Meta-Analysis

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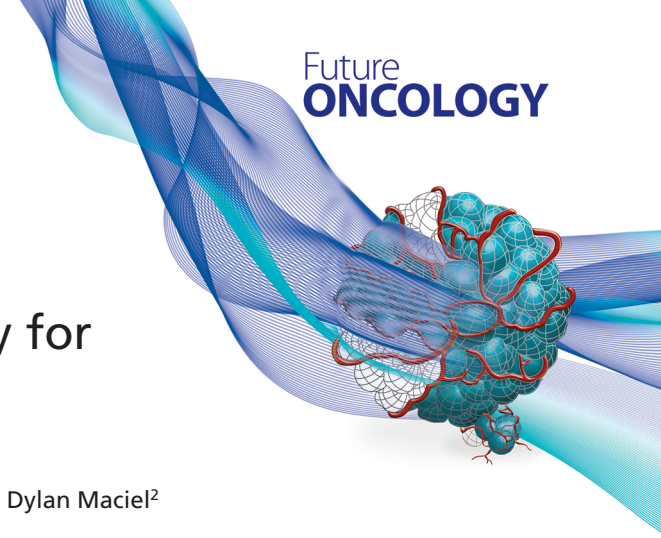

Pembrolizumab plus chemotherapy for first-line treatment of advanced triple-negative breast cancer

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Aim: A systematic review and network meta-analysis (NMA) was performed to evaluate the efficacy of first-line treatments for locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) patients. **Materials & methods:** Databases were searched for randomized controlled trials evaluating first-line treatments for locally recurrent unresectable or metastatic TNBC patients. NMA was performed to estimate relative treatment effects on overall and progression-free survival between pembrolizumab + chemotherapy and other interventions. **Results:** NMA including eight trials showed that the relative efficacy of pembrolizumab + chemotherapy was statistically superior to that of other immunotherapy- or chemotherapy-based treatment regimens. **Conclusion:** Pembrolizumab + chemotherapy confers benefits in survival outcomes versus alternative interventions for the first-line treatment of locally recurrent unresectable or metastatic TNBC patients.

Plain language summary – Clinical value of initial treatments for patients with advanced triple-negative breast cancer:

What is this article about?: Around 15% of breast cancer patients have the triple-negative breast cancer (TNBC) subtype, which has the worst prognosis. Treatments targeting the immune system, such as pembrolizumab, were recently found to improve the outcomes of patients with cancer that is at an advanced stage or resistant to standard therapies. However, clinical trials evaluating the efficacy of cancer treatments typically compare only two alternative treatments. Therefore, we conducted this study to understand the relative efficacy of several commonly used initial treatments for advanced TNBC by indirectly comparing the results of all available clinical trials that were sufficiently similar. We identified trials by systematically searching the medical literature and analyzed the results of several clinical trials together to estimate the efficacy of pembrolizumab + chemotherapy compared with several other initial treatment regimens for patients with advanced TNBC.

What were the results?: We identified eight randomized controlled trials evaluating treatment regimens containing chemotherapeutic or immunotherapeutic agents in patients with previously untreated advanced TNBC. Considering all these trials together, pembrolizumab + chemotherapy was found to prolong patient survival to a greater extent than several other treatment regimens including carboplatin, docetaxel, paclitaxel, nab-paclitaxel/paclitaxel, bevacizumab + paclitaxel, ixabepilone + paclitaxel and ixabepilone + bevacizumab depending on the specific set of trials analyzed.

What do the results of the study mean?: These results indicate that pembrolizumab + chemotherapy has beneficial effects on patient survival compared with other initial treatment regimens for patients with advanced TNBC.

Tweetable abstract: Pembrolizumab + chemotherapy confers benefits in survival outcomes versus alternative interventions for the first-line treatment of locally recurrent unresectable or metastatic TNBC patients.

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Breast cancer is the most common cancer in women, with 2.3 million new cases worldwide in 2020 [1]. A subtype of breast cancer, triple-negative breast cancer (TNBC) accounts for ~15% of all breast cancer cases and is characterized by the lack of ER, PR and HER2 [2]. TNBC has the worst prognosis among all breast cancer subtypes, with a median overall survival (OS) of 13 months in patients with metastatic TNBC compared with 38 months in patients with other types of breast cancer [3]. Thus, given the complex histology and aggressive nature of TNBC, new therapeutic approaches are warranted.

In recent years, PD-1 and PD-L1 inhibitors have been shown to improve OS in patients with advanced cancers or cancers refractory to standard treatments, with promising results for the treatment of breast cancer [4]. Based on statistically and clinically meaningful improvements in OS and progression-free survival (PFS) demonstrated in the phase III randomized controlled trial (RCT) KEYNOTE-355, pembrolizumab + chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine/carboplatin) was recently granted US FDA and European Medicines Agency approval for first-line treatment of locally recurrent unresectable or metastatic TNBC in patients whose tumors express PD-L1 at the cut-off of combined positive score (CPS) $\geq$10 [5,6].

Network meta-analysis (NMA) is a statistical method allowing indirect comparisons among treatment regimens that have not been directly compared in head-to-head RCTs [7–9]. This approach enables a variety of stakeholders, including clinicians, developers of guidelines and health technology assessment agencies, to assess the performance of new treatments against all existing evidence on other treatments [10,11]. More specifically, NMA can combine both direct and indirect evidence on any treatments that form a connected network of trials provided that there are minimal differences among trials in terms of patient characteristics, study characteristics and outcome definitions that could modify the relative treatment effects [12]. Although clinical trial evidence suggests that pembrolizumab + chemotherapy is an effective approach to treating locally recurrent unresectable or metastatic TNBC, it has not been compared against all other immunotherapy- and chemotherapy-based regimens in head-to-head RCTs. Therefore, we aimed to estimate the relative efficacy of pembrolizumab + chemotherapy in terms of OS and PFS compared with other interventions for the first-line treatment of locally recurrent unresectable or metastatic TNBC through a systematic review (SR) and NMA.

Materials & methods

Systematic review

The SR was performed following Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [13] and employed methodology similar to that used for an SR focused on a different TNBC patient population [14]. The review was not registered in a systematic review registry. Studies were selected using pre-specified population, intervention, comparator, outcome and study design (PICOS) criteria (Supplementary Table 1). Phase II or III RCTs were eligible for inclusion if they were enrolled patients with locally recurrent unresectable or metastatic TNBC who received first-line treatment with specific chemotherapy or immunotherapy regimens. Trials were eligible for inclusion in the SR if they enrolled only TNBC patients or enrolled a broader population of breast cancer patients and reported at least one outcome of interest in a >90% TNBC patient subgroup.

Trials were identified through searches of Embase, MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid on 21 April 2022 (full search strategies provided in Supplementary Table 2–4). Scottish Intercollegiate Guidelines Network (SIGN) filters (www.sign.ac.uk/what-we-do/methodology/search-filters/) were used to limit Embase and MEDLINE search results to RCTs. Conference abstracts from the American Society of Clinical Oncology (2021–2022), San Antonio Breast Cancer Symposium (2021) and European Society of Medical Oncology (2021) were hand-searched to identify trials that were not yet published as journal articles. To mitigate the risk of reporting biases (i.e., missing RCTs with null or negative results not published as journal articles or conference abstracts), the US National Institute of Health Clinical Trials Registry and European Union Clinical Trial Registry were searched to identify completed trials with results available.

Title/abstract screening, full-text screening and data extraction were performed by two independent reviewers. Any discrepancies between reviewers were resolved through discussion or by involving a third reviewer. The risk of bias in included trials was assessed using the Cochrane Collaboration's Risk of Bias tool [15].

Feasibility assessment & network meta-analysis

NMA is an extension of pairwise meta-analysis that enables the indirect comparison of treatments that have not been directly compared in head-to-head trials [16]. As the validity of an NMA depends on the absence of systematic

differences in treatment effects among trials in the network [16–20], a feasibility assessment was performed before commencing the NMA to determine whether the interventions of interest formed a single network of evidence for each outcome and evaluate distributions of study, patient, treatment and outcome characteristics across trials to identify potential treatment effect-modifiers [17].

After feasibility assessment, NMA was performed for the efficacy outcomes of OS and PFS. Although the assumptions of random-effects NMA models are generally preferred as they are usually more plausible than fixed-effect models, between-study heterogeneity could not be estimated in the present study because only one trial connected each intervention in the evidence networks. Therefore, NMA was performed using fixed-effects models. Proportional hazards between interventions were assumed using regression models with a contrast-based normal likelihood for the log hazard ratio (HR) and corresponding standard error for each trial [21].

Normal non-informative prior distributions for model parameters were estimated with a mean of 0 and variance of 10,000 [21]. NMA results are presented as HRs estimating of the treatment effect of each intervention relative to all other interventions in the network. The posterior distributions of relative treatment effects are summarized by the median and 95% credible interval (CrI), which reflects a 95% probability that the estimate is within the specified range. Analyses were conducted using R version 4.0.3 and OpenBugs version 3.2.3 [22].

Results

Systematic review & feasibility assessment

Study selection

The literature search yielded a total of 2930 records, of which 2332 abstracts and 154 full texts were screened by two independent reviewers (Figure 1). Six additional records were identified from conference proceedings, clinical trial registries and material provided by Merck & Co., Inc., Rahway (NJ, USA). In total, 19 records describing eight unique trials were included in the SR (Supplementary Table 5) [23–39].

Study characteristics

Of the eight RCTs, five were phase III, two were phase II and one was phase II/III (Table 1). Three trials were double blind, and five trials were open label. All trials were multicenter. Across trials, follow-up duration ranged from 14.8 to 43.5 months. All trials were considered to have an overall low risk of bias (Supplementary Table 6).

Treatment characteristics

Of the 18 treatment arms across the eight trials, three arms evaluated paclitaxel + bevacizumab, two arms evaluated nab-paclitaxel alone, two arms evaluated paclitaxel, two arms evaluated docetaxel, one arm evaluated carboplatin alone and the remaining arms evaluated other chemotherapy combinations. The ixabepilone + bevacizumab arm in Alliance did not meet the PICOS criteria and therefore was not included in the NMA. The nab-paclitaxel + bevacizumab arm in Alliance also did not match the PICOS criteria but was included in the NMA based on this chemotherapy combination being an approved substitute for paclitaxel for the treatment of metastatic HER2-negative breast cancer [40]. Only the pembrolizumab arm of KEYNOTE-355 and atezolizumab arm of IMpassion130 evaluated PD-1/PD-L1-directed therapies. Overall, dosing and administration schedules for treatment regimens included in the NMA were comparable (Supplementary Table 7).

Patient characteristics

Median patient age ranged from 53 to 60 years (Supplementary Table 8). Most trials included only female patients, whereas two included ≤1% males. All trials that reported race/ethnicity enrolled mostly White patients. All but one trial (TNT) enrolled patients with an ECOG performance score of 0 or 1, except for one or two patients. Thus, the distributions of patient age, sex, race/ethnicity and performance status were similar across trials. Three trials (KEYNOTE-355, IMpassion130 and tnAcity) exclusively enrolled TNBC patients, whereas the remaining trials enrolled a broader population of breast cancer patients but reported at least one efficacy outcome of interest for a TNBC subgroup. E2100 reported outcomes for patients whose tumors were ER- and PR-negative, but the proportion of patients whose tumors were HER2-negative was not reported.

All trials enrolled patients irrespective of PD-L1 expression status; however, KEYNOTE-355 and IMpassion130 reported outcomes separately for PD-L1-positive and -negative subgroups. PD-L1 expression was measured using the PD-L1 IHC 22C3 pharmDx test (Dako North America, Inc, CA, USA) in KEYNOTE-355 and the PD-L1 immunohistochemical assay (Ventana Medical Systems, IN, USA) in IMpassion130. Because these two assays do not

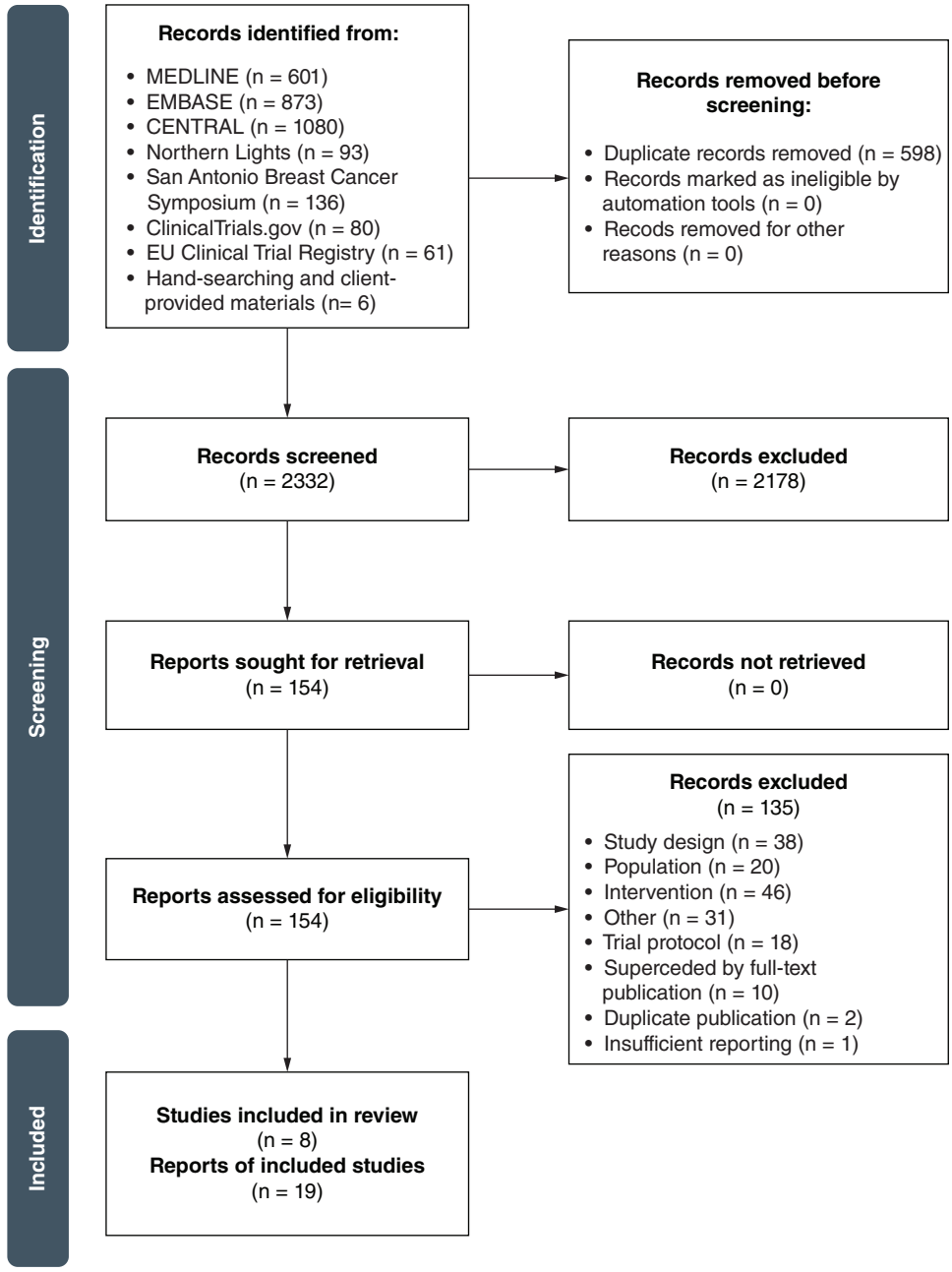

Figure 1. PRISMA flow diagram of the study identification and selection process.

identify comparable patient populations and PD-L1 expression was expected to modify the relative treatment effect in trials comparing a PD-L1-directed therapy to chemotherapy, data from a retrospective analysis of IMpassion130 patients identified during a targeted literature search was used in the NMA. In this retrospective analysis, a model was developed to estimate HRs for OS and PFS in IMpassion130 patients with PD-L1 CPS ≥10 [41], the threshold for determining PD-L1 positivity in KEYNOTE-355. The model was implemented by testing a subset of IMpassion130 patients with both the VENTANA SP142 assay (used to determine PD-L1 IC ≥1% status in all IMpassion130 patients) and the Dako 22C3 assay (used to determine PD-L1 CPS ≥10 status in KEYNOTE-355) and evaluating the concordance between the assays to create harmonized cutoffs.

Table 1. Study characteristics of included trials.

Trial ID	Phase	Masking	Disease stage	Multicenter	Treatment	Follow-up duration, months, median (IQR)	Ref.
Alliance (CALGB 40502)	II	Open label	Stage IIIC-IV locally recurrent or metastatic	Yes	Paclitaxel ± bevacizumab Nab-paclitaxel ± bevacizumab Ixabepilone ± bevacizumab	–	[19,20]
E2100	III	Open label	Stage IV metastatic	Yes	Paclitaxel ± bevacizumab Paclitaxel	41.6 (–)‡ 43.5 (–)‡	[21]
IMpassion130	III	Double blind	Metastatic or unresectable locally advanced	Yes	Atezolizumab ± nab-paclitaxel Placebo ± nab-paclitaxel	18.8 (8.9–34.7)	[22–27]
JapicCTI-090921	III	Open label	Metastatic or unresectable locally advanced	Yes	Nab-paclitaxel Docetaxel	23 (–)‡	[28]
KEYNOTE-355	III	Double blind	Locally recurrent or metastatic	Yes	Pembrolizumab ± chemotherapy† Chemotherapy†	25.9 (22.8–29.9) 26.3 (22.7–29.7)	[29–32]
MERiDiAN	III	Double blind	Metastatic	Yes	Placebo ± paclitaxel Bevacizumab ± paclitaxel	14.8 (–)‡ 15.0 (–)‡	[33]
tnAcity	II/III	Open label	Locally advanced inoperable or metastatic	Yes	Nab-paclitaxel ± carboplatin Nab-paclitaxel ± gemcitabine Gemcitabine ± carboplatin	–	[34]
TNT	II	Open label	Metastatic	Yes	Carboplatin Docetaxel	–	[35]

†Nab-paclitaxel, paclitaxel or gemcitabine/carboplatin.
‡Follow-up for duration for entire trial population, including non-TNBC patients.
*Intervention not of interest.
IQR: Interquartile range; TNBC: Triple-negative breast cancer.

Reported outcomes

Six trials provided a definition of OS that was similar across trials: time from study entry or randomization until death from any cause (Supplementary Table 9). Two trials (E2100 and MERiDiAN) reported OS only for a broader population of breast cancer patients and not specifically for the TNBC subgroup; thus, overall population OS data from these two trials were included in the NMA unless otherwise specified.

One trial (KEYNOTE-355) evaluated PFS with both blinded independent central review (BICR) and investigator assessment (IA), three trials evaluated PFS with IA (IMpassion130, MERiDiAN and tnAcity), and four trials did not report the method of PFS assessment (Alliance, E2100, JapicCTI-090921 and TNT). Because the effect of IA versus BICR assessment on PFS is unclear, it is generally preferred to construct networks of evidence using similar outcome assessment when possible [42,43]. To facilitate the most equitable comparisons among the three trials that evaluated PFS with IA, base case networks were constructed using IA PFS from KEYNOTE-355. The results of sensitivity analysis using BICR-assessed PFS from KEYNOTE-355 were concordant with the base case findings (data not shown).

Kaplan–Meier (KM) curves for the population of interest were available in only four trials (KEYNOTE-355, TNT, Alliance and tnAcity). Thus, as it was not possible to construct connected networks for the comparisons of interest using survival data from KM curves, NMA was conducted using reported HRs (Supplementary Table 10).

A summary of safety outcomes, which were reported by four trials, is provided in Supplementary Table 11.

Network meta-analysis

Networks were constructed to compare pembrolizumab + chemotherapy to other interventions under the assumption that PD-L1 status is only a relative treatment effect modifier for PD-1/PD-L1-directed therapies. Therefore, subgroup data for patients with a PD-L1 CPS ≥10 were used for KEYNOTE-355 and IMpassion130. KEYNOTE-355 evaluated the efficacy of pembrolizumab + chemotherapy relative to chemotherapy alone by pre-assigning all patients to investigator's choice of paclitaxel, nab-paclitaxel or gemcitabine/carboplatin; patients were then randomized to receive their chemotherapy assignment alone or in combination with pembrolizumab. In scenario 1 (Figure 2), paclitaxel and nab-paclitaxel were assumed to have different efficacy, and cohorts of KEYNOTE-355 patients assigned to nab-paclitaxel, paclitaxel or gemcitabine/carboplatin were analyzed separately. In scenario 2

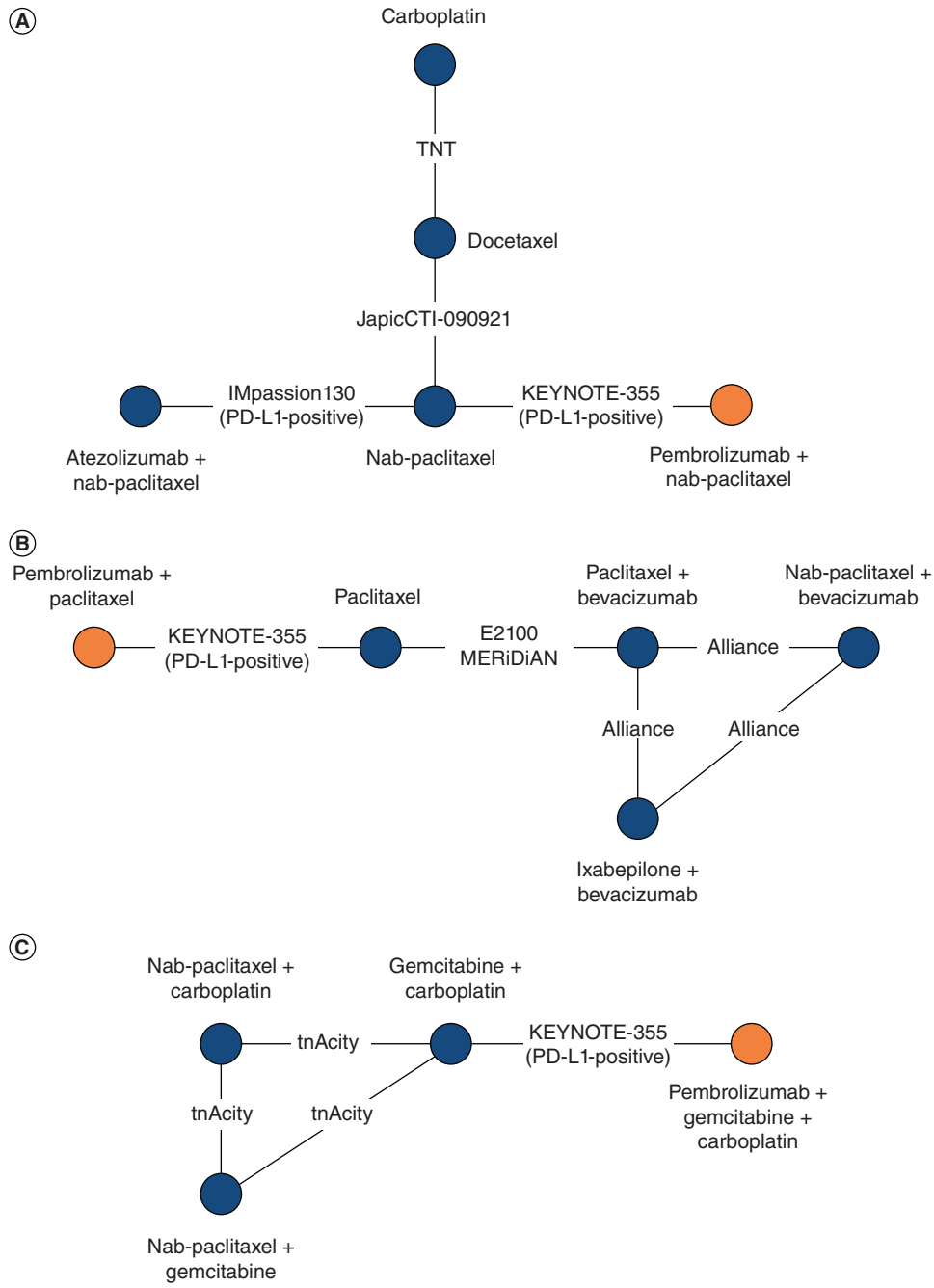

Figure 2. Evidence networks with KEYNOTE-355 patients assigned to nab-paclitaxel, paclitaxel and gemcitabine/carboplatin analyzed separately (scenario 1).
Cohorts of patients receiving nab-paclitaxel **(A)**, paclitaxel **(B)**, or gemcitabine/carboplatin **(C)** in KEYNOTE-355 were analyzed in separate networks, as these treatments were assumed to have different efficacies. Due to a lack of common comparators, the networks are disconnected.

(Figure 3), paclitaxel and nab-paclitaxel were assumed to have the same efficacy, and cohorts of KEYNOTE-355 patients assigned to nab-paclitaxel or paclitaxel were analyzed together. Data sources and populations for each clinical end point included in the NMA are presented in Supplementary Table 12, and statistical values (i.e., HRs, logHRs and standard errors) used in the NMA are shown in Supplementary Table 13.

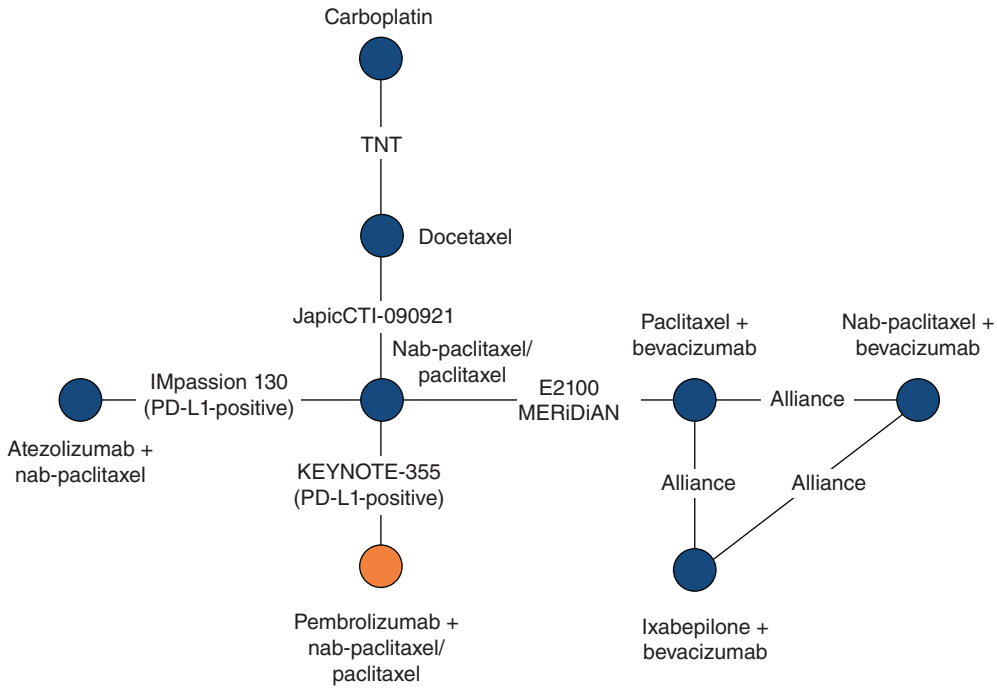

Figure 3. Evidence network with KEYNOTE-355 patients assigned to paclitaxel and nab-paclitaxel analyzed together (scenario 2).
Nab-paclitaxel and paclitaxel are assumed to have the same efficacy, thus cohorts of patients receiving these treatments in KEYNOTE-355 were analyzed in the same network.

Table 2. Network meta-analysis including KEYNOTE-355 patients assigned to nab-paclitaxel.

Overall survival				
Nab-paclitaxel	1.30 (0.97, 1.75)	0.66 (0.40, 1.09)	**0.56 (0.36, 0.86)**	1.59 (0.98, 2.57)
0.77 (0.57, 1.04)	**Atezolizumab + nab-paclitaxel**	**0.51 (0.28, 0.91)**	**0.43 (0.26, 0.73)**	1.22 (0.69, 2.16)
1.52 (0.92, 2.50)	**1.97 (1.10, 3.53)**	**Carboplatin**	0.85 (0.66, 1.10)	**2.41 (1.20, 4.83)**
1.78 (1.16, 2.74)	**2.32 (1.38, 3.89)**	1.18 (0.91, 1.53)	**Docetaxel**	**2.84 (1.49, 5.40)**
0.63 (0.39, 1.02)	0.82 (0.46, 1.44)	**0.41 (0.21, 0.83)**	**0.35 (0.19, 0.67)**	**Pembrolizumab + nab-paclitaxel**
Progression-free survival				
Nab-paclitaxel	**1.41 (1.10, 1.79)**	1.15 (0.73, 1.82)	1.2 (0.81, 1.79)	1.56 (0.99, 2.46)
0.71 (0.56, 0.91)	**Atezolizumab + nab-paclitaxel**	0.82 (0.49, 1.37)	0.85 (0.54, 1.36)	1.11 (0.66, 1.86)
0.87 (0.55, 1.36)	1.22 (0.73, 2.03)	**Carboplatin**	1.04 (0.84, 1.28)	1.35 (0.71, 2.57)
0.83 (0.56, 1.24)	1.17 (0.73, 1.87)	0.96 (0.78, 1.19)	**Docetaxel**	1.30 (0.71, 2.39)
0.64 (0.41, 1.01)	0.90 (0.54, 1.51)	0.74 (0.39, 1.41)	0.77 (0.42, 1.41)	**Pembrolizumab + nab-paclitaxel**

Each cell represents the comparison (hazard ratio and 95% credible interval) of the row treatment vs the column treatment. All bolded values are statistically meaningful at the 0.05 level.
Overall survival: deviance information criterion: 7.35; deviance: 3.35. Progression-free survival: Deviance information criterion: 7.36; deviance: 3.36.

KEYNOTE-355 patients assigned to nab-paclitaxel, paclitaxel & gemcitabine/carboplatin analyzed separately (scenario 1)

The networks for OS and PFS including KEYNOTE-355 patients assigned to nab-paclitaxel consisted of four trials evaluating five interventions (Figure 2A). For OS, the point estimates of the relative efficacy of pembrolizumab + nab-paclitaxel were statistically superior to that of carboplatin (HR: 0.41; 95% CrI: 0.21–0.83) and docetaxel (HR: 0.35; 95% CrI: 0.19–0.67; Table 2). Additionally, atezolizumab + nab-paclitaxel was statistically superior to carboplatin (HR: 0.51; 95% CrI: 0.28–0.91) and docetaxel (HR: 0.43; 95% CrI: 0.26–0.73). Finally, nab-paclitaxel was statistically superior to docetaxel (HR: 0.56; 95% CrI: 0.36–0.86) For PFS, the relative efficacy of pembrolizumab + nab-paclitaxel was statistically similar to that of other interventions. Atezolizumab + nab-paclitaxel was statistically superior to nab-paclitaxel (HR: 0.71; 95% CrI: 0.56–0.91).

Table 3. Network meta-analysis including KEYNOTE-355 patients assigned to paclitaxel.

Overall survival				
Paclitaxel	1.20 (0.95, 1.51)	0.94 (0.61, 1.43)	**1.62 (1.05, 2.52)**	**2.95 (1.39, 6.25)**
0.83 (0.66, 1.05)	**Bevacizumab + paclitaxel**	0.78 (0.55, 1.11)	1.35 (0.93, 1.96)	**2.45 (1.12, 5.39)**
1.07 (0.70, 1.63)	1.28 (0.90, 1.82)	**Ixabepilone + bevacizumab**	**1.73 (1.21, 2.48)**	**3.14 (1.33, 7.47)**
0.62 (0.40, 0.95)	0.74 (0.51, 1.07)	**0.58 (0.40, 0.83)**	**Nab-paclitaxel + bevacizumab**	1.82 (0.76, 4.34)
0.34 (0.16, 0.72)	**0.41 (0.19, 0.89)**	**0.32 (0.13, 0.75)**	0.55 (0.23, 1.31)	**Pembrolizumab + paclitaxel**
Progression-free survival				
Paclitaxel	**1.82 (1.41, 2.33)**	1.30 (0.85, 1.99)	**2.30 (1.48, 3.55)**	**2.70 (1.29, 5.64)**
0.55 (0.43, 0.71)	**Bevacizumab + paclitaxel**	0.72 (0.51, 1.01)	1.27 (0.89, 1.80)	1.49 (0.68, 3.25)
0.77 (0.50, 1.17)	1.39 (0.99, 1.96)	**Ixabepilone + bevacizumab**	**1.76 (1.24, 2.49)**	2.07 (0.88, 4.85)
0.44 (0.28, 0.67)	0.79 (0.55, 1.13)	**0.57 (0.40, 0.81)**	**Nab-paclitaxel + bevacizumab**	1.18 (0.50, 2.78)
0.37 (0.18, 0.77)	0.67 (0.31, 1.47)	0.48 (0.21, 1.14)	0.85 (0.36, 2.01)	**Pembrolizumab + paclitaxel**

Each cell represents the comparison (HR and 95% CrI) of the row treatment vs the column treatment. All bolded values are statistically meaningful at the 0.05 level. Overall survival: deviance information criterion: 7.39; deviance: 3.38. Progression-free survival: Deviance information criterion: 7.62; deviance: 3.62.
HR: Hazard ratio; CrI: Credible interval.

Table 4. Network meta-analysis including KEYNOTE-355 patients assigned to gemcitabine/carboplatin.

Overall survival			
Gemcitabine + carboplatin	1.25 (0.82, 1.91)	0.91 (0.66, 1.26)	1.14 (0.79, 1.63)
0.80 (0.52, 1.22)	**Nab-paclitaxel + carboplatin**	0.73 (0.50, 1.07)	0.91 (0.52, 1.58)
1.10 (0.79, 1.52)	1.37 (0.94, 2.00)	**Nab-paclitaxel + gemcitabine**	1.25 (0.77, 2.02)
0.88 (0.62, 1.26)	1.10 (0.63, 1.92)	0.80 (0.50, 1.30)	**Pembrolizumab + gemcitabine/carboplatin**
Progression-free survival			
Gemcitabine + carboplatin	**1.72 (1.10, 2.69)**	1.02 (0.77, 1.35)	1.21 (0.84, 1.72)
0.58 (0.37, 0.91)	**Nab-paclitaxel + carboplatin**	**0.59 (0.41, 0.86)**	0.70 (0.40, 1.24)
0.98 (0.74, 1.30)	**1.69 (1.17, 2.46)**	**Nab-paclitaxel + gemcitabine**	1.18 (0.75, 1.86)
0.83 (0.58, 1.18)	1.43 (0.81, 2.53)	0.84 (0.54, 1.33)	**Pembrolizumab + gemcitabine/carboplatin**

Each cell represents the comparison (HR and 95% CrI) of the row treatment vs the column treatment. All bolded values are statistically meaningful at the 0.05 level. Overall survival: deviance information criterion: 5.25; deviance: 2.25. Progression-free survival: Deviance information criterion: 5.25; deviance: 2.25.
HR: Hazard ratio; CrI: Credible interval.

The networks for OS and PFS including KEYNOTE-355 patients assigned to paclitaxel consisted of four trials evaluating five interventions (Figure 2B). For OS, the relative efficacy of pembrolizumab + paclitaxel was statistically superior to that of all other interventions, except nab-paclitaxel + bevacizumab (HR: 0.55; 95% CrI: 0.23–1.31; Table 3). Nab-paclitaxel + bevacizumab was statistically superior to ixabepilone + bevacizumab (HR: 0.58; 95% CrI: 0.40–0.83) and paclitaxel (HR: 0.62; 95% CrI: 0.40–0.95). For PFS, the relative efficacy of pembrolizumab + paclitaxel was statistically superior to that of paclitaxel (HR: 0.37; 95% CrI: 0.18–0.77). Nab-paclitaxel + bevacizumab was statistically superior to ixabepilone + bevacizumab (HR: 0.57; 95% CrI: 0.40–0.81) and paclitaxel (HR: 0.44; 95% CrI: 0.28–0.67). Finally, bevacizumab + paclitaxel showed statistically superior PFS versus paclitaxel (HR: 0.55; 95% CrI: 0.43–0.71).

The networks for OS and PFS including KEYNOTE-355 patients assigned to gemcitabine/carboplatin consisted of two trials evaluating five interventions (Figure 2C). For OS, no statistically meaningful differences between treatments were detected. For PFS, nab-paclitaxel + carboplatin was statistically superior to gemcitabine + carboplatin (HR: 0.58; 95% CrI: 0.37–0.91) and nab-paclitaxel + gemcitabine (HR: 0.59; 95% CrI: 0.41–0.86; Table 4).

KEYNOTE-355 patients assigned to nab-paclitaxel & paclitaxel analyzed together (scenario 2)

The networks for OS and PFS including KEYNOTE-355 patients assigned to nab-paclitaxel and paclitaxel combined consisted of seven trials evaluating eight interventions (Figure 3). For OS, pembrolizumab + nab-paclitaxel/paclitaxel was statistically superior to that of all other interventions, except atezolizumab + nab-paclitaxel (HR: 0.70; 95% CrI: 0.42–1.17), bevacizumab + paclitaxel (HR: 0.65; 95% CrI: 0.40–1.04) and nab-paclitaxel + bevacizumab (HR: 0.88; 95% CrI: 0.48–1.60). Atezolizumab + nab-paclitaxel was statistically superior to carboplatin (HR: 0.51; 95% CrI: 0.29–0.89) and docetaxel (HR: 0.43; 95% CrI: 0.26–0.71).

Table 5. Network meta-analysis including KEYNOTE-355 patients assigned to nab-paclitaxel or paclitaxel combined.

Overall survival							
Nab-paclitaxel/paclitaxel	1.30 (0.97, 1.75)	1.20 (0.95, 1.51)	0.66 (0.41, 1.06)	**0.56 (0.37, 0.84)**	0.94 (0.61, 1.43)	**1.62 (1.05, 2.52)**	**1.85 (1.23, 2.79)**
0.77 (0.57, 1.04)	**Atezolizumab + nab-paclitaxel**	0.92 (0.63, 1.35)	**0.51 (0.29, 0.89)**	**0.43 (0.26, 0.71)**	0.72 (0.43, 1.21)	1.25 (0.74, 2.12)	1.42 (0.86, 2.37)
0.83 (0.66, 1.05)	1.08 (0.74, 1.58)	**Bevacizumab + paclitaxel**	**0.55 (0.32, 0.94)**	**0.47 (0.29, 0.74)**	0.78 (0.55, 1.11)	1.35 (0.93, 1.96)	1.54 (0.96, 2.47)
1.52 (0.94, 2.45)	**1.97 (1.12, 3.47)**	**1.82 (1.07, 3.10)**	**Carboplatin**	0.85 (0.66, 1.10)	1.42 (0.75, 2.69)	**2.46 (1.29, 4.71)**	**2.81 (1.49, 5.26)**
1.79 (1.19, 2.67)	**2.32 (1.40, 3.84)**	**2.14 (1.34, 3.42)**	1.18 (0.91, 1.52)	**Docetaxel**	1.68 (0.93, 3.00)	**2.90 (1.59, 5.25)**	**3.31 (1.86, 5.87)**
1.07 (0.70, 1.63)	1.38 (0.83, 2.31)	1.28 (0.90, 1.82)	0.70 (0.37, 1.33)	0.60 (0.33, 1.07)	**Ixabepilone + bevacizumab**	**1.73 (1.20, 2.48)**	**1.97 (1.09, 3.55)**
0.62 (0.40, 0.95)	0.80 (0.47, 1.36)	0.74 (0.51, 1.07)	**0.41 (0.21, 0.78)**	**0.35 (0.19, 0.63)**	**0.58 (0.40, 0.83)**	**Nab-paclitaxel + bevacizumab**	1.14 (0.62, 2.08)
0.54 (0.36, 0.82)	0.70 (0.42, 1.17)	0.65 (0.40, 1.04)	**0.36 (0.19, 0.67)**	**0.30 (0.17, 0.54)**	**0.51 (0.28, 0.92)**	0.88 (0.48, 1.60)	**Pembrolizumab + nab-paclitaxel/paclitaxel**
Progression-free survival							
Nab-paclitaxel/paclitaxel	**1.41 (1.10, 1.80)**	**1.81 (1.41, 2.33)**	1.15 (0.73, 1.81)	1.20 (0.80, 1.79)	1.30 (0.86, 2.00)	**2.30 (1.48, 3.55)**	**1.72 (1.17, 2.55)**
0.71 (0.56, 0.91)	**Atezolizumab + nab-paclitaxel**	1.29 (0.91, 1.83)	0.82 (0.49, 1.37)	0.85 (0.53, 1.36)	0.93 (0.57, 1.51)	1.63 (0.99, 2.68)	1.22 (0.77, 1.94)
0.55 (0.43, 0.71)	0.78 (0.55, 1.10)	**Bevacizumab + paclitaxel**	0.64 (0.38, 1.07)	0.66 (0.41, 1.06)	0.72 (0.51, 1.01)	1.27 (0.89, 1.81)	0.95 (0.60, 1.51)
0.87 (0.55, 1.36)	1.22 (0.73, 2.04)	1.57 (0.94, 2.63)	**Carboplatin**	1.04 (0.84, 1.28)	1.13 (0.61, 2.11)	**1.99 (1.06, 3.74)**	1.50 (0.82, 2.72)
0.83 (0.56, 1.25)	1.18 (0.73, 1.87)	1.51 (0.94, 2.43)	0.96 (0.78, 1.19)	**Docetaxel**	1.09 (0.61, 1.95)	**1.91 (1.06, 3.46)**	1.44 (0.82, 2.51)
0.77 (0.50, 1.17)	1.08 (0.66, 1.76)	1.39 (0.99, 1.96)	0.88 (0.47, 1.64)	0.92 (0.51, 1.65)	**Ixabepilone + bevacizumab**	**1.76 (1.24, 2.49)**	1.32 (0.74, 2.35)
0.44 (0.28, 0.67)	0.61 (0.37, 1.01)	0.79 (0.55, 1.13)	**0.50 (0.27, 0.94)**	**0.52 (0.29, 0.95)**	**0.57 (0.40, 0.81)**	**Bevacizumab + nab-paclitaxel**	0.75 (0.42, 1.35)
0.58 (0.39, 0.86)	0.82 (0.51, 1.29)	1.05 (0.66, 1.67)	0.67 (0.37, 1.22)	0.70 (0.40, 1.22)	0.76 (0.43, 1.35)	1.33 (0.74, 2.39)	**Pembrolizumab + nab-paclitaxel/paclitaxel**

Each cell represents the comparison (HR and 95% CrI) of the row treatment vs the column treatment. All bolded values are statistically meaningful at the 0.05 level. Overall survival: deviance information criterion: 13.37; deviance: 6.38. Progression-free survival: Deviance information criterion: 13.67; deviance: 6.66.
HR: Hazard ratio; CrI: Credible interval.

Nab-paclitaxel + bevacizumab was statistically superior to ixabepilone + bevacizumab (HR: 0.58; 95% CrI: 0.40–0.83), docetaxel (HR: 0.35; 95% CrI: 0.19–0.63), carboplatin (HR: 0.41; 95% CrI: 0.21–0.78) and nab-paclitaxel/paclitaxel (HR: 0.62; 95% CrI: 0.40–0.95). Finally, bevacizumab + paclitaxel showed a statistically meaningful improvement over carboplatin (HR: 0.55; 95% CrI: 0.32–0.94) and docetaxel (HR: 0.47; 95% CrI: 0.29–0.74; Table 5). For PFS, the relative efficacy of pembrolizumab + nab-paclitaxel/paclitaxel was statistically superior to that of nab-paclitaxel/paclitaxel (HR: 0.58; 95% CrI: 0.39–0.86). Atezolizumab + nab-paclitaxel was statistically superior to nab-paclitaxel/paclitaxel (HR: 0.71; 95% CrI: 0.56–0.91). Bevacizumab + nab-paclitaxel was statistically superior to ixabepilone + bevacizumab (HR: 0.57; 95% CrI: 0.40–0.81), docetaxel (HR: 0.52; 95% CrI: 0.29–0.95), carboplatin (HR: 0.50; 95% CrI: 0.27–0.94) and nab-paclitaxel/paclitaxel (HR: 0.44; 95% CrI: 0.28–0.67). Finally, bevacizumab + paclitaxel showed a statistically meaningful improvement in PFS relative to nab-paclitaxel/paclitaxel (HR: 0.55; 95% CrI: 0.43–0.71).

Sensitivity analysis was also performed for a network for OS that did not include E2100 and MERiDiAN because these trials reported OS for the overall breast cancer population rather than the TNBC subgroup. In this analysis, the relative efficacy of pembrolizumab + nab-paclitaxel/paclitaxel in terms of OS was statistically superior to that of all other interventions, except atezolizumab + nab-paclitaxel (Supplementary Tables 14 & 15).

Discussion

A total of 19 records pertaining to eight unique RCTs that enrolled patients with locally recurrent inoperable or metastatic TNBC receiving first-line treatment were identified through a systematic literature search. These trials were assessed for their feasibility of inclusion in NMA, and networks of evidence were constructed to compare

pembrolizumab + chemotherapy to other interventions. Further, separate evidence networks were constructed based on patient assignment to nab-paclitaxel, paclitaxel, nab-paclitaxel/paclitaxel combined or gemcitabine/carboplatin in KEYNOTE-355.

Considering OS, NMA showed that the relative treatment efficacy of pembrolizumab + different chemotherapy agents (nab-paclitaxel, paclitaxel, nab-paclitaxel/paclitaxel combined or gemcitabine/carboplatin) was statistically superior to that of carboplatin, docetaxel, paclitaxel, bevacizumab + paclitaxel, ixabepilone + paclitaxel or ixabepilone + bevacizumab depending on the evidence network analyzed. Considering PFS, the relative treatment efficacy of pembrolizumab + different chemotherapy agents (nab-paclitaxel, paclitaxel, nab-paclitaxel/paclitaxel combined or gemcitabine/carboplatin) was statistically superior to that of paclitaxel or nab-paclitaxel/paclitaxel combined depending on the evidence network analyzed. In the absence of clear evidence for the superiority of nab-paclitaxel over paclitaxel for TNBC patients in the first-line setting [44], we ran our analyses in two scenarios – one assuming different efficacy and one assuming the same efficacy of nab-paclitaxel and paclitaxel and found similar overall relative efficacies of pembrolizumab + chemotherapy between scenarios. Also, despite no evidence of the statistical superiority of pembrolizumab + chemotherapy over atezolizumab + chemotherapy, a numerical benefit of pembrolizumab + chemotherapy versus atezolizumab + chemotherapy was observed in all models comparing these two PD-1/PD-L1-directed therapies. Overall, these results suggest that as a first-line treatment for locally recurrent unresectable or metastatic TNBC, pembrolizumab + chemotherapy is more efficacious in improving survival outcomes compared with other interventions, with greater improvements observed for OS than for PFS.

Several factors limit the conclusions that can be drawn from this study. First, the use of subgroup data from several comparator trials precludes comparison of baseline patient characteristics for the population of interest. Five of the included trials enrolled a broader population of breast cancer patients, and although subgroup data for TNBC patients were used in the analyses when possible, baseline patient characteristics were not reported by subgroup. Therefore, this study assumed that the baseline patient characteristics for the overall study population reflect those of the TNBC subgroup. Second, the HRs in the PD-L1 CPS $\geq$10 population of IMpassion130 were derived in a *post hoc* analysis employing a model to estimate HRs for OS and PFS in all patients with CPS $\geq$10 as determined with IHC 22C3 pharmDx [41]. Third, because of the different chemotherapy partner options evaluated in KEYNOTE-355, networks were constructed based on chemotherapy pre-assignment. This reduced the sample size for the KEYNOTE-355 cohorts included in each analysis network and thereby decreased statistical power. Fourth, limited data availability for each comparison included in the networks restricted the analyses in several ways. Because only one trial connected each treatment in the network of evidence, between-study heterogeneity could not be estimated. Therefore, NMA was performed with a fixed-effects assumption. Fifth, most trials did not provide KM curves for the population of interest, precluding evaluation of the proportional hazards assumption. Therefore, NMA was conducted with a proportional hazard ratios model, which may not reflect variability in HRs between treatments over time. Furthermore, whereas the age and sex distributions of patients enrolled in the included trials were similar to those in the general TNBC patient population [45,46], White patients were overrepresented in most trials, thus limiting the generalizability of the results of the individual trials, as well as the NMA, to patients of other races/ethnicities.

Despite these limitations, this study also has several strengths that maximize its comprehensiveness and rigor. First, 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 first-line treatment for locally recurrent unresectable or metastatic TNBC. Second, the review process followed PRISMA guidelines, was guided by pre-defined eligibility criteria, and involved two independent reviewers in the study selection and data extraction processes to reduce bias in study selection and ensure data accuracy. Third, detailed feasibility assessment was conducted before proceeding with the NMA to confirm that there were minimal differences among trials included in the network that would jeopardize the validity or reliability of the analyses. Fourth, we performed scenario analyses to explore the impact of potentially different treatment efficacy between paclitaxel and nab-paclitaxel as well as sensitivity analysis to assess the impact of excluding trials that reported OS for the overall breast cancer population rather than the TNBC subgroup.

Conclusion

In conclusion, the results of this NMA suggest that among patients with locally recurrent inoperable or metastatic TNBC, first-line pembrolizumab + chemotherapy confers greater benefits in OS versus first-line carboplatin, docetaxel, paclitaxel, bevacizumab + paclitaxel, ixabepilone + paclitaxel or ixabepilone + bevacizumab and in PFS

versus first-line paclitaxel or nab-paclitaxel/paclitaxel depending on the evidence network analyzed. These findings may be of value to several stakeholders including oncologists and cancer patients, health technology assessment agencies, policymakers, oncology drug developers and medical researchers. In particular, oncologists could use this information in the treatment decision-making process and to communicate with their patients, and health technology assessment agencies and policymakers could use these results as clinical benchmarks for evaluating relative efficacy of available first-line treatments for advanced TNBC patients.

Summary points

- Patients with triple-negative breast cancer (TNBC) have the worst prognosis among all breast cancer patients.
- Pembrolizumab + chemotherapy was recently shown to improve the survival of patients with advanced cancers or cancers refractory to standard treatments, with promising results for the treatment of breast cancer.
- The purpose of this study was to compare the relative efficacy of pembrolizumab + chemotherapy to other interventions for the first-line treatment of locally recurrent unresectable or metastatic TNBC through a systematic review and network meta-analysis.
- EMBASE, MEDLINE, CENTRAL, conference abstracts and clinical trial registries were searched for randomized controlled trials evaluating immunotherapy- or chemotherapy-based treatments for patients with locally recurrent unresectable or metastatic TNBC who were previously untreated for advanced disease.
- Following study screening and feasibility assessment, eight unique trials were included in the network meta-analysis.
- In terms of overall survival, the relative treatment efficacy of pembrolizumab + different chemotherapy agents was statistically superior to that of carboplatin, docetaxel, paclitaxel, bevacizumab + paclitaxel, ixabepilone + paclitaxel or ixabepilone + bevacizumab depending on the evidence network analyzed.
- In terms of progression-free survival, the relative treatment efficacy of pembrolizumab + different chemotherapy agents was statistically superior to that of paclitaxel or nab-paclitaxel/paclitaxel combined depending on the evidence network analyzed.
- These results suggest that as a first-line treatment for locally recurrent unresectable or metastatic TNBC, pembrolizumab + chemotherapy is more efficacious in improving survival outcomes compared with other interventions, with greater improvements observed for overall survival than for progression-free survival.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2023-0301

Author contributions

Conception and design (all authors); acquisition and collection of data (KG Akers, AM Frederickson); statistical analyses (D Maciel); interpretation of data (all authors); draft manuscript (KG Akers, AM Frederickson); critical review of manuscript (all authors). All authors have read and approved the final version of this manuscript.

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The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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