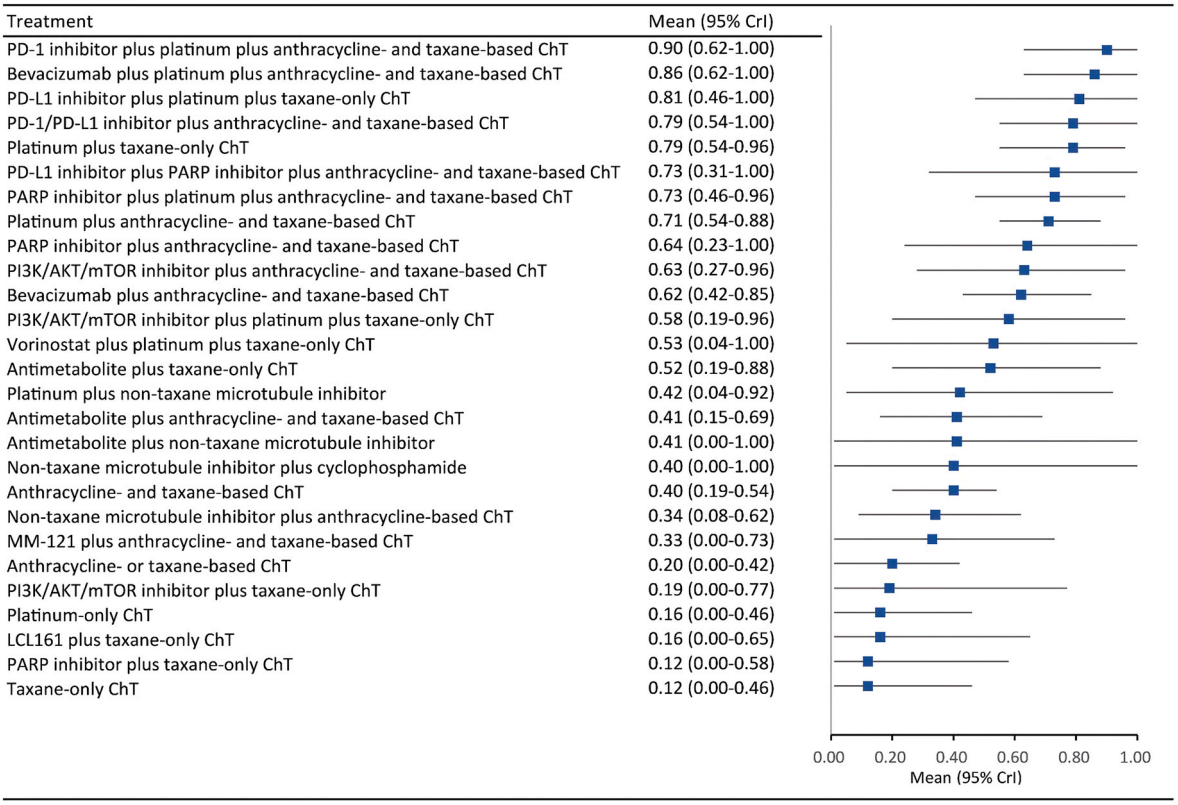

Fig. 3. Surface under the cumulative ranking curve for pathologic complete response (a 2-column fitting image). The surface under the cumulative ranking curve would be 1 when a treatment is certain to be the best, and 0 when a treatment is certain to be the worst. CrI = credible interval. ChT = chemotherapy.

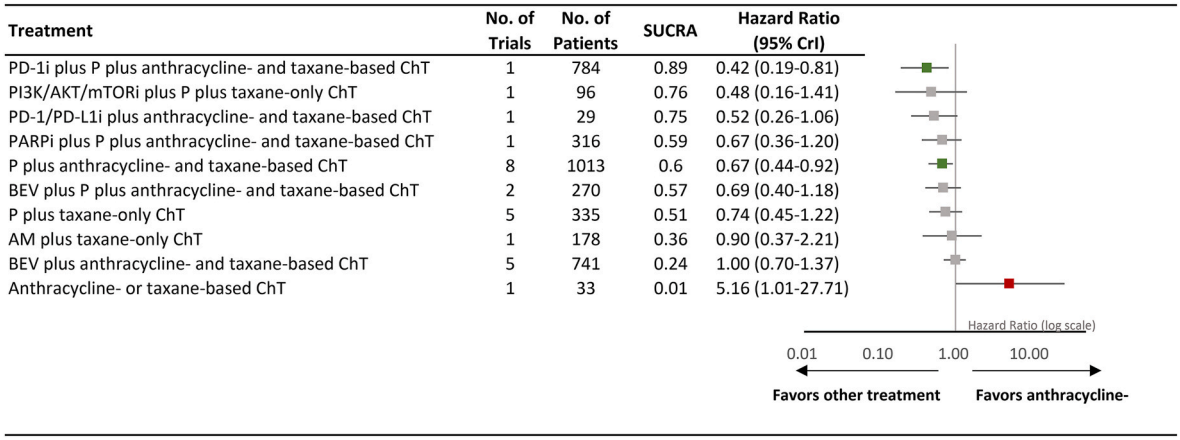

Fig. 4. Forest plot for the estimates of disease-free/event-free survival improvement of different treatments using anthracycline- and taxane-based chemotherapy as a reference treatment (a 2-column fitting image). Green box indicates significantly in favor of the compared treatment. Grey box indicates non-significant result. Red box indicates significantly in favor of the reference treatment. SUCRA = surface under the cumulative ranking curve. CrI = credible interval. ChT = chemotherapy. PD-1i = PD-1 inhibitor. PI3K/AKT/mTORi = PI3K/AKT/mTOR inhibitor. P = platinum. PD-1/PD-L1i = PD-1/PD-L1 inhibitor. PARPi = PARP inhibitor. BEV = bevacizumab. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

were associated with significantly improved DFS/EFS (Fig. 4). Complete results of indirect estimates are showed in eTable 10. PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT was associated with the highest likelihood of prolonged DFS/EFS (SUCRA = 0.89) (eTable 11). Significant heterogeneity was seen in one comparison (Appendix 4). No inconsistency, no strong evidence of publication bias was found (Appendix 4; eFig. 3f). Data for OS was extractable from 15 RCTs (N = 4863). 10 treatment strategies were included (eFig. 8b). Compared with anthracycline- and taxane-based ChT, PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT was not associated with improved OS (0.55; 0.24–1.15; 0.82) (eTable 12-13). There was no significant evidence of heterogeneity, inconsistency, or publication bias (Appendix 4, eFig. 3g).

The proportions of patients developing common grade 3–4 AEs are summarized in Appendix 5. The most frequent AEs in all neoadjuvant regimens were mainly associated with chemotherapeutic agents. Some distinct grade 3–4 AEs associated with angiogenesis inhibitors were infections, hypertension, thromboembolic events, and surgical complications. Some distinct grade 3–4 AEs seen with PD-1/PD-L1 inhibitors were adrenal insufficiency, hepatitis, severe skin reaction, and infusion reaction.

3.3. Sensitivity analyses and network meta-regression

Results from the sensitivity analyses did not show obvious deviations from the previous network meta-analysis (Appendix 6). Meta-regression demonstrated that different cut-off values for ER negativity was not the primary source of heterogeneity and inconsistency (CrIs for interaction parameter B were statistically insignificant).

4. Discussion

This systematic review and network meta-analysis comprehensively summaries existing evidence from RCTs investigating neoadjuvant treatment for TNBC patients and establishes the combination of PD-1 inhibitor with platinum and anthracycline- and taxane-based ChT as currently the most efficacious regimen for improving pCR and DFS/EFS in early TNBC. Substantial improvements in clinical outcomes come at the cost of increased treatment discontinuation attributed to wider toxicity spectrums from the combinatorial therapy.

Compared with other neoadjuvant therapies, PD-1 inhibitor plus platinum combined with anthracycline- and taxane-based ChT was the most effective neoadjuvant treatment for TNBC in terms of pCR improvement. PD-1 and PD-L1 axis plays a pivotal role in immune homeostasis by downregulating T-cell mediated immune responses to maintain peripheral tolerance and protect the host against allergy and autoimmunity [27,28]. PD-1 is highly expressed in tumor infiltrating lymphocytes (TILs) in a large proportion among different types of cancer [29]. TNBC patients are suitable candidates for immunotherapy considering the distinct immunological characteristics of TNBC such as higher PD-1/PD-L1 expression [30,31] and increased TILs levels [32]. In primary TNBC, PD-1 inhibitor combined with platinum-based neoadjuvant ChT produced significantly higher pCR rates across all subgroups [33,34]. Encouraging findings from clinical studies and the present network meta-analysis corroborate the neoadjuvant use of PD-1 inhibitor and platinum-containing, anthracycline- and taxane-based ChT in TNBC.

The choice of chemotherapy backbone might be vital for the maximization of antitumor activity of PD-1/PD-L1 inhibitors. Adding PD-L1 inhibitor to platinum plus taxane-only ChT failed to yield a significant pCR improvement in comparison to platinum plus taxane-only ChT [35]. One possible explanation is the use of a different type of immune checkpoint inhibitor [35]. More importantly, preoperative use of anthracycline and cyclophosphamide may enhance the efficacy of PD-1 inhibitor. Conventional chemotherapy was found to possess immunomodulatory properties [36,37], and anthracyclines, in particular, were capable of restoring immune surveillance and eliciting immunogenic cell death by depleting circulating regulatory T cells and increasing the infiltration of effector T cells in breast tumors [38]. Regarding the role of platinum agents, between-treatment estimations showed that pCR benefits from platinum-containing ChT was generally more pronounced than the platinum-free counterpart, which is consistent with previous meta-analysis that addition of platinum agents to neoadjuvant therapies further improved pCR in TNBC [39]. Additionally, PD-1 inhibitor combined with regular-dose ChT was not associated with significant pCR improvement when compared to dose-dense anthracycline- and taxane-based ChT, suggesting that dose-dense ChT might be somewhat equipoise to PD-1 inhibitor plus non-dose-dense ChT. Increasing dose density of adjuvant ChT was found to decrease the 10-year risk of breast cancer recurrence and death without increasing mortality from other causes [40]. Though whether dose-dense neoadjuvant ChT could result in survival benefit is yet to be defined, higher pCR rates were seen with more frequent administration of ChT in TNBC, and the combination of PD-1 inhibitor with dose-dense ChT may be considered for high-risk patients.

Combination of PD-1/PD-L1 inhibitor with other targeted therapy is

a promising treatment option warranting further investigations. One potential choice is PARP inhibitors. Despite limited sample size, PD-L1 inhibitor plus PARP inhibitor combined with anthracycline- and taxane-based ChT demonstrated a trend toward improved pCR. Several molecular and cellular mechanisms were associated with the synergy between immune checkpoint inhibitors and PARP inhibitors [41], including upregulated PD-L1 expression in breast cancer cells and immune pathway activation [42]. In early, high-risk breast cancer, incorporation of PD-L1 inhibitor and PARP inhibitor to neoadjuvant therapy improved pCR rate in TNBC and reduced residual cancers across the entire residual disease spectrum in all HER2-negative subtypes [43]. Follow-up data are eagerly awaited to determine whether the observed benefits can translate into prolonged survival. Another appealing option is angiogenesis inhibitors. Normalization of vasculature in tumor microenvironment could potentiate tumor responses to immunomodulation by increasing trafficking and activation of effector T cells [44]. Angiogenesis inhibitors increased $CD8^+$ T cells infiltration and PD-L1 expression in breast tumor tissues, and the introduction of a single dose bevacizumab improved $CD4^+$ T and $CD8^+$ T cells, and mature dendritic cells in primary TNBC [45,46]. Clinically, different combinations of immune checkpoint inhibitor with angiogenesis inhibitor are being investigated in various advanced solid tumors with favorable preliminary results [47–49]. Angiogenesis inhibitor used in conjunction with PD-1 inhibitor and taxane in immune-modulatory advanced TNBC was found to increase the efficacy of immunotherapy with manageable safety profile [50]. At present, whether the combination of PD-1/PD-L1 inhibitor with angiogenesis inhibitor and neoadjuvant ChT could yield synergistic antitumor activity in the primary setting of TNBC is yet to be validated with rigorous clinical trials.

The practice-changing success of PD-1 inhibitor plus platinum plus anthracycline- and taxane-based neoadjuvant therapy was accompanied with a significant increase in premature treatment discontinuation primarily driven by treatment-related AEs. Although most immune-related AEs can be successfully managed with systemic corticosteroid, the combinatorial regimen still resulted in a 0.3% increase in death associated with immune-mediated AEs and infusion reactions [34]. Furthermore, immune-mediated endocrinopathies are generally irreversible and may lead to long-term use of hormone-replacement therapy [51]. Therefore, the application of PD-1 inhibitor warrants careful decision-making balancing clinical risks and gains. For patients intolerable to AEs, de-escalation of ChT backbone may be considered. PD-1/PD-L1 inhibitor combined with platinum-free anthracycline- and taxane-based ChT was non-inferior to platinum plus anthracycline- and taxane-based ChT in terms of pCR improvement and was associated with a comparatively lower treatment discontinuation rate with more tolerable and manageable toxicity profiles [52,53].

Results from the indirect analysis of time-to-event endpoints, though limited by fewer number of studies involved, demonstrated the strongest association between PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT and prolonged DFS/EFS. However, whether the combination is associated with improved OS remains to be seen. Noticeably, in contrast with other neoadjuvant regimens, postoperative PD-1/PD-L1 inhibitor was administered for up to 1 year, and additional trials are required to better defined the contribution of adjuvant immune checkpoint inhibitor to the overall survival benefit. Platinum plus anthracycline- and taxane-based ChT was also associated with improved DFS/EFS. Combined with the findings from the latest meta-analysis that platinum-based neoadjuvant ChT significantly increased EFS as compared with platinum-free regimens [54], the introduction of a platinum agent to anthracycline- and taxane-based ChT should be considered the preferred neoadjuvant treatment backbone in early TNBC. Meanwhile, optimizing patient selection with close follow-up and proactive symptomatic treatments is vital for maintaining patient compliance to ensure treatment efficacy. The remarkable pCR improvements from the addition of bevacizumab to neoadjuvant regimens failed to translate into survival advantages. A recent meta-analysis revealed that HER2-negative breast cancer patients who received neoadjuvant bevacizumab and achieved pCR had inferior DFS [55], suggesting that, unlike immune checkpoint inhibitors and platinum agents, pCR was not a suitable predictor of survival benefits [56]. Given the critical role of angiogenesis in cancer pathogenesis, more well-designed studies are required to explore the clinical applications and predictive markers for anti-angiogenic agents in early breast cancer.

The presence network meta-analysis had several limitations. First, there was uncertainty regarding all estimates stemming from the heterogeneity among the eligible studies in terms of patient populations, treatment durations, and drug dosages. Hence, strict inclusion criteria for eligible studies were applied, and transitivity assumption was carefully assessed. Sensitivity analyses and meta-regression were also conducted to ensure the robustness of indirect inferences. Still, TNBC is a remarkably heterogenous disease and further characterization of target patient population is needed for our findings to be implemented in clinical practices. Second, only 11 of 27 interventions were investigated in two or more RCTs. Though omission of certain unattracted treatments or combination of different regimens in the analysis increases the proportion of direct comparisons, the results are less representative of the current neoadjuvant treatment landscape in TNBC, and therefore would not be as instructive as the present analysis in terms of clinical practice. Third, some comparisons were informed by a small number of patients, which resulted in some effect sizes limited by wide 95% CrI and carried a risk of introducing publication bias. Therefore, additional analysis excluding trials with 25% of the smallest sample size was performed to surmount small study effects. Fourth, this study was only designed to evaluate the therapeutic classes of each neoadjuvant therapy, and was less informative in terms of treatment schedule, sequencing, and dosage form. Including dosing information for all interventions in the analysis was impractical, as it would create a disjointed treatment network and increase the instability of treatment estimations. Fifth, the study did not have access to individual patient data and was unable to identify patients who might also benefit from treatment de-escalation. Sixth, time-to-event data for neoadjuvant therapies were not universally available, limiting the ability to define the association between treatment regimens and survival benefits. Seventh, there are subtle differences between the definitions of DFS and EFS in different trials [57], and the combined analysis of DFS and EFS might introduce heterogeneity and potential bias. Eighth, patients with inflammatory breast cancer were not excluded from the analysis, which might bias the results due to their higher responses if antiangiogenics are used. Ninth, the SUCRA curve has limitations, and the interpretation of SUCRA values should be in the context of the size of treatment effect [58].

Nonetheless, the present study has several highlights and yields strong implications for clinical practice. Another network meta-analysis of neoadjuvant treatments of TNBC involved more incomplete results and placed more emphasis on the role of platinum agents [59]. In contrast, the current study comprehensively assesses the clinical applicability of different neoadjuvant therapies in TNBC and identified that PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT was the most efficacious regimens for TNBC patients by consistently producing significant pCR and DFS/EFS improvement. Furthermore, selection of ChT partner might be critical for meaningful benefits from PD-1 inhibitor. In addition, a higher dropout rate for PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT was observed, and treatment-related AEs was the leading cause of early treatment discontinuation. In view of the current findings, it would be interesting to see whether the concomitant use of PD-1/PD-L1 inhibitor with angiogenesis inhibitor or PARP inhibitor combined with platinum-based ChT can exert synergistic action to further improve pCR in early TNBC. An open-label, phase II, single-arm trial was recently initiated to explore the effectiveness and safety of penpulimab plus anlotinib combined with carboplatin and nab-paclitaxel, followed by epirubicin and cyclophosphamide as neoadjuvant therapy in TNBC (NCT04877821).

5. Conclusions

This systematic review and network meta-analysis identified PD-1 inhibitor combined with platinum and anthracycline- and taxane-based ChT as the superior neoadjuvant regimen in TNBC, with consistent improvement in pCR and DFS/EFS. The choice of chemotherapy backbone might be vital for maximizing the antitumor activity of PD-1 inhibitor. Meanwhile, optimizing patient selection and taking precautionary measures are essential to reduce severe AEs and ensure treatment adherence. These findings substantiate the treatment strategies recommended by official oncology guidelines and provide auspicious directions for future trial design in early TNBC.

Funding acknowledgment

This work was supported by the National Natural Science Foundation of China (Grant No. 81871513); the Science and Technology Planning Project of Guangzhou City (202002030236); the Science and Technology Special Fund of Guangdong Provincial People's Hospital (No. Y012018218); the CSCO-Hengrui Cancer Research Fund (Y-HR2016-067); and the Guangdong Provincial Department of Education Characteristic Innovation Project (2015KTSCX080). Funding sources were not involved in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Author contributions

HFG and YYL conceived and designed the study. YYL and TZ did the literature search and selected eligible articles. YYL, XY, and XXZ extracted study data and performed risk of bias assessment. YYL, XY, and ZT analyzed the data. YYL and HFG wrote the first draft of the manuscript. TZ, XY, XXZ, KW, LLZ, CQY, MY, FJ, JQL and MYC contributed to data interpretation and participated in the critical revision of the manuscript. All authors have full access to the data in the study and accept responsibility to submit for publication. All authors read and approve the final manuscript. The corresponding author affirms that all listed authors meet authorship criteria and that no others meeting the criteria are omitted.

Data availability statement

Study data would be available upon reasonable request.

Declaration of competing interest

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.08.006.

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