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Neoadjuvant immunotherapy and chemotherapy regimens for the treatment of high-risk, early-stage triple-negative breast cancer: a systematic review and network meta-analysis

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Abstract

Background Patients with triple-negative breast cancer (TNBC) are generally younger and more likely to experience disease recurrence and have the shortest survival among all breast cancer patients. Recently, neoadjuvant delivery of the programmed cell death protein-1 inhibitor pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab was approved for patients with high-risk, early-stage TNBC, but this treatment regimen has not been evaluated in head-to-head trials with other neoadjuvant treatment regimens. Therefore, the objective of this study was to estimate the relative efficacy of neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab versus other neoadjuvant treatments for early-stage TNBC through a systematic review and network meta-analysis (NMA).

Methods EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials, conference abstracts, and clinical trial registries were searched for randomized controlled trials evaluating neoadjuvant treatments for early-stage TNBC. NMA was performed to estimate relative treatment effects among evaluated interventions.

Results Five trials met the inclusion criteria and were included in the NMA. The relative efficacy of neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab was favorable to paclitaxel followed by anthracycline + cyclophosphamide in terms of pathologic complete response (pCR), event-free survival (EFS), and overall survival; paclitaxel + carboplatin followed by anthracycline + cyclophosphamide in terms of pCR and EFS; paclitaxel + bevacizumab followed by anthracycline + cyclophosphamide + bevacizumab in terms of pCR; and paclitaxel + carboplatin + veliparib followed by anthracycline + cyclophosphamide in terms of EFS.

Conclusions Neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab confers benefits in response and survival outcomes versus alternative neoadjuvant treatments for early-stage TNBC.

Keywords Triple-negative breast cancer, Chemotherapy, Immunotherapy, Neoadjuvant therapy, PD-1, PD-L1, Network meta-analysis

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Background

Breast cancer is the most frequently diagnosed cancer, with an estimated 2.3 million new cases worldwide in 2020, and the leading cause of cancer death among women [1]. Approximately 15–20% of breast cancer cases are molecularly classified as triple-negative breast cancer (TNBC), which is characterized by tumors lacking expression of the estrogen receptor, progesterone receptor, and epidermal growth factor receptor 2 [2, 3]. Compared with women with other molecular subtypes of breast cancer, women with TNBC generally present at younger ages and are more likely to experience early recurrence after treatment and distant metastasis to visceral organs including the brain [3–5]. Moreover, women with TNBC exhibit the shortest survival time among all breast cancer patients, with a mortality rate of 40% within 5 years of diagnosis [3, 5].

As TNBC is insensitive to endocrine therapy due to its molecular phenotype, cytotoxic chemotherapy has historically been the mainstay treatment approach. Chemotherapy combinations involving doxorubicin, cyclophosphamide, anthracycline, paclitaxel, or platinum-based agents administered before tumor resection are shown to improve early outcomes, including pathologic complete response (pCR) and event-free survival (EFS), among women with early-stage or locally advanced TNBC [3]. Advances in our understanding of the molecular mechanisms of cancer, however, have led to the development of new targeted therapies that may achieve even greater improvements in TNBC patient outcomes. Of particular interest, immunotherapies that inhibit immune checkpoints such as programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PD-L1), which are leveraged by tumor cells to evade recognition and destruction by the immune system, can restore the body's ability to effectively attack tumors. Indeed, neoadjuvant delivery of the PD-1 inhibitor pembrolizumab + chemotherapy followed by adjuvant pembrolizumab was granted U.S. Food and Drug Administration approval in July 2021 for treating high-risk, early-stage TNBC based on statistically significant and clinically meaningful improvements in pCR and EFS in a phase III randomized controlled trial (RCT) [6, 7]. Furthermore, another phase III RCT shows that neoadjuvant treatment with the PD-L1 inhibitor atezolizumab + chemotherapy improves pCR among early-stage TNBC patients [8].

Network meta-analysis (NMA) is a statistical method that enables indirect comparisons between treatments where head-to-head evidence may not be available, which allows clinicians, guideline developers, and health technology assessment agencies to evaluate evidence on new treatments within the context of all existing evidence [9, 10]. Specifically, NMA can be used to combine direct and indirect evidence regarding any interventions that form a connected network of RCTs wherein each trial has at least one intervention (active or placebo) in common with another trial and all trials are sufficiently similar [11]. Clinical trial evidence suggests that neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab is an effective and safe approach to treating early-stage or locally advanced TNBC; however, this treatment regimen has not been compared against all alternative neoadjuvant treatment regimens in head-to-head trials. As the relative efficacy of various immunotherapy- and chemotherapy-based regimens is of interest to both clinicians and healthcare policymakers, the aim of this analysis was to estimate the comparative efficacy of neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab versus other neoadjuvant treatments for patients with high-risk, early-stage TNBC in terms of pCR, EFS, and overall survival (OS) through a systematic review and NMA.

Methods

Systematic review

The systematic review and NMA were performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [12] and followed a pre-specified protocol. Selection criteria for the population, interventions, comparators, outcomes, and study design (PICOS) are outlined in Table 1. RCTs were included if they enrolled patients with early-stage and locally recurrent non-metastatic TNBC, evaluated interventions of interest, reported outcomes of interest, and were published in English. Due to an anticipated lack of trials conducted solely in TNBC patients, trials were eligible for inclusion if they enrolled TNBC patients exclusively and reported at least one outcome of interest or if they enrolled patients from a broader population of breast cancer patients and reported at least one outcome of interest in a subgroup composed of > 90% TNBC patients. As the primary purpose of this systematic review and NMA was to identify and synthesize evidence from the clinical literature to support health technology assessment submissions, the interventions of interest included only those treatment regimens used in clinical practice in multiple countries, and the protocol was not registered in a systematic review registry.

Relevant trials were identified by searching Excerpta Medica DataBASE (EMBASE), Medical Literature Analysis and Retrieval System Online (MEDLINE), and Cochrane Central Register of Controlled Trials (CENTRAL) through the OVID platform on April 21, 2022 (Additional Tables 1-3). EMBASE and MEDLINE searches were limited to RCTs using the Scottish Intercollegiate Guidelines Network (SIGN) filter

Table 1 PICOS criteria to identify trials for the systematic literature review

Population	Early-stage and locally advanced non-metastatic triple-negative breast cancer
Interventions	**Neoadjuvant pembrolizumab regimens:**
	• Pembrolizumab (200 mg q3w × 4 cycles) + carboplatin (AUC 5 q3w × 4 cycles or AUC 1.5 qw × 4 cycles) + paclitaxel (80 mg/ml qw × 4 cycles)
	• Pembrolizumab (200 mg q3w × 4 cycles) + doxorubicin (60 mg/m^2) or epirubicin (90 mg/ml^2) + cyclophosphamide (600 mg/m^2 q3w × 4 cycles)
	• Post-surgery: Pembrolizumab (200 mg q3w × 9 cycles)
	Preferred neoadjuvant regimens:
	• Dose-dense doxorubicin + cyclophosphamide followed by paclitaxel every 3 weeks
	• Dose-dense doxorubicin + cyclophosphamide followed by weekly paclitaxel
	• Docetaxel + cyclophosphamide
	Other neoadjuvant regimens:
	• Dose-dense doxorubicin + cyclophosphamide
	• Doxorubicin + cyclophosphamide every 3 weeks (category 2B)
	• Cyclophosphamide + methotrexate + fluorouracil
	• Doxorubicin + cyclophosphamide followed by docetaxel every 3 weeks
	• Doxorubicin + cyclophosphamide followed by weekly paclitaxel
	• Epirubicin + cyclophosphamide
	• Docetaxel + doxorubicin + cyclophosphamide
	• Carboplatin + paclitaxel (80 mg/ml qw × 4 cycles)
	• Paclitaxel every 3 weeks followed by dose-dense doxorubicin + cyclophosphamide/ epirubicin/cyclophosphamide
	• Paclitaxel weekly followed by dose-dense doxorubicin + cyclophosphamide
	• Paclitaxel every 3 weeks followed by doxorubicin + cyclophosphamide/ epirubicin/cyclophosphamide
	• Paclitaxel weekly followed by doxorubicin + cyclophosphamide/ epirubicin/cyclophosphamide
	• Nab-paclitaxel followed by (dose-dense) doxorubicin + cyclophosphamide/ epirubicin/cyclophosphamide
	• Nab-paclitaxel + carboplatin followed by (dose-dense) doxorubicin + cyclophosphamide/ epirubicin/cyclophosphamide
	Neoadjuvant immunotherapy agents:
	• Atezolizumab + nab-paclitaxel
	• Atezolizumab + nab-paclitaxel followed by atezolizumab + dose-dense doxorubicin + cyclophosphamide
Comparators	• Any of the interventions listed above • Any intervention that has been compared to two or more of the above treatments
Outcomes	**Efficacy outcomes:**
	• Pathologic complete response (pCR)
	• Event-free survival (EFS)
	• Overall survival (OS)
	• Disease-free survival (DFS)
	• Landmark survival rates
	• Landmark EFS
	• Landmark DFS
	• Treatment duration/time to treatment discontinuation
	Safety outcomes:
	• Any adverse events
	• Any grade 3 or higher adverse events
	• Immune-related toxicity
	• Treatment-emergent adverse events (any grade, and grade 3 or higher)
	• Study withdrawals
	Patient-reported outcomes, including quality of life measures:
	• EQ-5D
	• EORTC QLQ-C30
	• EORTC QLQ-BR23
	• FACT-B-FBSI

Table 1 (continued)

Population	Early-stage and locally advanced non-metastatic triple-negative breast cancer
Time	Unrestricted
Study design	Phase II and III RCTs • Parallel group (triple-blind/double-blind) • RCT—cross over (triple-blind/double-blind) • RCT—post hoc and open-label extension
Language	English language

Abbreviations: *AUC* Area under the curve, *EQ-5D* European Quality of Life-5D, *EORTC QLQ-C30* European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30, *EORTC QLQ-BR23* European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires-Breast 23, *FACT-B-FBSI* Functional Assessment of Cancer Therapy-Breast-Functional Assessment of Cancer Therapy-Breast Cancer Symptom Index, *RCT* Randomized controlled trial, *TNBC* Triple-negative breast cancer

(https://www.sign.ac.uk/what-we-do/methodology/search-filters/). Manual searches American Society of Clinical Oncology (2021–2022), European Society of Medical Oncology (2021), and San Antonio Breast Cancer Symposium (2021) conference proceedings were conducted to identify RCTs that had not yet been published in full-text form. In addition, the U.S. National Institute of Health Clinical Trials Registry (clinicaltrials.gov) and European Union Clinical Trial Registry (clinicaltrialsregister.eu) were searched to identify completed RCTs with results available that had not yet been published.

Two reviewers performed abstract selection, full-text selection, and data extraction in duplicate. Any unresolved discrepancies between the two reviewers were resolved by involving a third reviewer and reaching consensus. The Cochrane Collaboration's Risk of Bias tool was used to assess the risk of bias of included RCTs [13].

Following completion of the systematic review, the comparators component of the PICOS was broadened to include any intervention that was compared to two or more interventions of interest, and a targeted literature review was conducted to identify additional RCTs to form a connected network for the NMA.

Feasibility assessment and network meta-analysis

An extension of pairwise meta-analysis, NMA allows indirect comparisons of interventions that have not been evaluated in head-to-head trials [11]. As the validity of any NMA is based on whether there are systematic differences among trials included in the network across treatment comparisons [11, 14–17], a feasibility assessment was conducted before proceeding with the NMA [14].

As only one trial connected each treatment in the networks of evidence, between-study heterogeneity could not be reliably estimated; therefore, NMA was performed with a fixed-effects assumption. The NMA of reported hazard ratios (HRs) in terms of EFS and OS assuming proportional hazards between treatments was performed using a regression model with a contrast-based normal likelihood for the log HR and corresponding standard error of each trial in the network [18]. Normal non-informative prior distributions for the parameters were estimated with a mean of 0 and a variance of 10,000.

NMA of reported Kaplan–Meier (KM) curves in terms of EFS and OS assuming time-varying hazards between treatment was performed using a fractional polynomial model [11, 19]. Weibull, Gompertz, and second-order fractional polynomial models were considered using a multivariant NMA framework. Reported KM curves were digitized for each treatment arm included in the NMA using DigitizeIt (http://www.digitizeit.xyz). Goodness-of-fit was compared across competing survival models using the deviance information criterion, with a model having a better trade-off between fit and parsimony having a lower deviance information criterion. Relative treatment effects were expressed as odds ratios for pCR and HRs for EFS and OS with 95% credible intervals (CrIs), which reflect a 95% probability that the estimate is within the specified range. Additionally, to allow for time-varying HRs, NMAs with fractional polynomial models representing different survival distributions were fit to the data under a variety of different assumptions about the shape of the hazard function. All analyses were performed using R version 4.0.3 (http://www.r-project.org/) and OpenBugs version 3.2.3 (OpenBUGS Project Management Group) [20].

Results

Systematic review

The study selection process for identifying trials of interest is outlined in Fig. 1. Thirteen citations pertaining to seven unique trials were identified in the systematic review (Additional Table 4) [6, 8, 21–30]. As the trials identified by the systematic review did not form a connected network of evidence, a targeted literature search was conducted to include any intervention that was compared to two or more treatments of interest, which resulted in the inclusion of five additional citations pertaining to three unique trials. Trials that were not connected in a network, including IMpassion031 evaluating

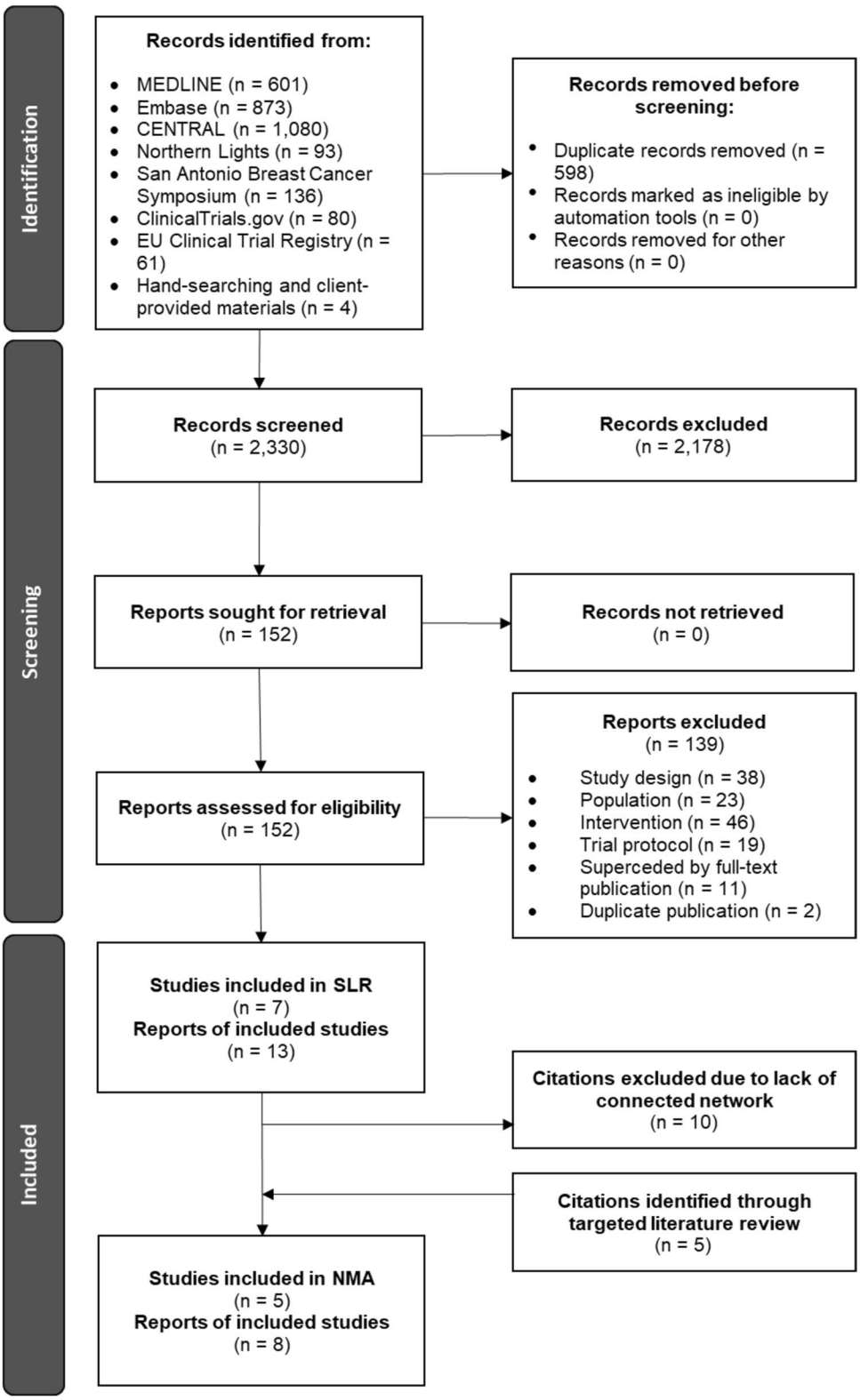

Fig. 1 PRISMA flow diagram

atezolizumab + chemotherapy, were excluded. As a result, a total of eight citations pertaining to five unique trials were included in the feasibility assessment and NMA (Additional Table 5) [22, 23, 31–35].

Feasibility assessment

Two trials were multinational (KEYNOTE-522 and BrighTNess), two trials were conducted in the U.S. (CALGB 40603 and NeoSTOP), and one trial was conducted in Germany (GeparSepto-GBG 69). KEYNOTE-522 employed quadruple-blind masking, whereas the other trials were open-label (Table 2). All trials exclusively enrolled patients with early-stage, locally advanced non-metastatic TNBC. Patients were enrolled in all trials irrespective of PD-L1 status; however, KEYNOTE-522 measured PD-L1 status using the PD-L1 IHC 22C3 pharmDx test (Dako North America, Inc.) and reported outcomes for PD-L1 subgroups. All trials employed comparable treatment dosing and administration schedules (Additional Table 6).

Although baseline patient characteristics were not reported for most trials, the available data on patient characteristics and enrollment criteria suggest no important between-trial differences (Additional Table 7). Among the trials reporting baseline patient characteristics, median age ranged from 48 to 54 years, 99.9–100% of patients were female, and 69–74% of patients were Caucasian. Based on trial eligibility criteria, four trials enrolled patients with an ECOG performance score of 0 or 1, whereas one trial (GeparSepto-GBG 69) enrolled patients with a Karnofsky performance score of 70–80% or better.

All five trials reported pCR. Survival outcomes for CALGB 40603 were only available from the US National Institutes of Health Clinical Trial Registry, which reported identical HRs and 95% confidence intervals for both OS and recurrence-free survival (which was defined similarly as EFS in the other included trials, Additional Table 8). As this appeared to be a reporting error, CALGB 40603 was excluded from the primary NMA of OS and EFS; sensitivity analyses including this trial are reported in Additional Fig. 4 and Additional Tables 19–20. In addition, as GeparSepto-GBG 69 did not provide KM curves for OS, this trial was only included in the constant HR NMA model for OS. Data sources for each outcome measure are presented in Additional Table 9.

Network meta-analysis

Networks were constructed to compare neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab to other neoadjuvant treatment

Table 2 Characteristics of trials included in the feasibility assessment and network meta-analysis

Trial ID	Phase	Treatment	Number of patients	Masking	Multicenter	Disease/tumor stage
CALGB 40603[31, 32]	III	Pac + carb➔anthra + cyclo	113	Open-label	Yes	Stage II-III
		Pac + carb + bev➔anthra + cyclo + bev	112			
		Pac + bev➔anthra + cyclo + bev	110			
		Pac➔anthra + cyclo	108			
BrighTNess[34, 35]	III	Pac + carb➔anthra + cyclo	160	Open-label	Yes	Clinical stage T2-3 N0-2 or T1 N1-2
		Pac➔anthra + cyclo	158			
		Pac + carb + veli➔anthra + cyclo	316			
GeparSepto-GBG 69[22, 23]	III	Pac➔anthra + cyclo	606	Open-label	Yes	cT2—cT4a-d, cT1c and cN + , cT1c and pNSLN + , cT1c and ER-negative and PR-negative, or cT1c and Ki67 > 20%, or cT1c and HER2-positive
		Nab-pac➔anthra + cyclo	606			
KEYNOTE-522	III	Pembro + pac + carb➔pembro + anthra + cyclo➔adjuvant pembro	784	Quadruple-blind	Yes	Stage II-III
		Pac + carb➔anthra + cyclo	390			
NeoSTOP[33]	II	Pac + carb➔anthra + cyclo	48	Open-label	Yes	Stage I-III
		Doc + carb➔anthra + cyclo	52			

Abbreviations: *Anthra* Anthracycline, *bev* Bevacizumab, *carb* Carboplatin; *cyclo* Cyclophosphamide, *doc* Docetaxel, *dox* Doxorubicin, *nab-pac* Nab-paclitaxel, *pac* Paclitaxel, *pembro* Pembrolizumab, *veli* Veliparib

Arrows (➔) indicate where treatment was administered sequentially; treatments to the left of the arrow were administered first. Anthra includes dox and epi, which were assumed to be equivalent

regimens. A fundamental assumption was made in the inclusion of trials evaluating chemotherapy regimens without analyses by PD-L1 subgroups: PD-L1 expression levels only influenced the PD-L1-directed therapy-containing regimen (i.e., pembrolizumab). Also, as doxorubicin and epirubicin have similar efficacy profiles [36], networks of evidence were constructed by treating cohorts assigned to doxorubicin or epirubicin as equivalent (classified as anthracycline). Five trials were included in the pCR network (Fig. 2), and four trials were included in the OS and EFS networks (Fig. 3).

For pCR, neoadjuvant pembrolizumab + paclitaxel + carboplatin followed by pembrolizumab + anthracycline + cyclophosphamide followed by adjuvant pembrolizumab showed statistically favorable improvements in pCR versus paclitaxel + carboplatin followed by anthracycline + cyclophosphamide, paclitaxel followed by anthracycline + cyclophosphamide, and paclitaxel + bevacizumab followed by anthracycline + cyclophosphamide + bevacizumab (Table 3).

For EFS, neoadjuvant pembrolizumab + paclitaxel + carboplatin followed by pembrolizumab + anthracycline + cyclophosphamide followed by adjuvant pembrolizumab showed statistically favorable improvements in EFS versus paclitaxel followed by anthracycline + cyclophosphamide, paclitaxel + carboplatin followed by anthracycline + cyclophosphamide, and paclitaxel + carboplatin + veliparib followed by anthracycline + cyclophosphamide (Table 4).

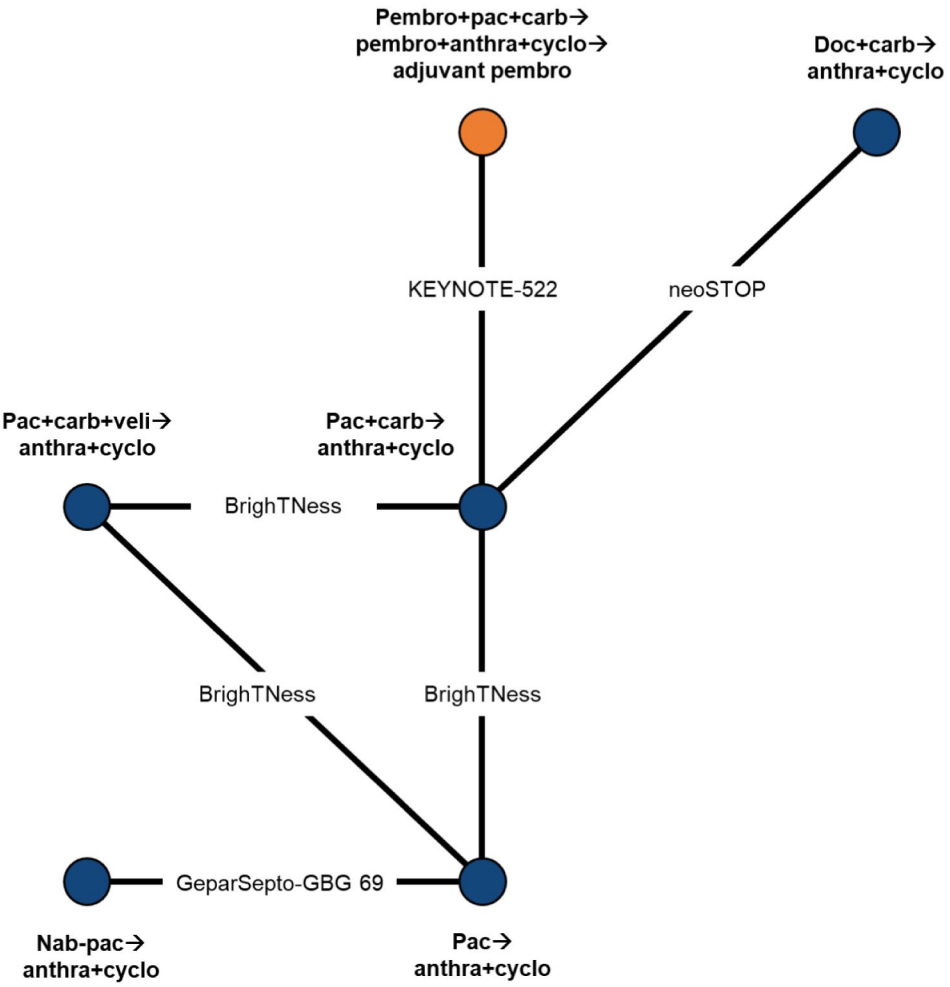

Fig. 2 Network of evidence for pathologic complete response. Arrows (→) indicate where treatment was administered sequentially, with treatments to the left of the arrow administered first. The orange circle denotes the primary treatment regimen of interest. Anthra includes doxorubicin and epirubicin, which were assumed to be equivalent. Anthra = anthracycline; bev = bevacizumab; carb = carboplatin; cyclo = cyclophosphamide; doc = docetaxel; nab-pac = nab-paclitaxel; pac = paclitaxel; pembro = pembrolizumab; veli = veliparib

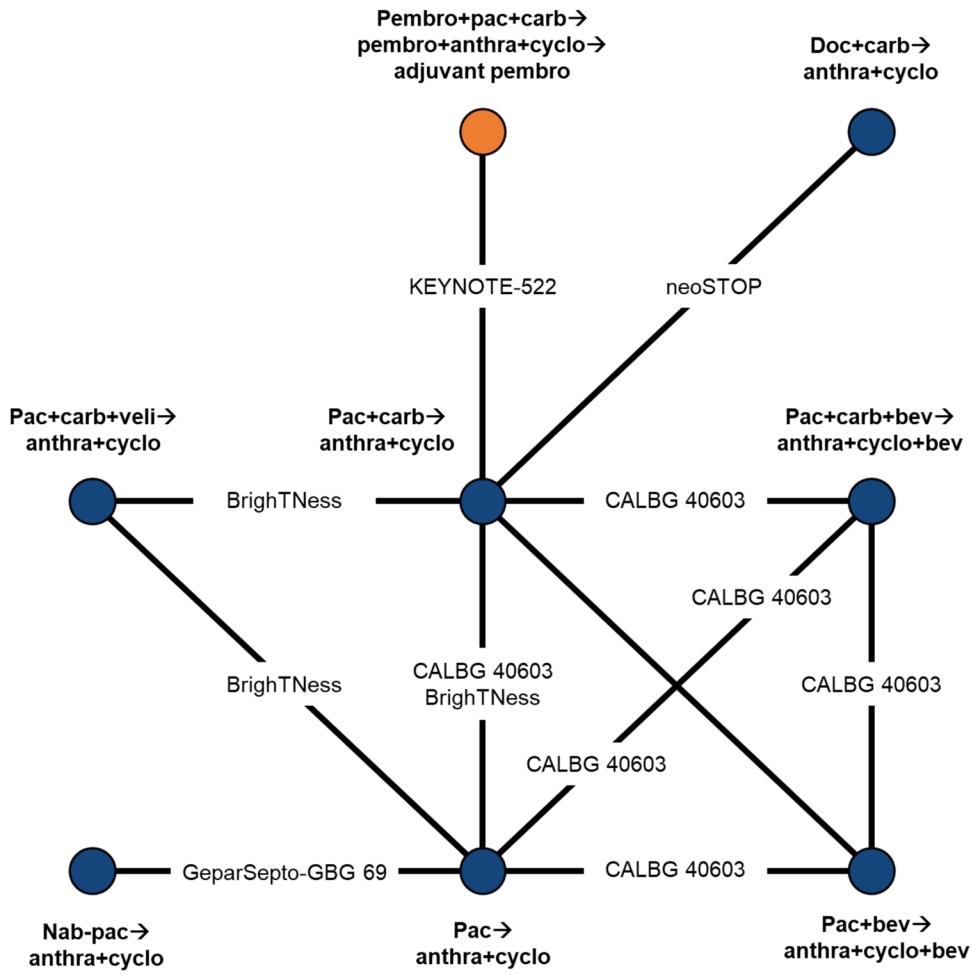

Fig. 3 Network of evidence for event-free survival and overall survival. Arrows (→) indicate where treatment was administered sequentially, with treatments to the left of the arrow administered first. The orange circle denotes the primary treatment regimen of interest. Anthra includes doxorubicin and epirubicin, which were assumed to be equivalent. Anthra = anthracycline; bev = bevacizumab; carb = carboplatin; cyclo = cyclophosphamide; doc = docetaxel; nab-pac = nab-paclitaxel; pac = paclitaxel; pembro = pembrolizumab; veli = veliparib

For OS, neoadjuvant pembrolizumab + paclitaxel + carboplatin followed by pembrolizumab + anthracycline + cyclophosphamide followed by adjuvant pembrolizumab showed statistically favorable OS results versus paclitaxel followed by anthracycline + cyclophosphamide (Table 5).

As there were no major violations of the assumption that HRs were proportional over time (determined by log–log and Schoenfeld residual plots), the best-fitting models were determined to be constant HR models. Further, the best-fitting time-varying models for both EFS and OS did not show statistically meaningful changes in HR over time for any treatment (Additional Figs. 1-3, Additional Tables 10–17). Therefore, the constant HR results provided the best combination of fit and parsimony for all treatments.

Discussion

NMA including five RCTs of neoadjuvant immunotherapy or chemotherapy regimens for patients with early-stage or locally advanced, non-metastatic TNBC demonstrated that neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab had more favorable treatment outcomes than certain other neoadjuvant treatment regimens. In particular, the relative efficacy of neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab was statistically favorable to paclitaxel followed by anthracycline + cyclophosphamide in terms of pCR, EFS, and OS; to paclitaxel + carboplatin followed by anthracycline + cyclophosphamide in terms of pCR and EFS; to paclitaxel + bevacizumab followed

Table 3 Results of network meta-analysis for pathologic complete response

Intervention	Pac + carb➔anthra + cyclo	Pac➔anthra + cyclo	Doc + carb➔anthra + cyclo	Nab-pac➔anthra + cyclo	Pac + bev➔anthra + cyclo + bev	Pac + carb + bev➔anthra + cyclo + bev	Pac + carb + vel➔anthra + cyclo	Pembro + pac + carb➔pembro + anthra + cyclo➔adjuvant pembro
Pac + carb➔anthra + cyclo	1	–	–	–	–	–	–	–
Pac➔anthra + cyclo	0.43 (0.30, 0.61)	1	–	–	–	–	–	–
Doc + carb➔anthra + cyclo	0.99 (0.45, 2.16)	2.27 (0.97, 5.37)	1	–	–	–	–	–
Nab-pac➔anthra + cyclo	1.13 (0.62, 2.13)	**2.61 (1.58, 4.41)**	1.16 (0.42, 3.12)	1	–	–	–	–
Pac + bev➔anthra + cyclo + bev	0.72 (0.43, 1.19)	1.65 (0.99, 2.71)	0.73 (0.29, 1.84)	0.63 (0.30, 1.28)	1	–	–	–
Pac + carb + bev➔anthra + cyclo + bev	1.51 (0.90, 2.55)	**3.47 (2.08, 5.93)**	1.54 (0.61, 3.94)	1.33 (0.63, 2.76)	**2.12 (1.21, 3.68)**	1	–	–
Pac + carb + vel➔anthra + cyclo	0.95 (0.67, 1.36)	**2.19 (1.53, 3.17)**	0.96 (0.41, 2.28)	0.84 (0.44, 1.56)	1.33 (0.75, 2.34)	0.63 (0.35, 1.13)	1	–
Pembro + pac + carb➔pembro + anthra + cyclo➔adjuvant pembro	**1.36 (1.06, 1.73)**	**3.12 (2.04, 4.85)**	1.37 (0.61, 3.14)	1.19 (0.61, 2.30)	**1.89 (1.07, 3.30)**	0.89 (0.50, 1.59)	1.42 (0.92, 2.21)	1

Abbreviations: *Anthra* Anthracycline, *bev* bevacizumab, *carb* Carboplatin, *cyclo* Cyclophosphamide, *doc* Docetaxel, *nab-pac* Nab-paclitaxel, *pac* Paclitaxel, *pembro* Pembrolizumab, *veli* Veliparib

Each cell represents the comparison (odds ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level. Deviance information criterion: 26.59; Deviance: 14.65

Table 4 Results of network meta-analysis for event-free survival

Intervention	Pac→anthra + cyclo	Pac + carb→anthra + cyclo	Doc + carb→anthra + cyclo	Nab-pac→anthra + cyclo	Pac + carb + veli→anthra + cyclo	Pembro + pac + carb→pembro + anthra + cyclo→adjuvant pembro
Pac→anthra + cyclo	1	–	–	–	–	–
Pac + carb→anthra + cyclo	**0.57 (0.36, 0.90)**	1	–	–	–	–
Doc + carb→anthra + cyclo	0.66 (0.17, 2.59)	1.16 (0.32, 4.26)	1	–	–	–
Nab-pac→anthra + cyclo	**0.62 (0.39, 0.99)**	1.09 (0.56, 2.13)	0.94 (0.22, 4.06)	1	–	–
Pac + carb + veli→anthra + cyclo	**0.63 (0.43, 0.93)**	1.10 (0.71, 1.71)	0.95 (0.24, 3.77)	1.01 (0.56, 1.88)	1	–
Pembro + pac + carb→pembro + anthra + cyclo→adjuvant pembro	**0.36 (0.21, 0.61)**	**0.63 (0.48, 0.82)**	0.54 (0.14, 2.09)	0.58 (0.28, 1.17)	**0.57 (0.34, 0.95)**	1

Abbreviations: *Anthra* Anthracycline, *carb* Carboplatin, *CrI* Credible Interval, *cyclo* Cyclophosphamide, *doc* Docetaxel, *HR* Hazard ratio, *nab-pac* nab-paclitaxel, *pac* Paclitaxel, *pembro* Pembrolizumab, *veli* Veliparib

Each cell represents the comparison (HR and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level. Deviance information criterion: 9.23; Deviance: 4.26

by anthracycline + cyclophosphamide + bevacizumab in terms of pCR; and to paclitaxel + carboplatin + veliparib followed by anthracycline + cyclophosphamide in terms of EFS. Thus, neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab may be more efficacious than other neoadjuvant treatment regimens for patients with high-risk, early-stage TNBC.

The validity of NMA findings are dependent on the quality of the individual RCTs included in the network and the degree to which these RCTs are similar in terms of populations and methodology [9–11]. In an NMA of RCTs involving multiple treatment comparisons, randomization holds only within individual RCTs and not across RCTs. Thus, if the direct comparisons between treatments in the network involve systematic between-trial differences in study or patient characteristics, and these differences are treatment effect modifiers, then the estimates of indirect comparisons will be biased. In this study, the feasibility assessment demonstrated that the distribution of most potential treatment effect modifiers was balanced across the RCTs. However, KEYNOTE-522 was the only trial that evaluated a treatment regimen spanning both the neoadjuvant and adjuvant phases, which may have served to influence the relative treatment effects.

Some factors limit the conclusions that can be drawn from this NMA. First, ambiguity in the reporting of recurrence-free survival and OS for CALGB 40603 precluded the inclusion of this trial in the survival analyses. Second, because only one study connected each treatment in the network of evidence, between-study heterogeneity could not be estimated, and the NMA was performed with a fixed-effects assumption. Third, the systematic review did not identify sufficient data to answer questions such as which biomarkers predict pCR, which patients may achieve pCR without pembrolizumab, or the ideal dosage of pembrolizumab to achieve an ideal risk/benefit ratio, which could be investigated in future studies.

Despite these limitations, this study has several strengths that maximize its comprehensiveness and rigor. In particular, highly sensitive systematic searches in the peer-reviewed literature, recent conferences, and clinical trial registries were employed to identify all published evidence from RCTs of neoadjuvant immunotherapy and chemotherapy treatments for early-stage, locally advanced, non-metastatic TNBC. In addition, the review process was guided by pre-defined eligibility criteria, and data quality was ensured through the involvement of two independent reviewers in the study selection and data extraction processes.

Table 5 Results of network meta-analysis for overall survival

Intervention	Pac→anthra + cyclo	Pac + carb→anthra + cyclo	Doc + carb→anthra + cyclo	Nab-pac→anthra + cyclo	Pac + carb + veli→anthra + cyclo	Pembro + pac + carb→pembro + anthra + cyclo→adjuvant pembro
Pac→anthra + cyclo	1	–	–	–	–	–
Pac + carb→anthra + cyclo	0.63 (0.33, 1.20)	1	–	–	–	–
Doc + carb→anthra + cyclo	0.82 (0.16, 4.18)	1.30 (0.29, 5.87)	1	–	–	–
Nab-pac→anthra + cyclo	0.74 (0.40, 1.38)	1.18 (0.48, 2.86)	0.91 (0.16, 5.32)	1	–	–
Pac + carb + veli→anthra + cyclo	0.82 (0.48, 1.39)	1.30 (0.72, 2.35)	1.00 (0.20, 4.94)	1.11 (0.50, 2.54)	1	–
Pembro + pac + carb→pembro + anthra + cyclo→adjuvant pembro	**0.45 (0.22, 0.95)**	0.72 (0.51, 1.02)	0.55 (0.12, 2.59)	0.61 (0.23, 1.60)	0.55 (0.28, 1.09)	1

Abbreviations: *Anthra* Anthracycline, *Carb* Carboplatin, *Cyclo* Cyclophosphamide; *CrI* Credible interval, *DIC* Deviance information criterion, *Doc* Docetaxel, *HR* Hazard ratio, *Nab-pac* Nab-paclitaxel, *Pac* Paclitaxel, *Pembro* Pembrolizumab, *Veli* Veliparib

Each cell represents the comparison (HR and 95% CrI) of the row treatment versus the column treatment

All bolded values are statistically meaningful at the 0.05 significance level. DIC: 9.25; Deviance: 4.26

Conclusions

The results of this systematic review and NMA suggest that neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab is an effective treatment compared with other neoadjuvant treatments for patients with previously untreated, locally advanced, non-metastatic TNBC.

Abbreviations

CENTRAL	Cochrane Central Register of Controlled Trials
EFS	Event-free survival
EMBASE	Excerpta Medica DataBASE
HR	Hazard ratio
KM	Kaplan-Meier
MEDLINE	Medical Literature Analysis and Retrieval System Online
NMA	Network meta-analysis
OS	Overall survival
pCR	Pathologic complete response
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PICOS	Population, intervention, comparator, outcomes, study design
PFS	Progression-free survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
RCT	Randomized controlled trial
SIGN	Scottish Intercollegiate Guidelines Network
TNBC	Triple-negative breast cancer

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-023-11293-4.

Additional file 1: Additional Table 1. PRISMA 2020 checklist. **Additional Table 2.** Search strategy for EMBASE 1974 to 2022 April 20.**Additional Table 3.** Search strategy for Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to April 20, 2021.**Additional Table 4.** Search strategy for EBM Reviews - Cochrane Central Register of Controlled Trials March 2022. **Additional Table 5.** Trials identified in the systematic review.**Additional Table 6.** Trials included in the feasibility assessment and network meta-analysis.**Additional Table 7.** Treatment characteristics of included trials. **Supplementary Table 8.** Baseline patient characteristics of included trials.**Additional Table 9.** Definitions of pathological complete response, overall survival, and event-free survival used in the included trials.**Additional Table 10.** Data sources for feasibility assessment and network meta-analysis**. Additional Figure 1.** Results of network meta-analysis for event-free survival based on time-varying hazard ratios (constant hazards with p_1=0.5, p_2=0). **Additional Figure 2.** Best-fitting model: Results of network meta-analysis for overall survival based on constant hazard ratio model with p_1=0, p_2=0.**Additional Figure 3.** Second best-fitting model: Results of network meta-analysis for overall survival based on second-order fractional polynomial model with p_1=0, p_2=0.5; scale and second shape. **Additional Table 11.** Model fit estimate for network meta-analysis for event-free survival with parametric survival models. **Additional Table 12.** Estimated hazard ratios for event-free survival versus paclitaxel followed by anthracycline + cyclophosphamide at select time points based on time-varying hazard ratio assumption (constant hazard ratio with p_1=0.5, p_2=0). **Additional Table 13.** Basic parameter estimates of constant hazard ratio model with p_1=0.5, p_2=0 for event-free survival. **Additional Table 14.** Model fit estimate for network meta-analysis for overall survival with parametric survival models. **Additional Table 15.** Best-fitting model for overall survival: Estimated hazard ratios versus paclitaxel followed by anthracycline + cyclophosphamide at select time points based on time-varying hazard ratio assumption (constant hazard ratio with p_1=0, p_2=0). **Additional Table 16.** Best-fitting model for overall survival: Basic parameter estimates of constant hazard ratio model with p_1=0, p_2=0. **Additional Table 17.** Second best-fitting model for overall survival: Estimated hazard ratios versus paclitaxel followed by anthracycline + cyclophosphamide at select time points based on time-varying hazard ratio assumption (second-order fractional polynomial with p_1=0, p_2=0.5). **Additional Table 18.** Second best-fitting model for overall survival: Basic parameter estimates of second-order polynomial model with p_1=0, p_2=0.5. **Additional Figure 4.** Network of evidence for event-free survival and overall survival including CALGB 40603 (Alliance). Arrows (➔) indicate where treatment was administered sequentially, with treatments to the left of the arrow administered first. The orange circle denotes the primary treatment regimen of interest. Anthra includes doxorubicin and epirubicin, which were assumed to be equivalent. Anthra = anthracycline; bev = bevacizumab; carb = carboplatin; cyclo = cyclophosphamide; doc = docetaxel; nab-pac = nab-paclitaxel; pac = paclitaxel; pembro = pembrolizumab; veli = veliparib. **Additional Table 19.** Results of network-analysis for event-free survival including CALGB 40603 (Alliance). **Additional Table 20.** Results of network-analysis for event-free survival including CALGB 40603 (Alliance).

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Authors' contributions

AH, MH, WP, and AMF conceived of and designed the study; JP, KGA, and AMF collected the data; JP performed statistical analyses; JC, AH, MH, WP, PS, KGA, JP, AMF, PAF, and JO interpreted the data; KGA and AF drafted the manuscript; JC, AH, MH, WP, PS, PAF, and JO critically reviewed the manuscript. All authors have read and approved the final version of this manuscript.

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Availability of data and materials

The datasets analyzed in this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

MH, AH, and WP are employees of Merck & Co., Inc. KGA, JP, and AMF are employees of PRECISIONheor, a healthcare research consultancy that received funding from Merck and Co, Inc. to conduct the research described in this manuscript. PS, PAF, and JO declare no competing interests.

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