Adjuvant chemotherapy for resected triple negative breast cancer patients: A network meta-analysis

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ABSTRACT

The current standard of care for resected early-stage triple negative breast cancer (TNBC) patients who did not receive systemic preoperative therapy is adjuvant anthracycline- and taxane-based chemotherapy (CT). A network meta-analysis (NMA) of randomized controlled trials (phase III) enrolling patients with resected stage I-III TNBC comparing adjuvant regimens was performed. Overall survival (OS) and disease-free survival (DFS) data were extracted. A total of 27 phase III clinical trials were selected including 15,242 TNBC patients. This NMA showed an OS benefit from the incorporation of capecitabine into classic anthracycline/taxane-based combinations compared to anthracyclines with or without taxanes alone.

1. Introduction

Triple negative breast cancer (TNBC) is a clinical subtype defined by the lack of expression of hormone and HER2 receptors. It is often characterized by early relapse after adjuvant treatments, usually in visceral organs (including brain), leading to a dismal prognosis [1]. In recent years, neoadjuvant chemotherapy has become the standard of care for TNBC patients diagnosed with >cT2 (>20 mm) and/or > cN1 (at least one positive regional lymph node) early-stage tumors (NCCN 2022 breast cancer guidelines). Notably, two Asian studies recently showed that adding capecitabine reduces recurrence risk, and also that the additional use of adjuvant capecitabine after neoadjuvant chemotherapy improved outcomes in patients with residual disease [2,3].

The wider employment of neoadjuvant systemic treatment narrowed the administration of a post-surgical adjuvant treatment to previously untreated patients diagnosed with >10 mm primary tumor (pT1c) and/or >1 or at least >2 mm in the regional lymph node(s). Adjuvant treatment is also often administered if pT > 6 mm and/or > pN1mi

(NCCN 2022 breast cancer guidelines). In either case, the standard systemic treatment is chemotherapy (CT) with sequential anthracycline/taxane-based regimens. So far, adjuvant platinum use is not a standard of care [3].

To the best of our knowledge a direct comparison among all adjuvant regimens (including other cytotoxic or targeted/biological therapies) is not available. Therefore, we performed a network meta-analysis (NMA) of the relative efficacy of different adjuvant treatments for early-stage, resected TNBC in terms of overall (OS) and disease-free survival (DFS).

2. Material and methods

This study followed the PRISMA extension statement for reporting NMA. We systematically searched online databases including MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials for all randomized trials published up to August 1st, 2022. For search terms, we used the medical subject headings of (*"HER-2 negative" or "triple nega-tive" or "ER negative"*) and (*"breast cancer"*) and *randomized* and

adjuvant. Inclusion criteria of this study were: (a) randomized phase 3 trials, (b) inclusion of at least 100 patients treated with resected early-stage TNBC, (c) trials that compared adjuvant regimens, (d) trials that reported OS and/or DFS and their respective hazard ratios with 95% confidence interval (HRs, 95% CIs) of the intention-to-treat population, and (e) articles published in English. We excluded the following: (a) studies that included experimental agents not yet approved for use in any stage of BC, (b) trials that compared neoadjuvant CT, (c) a former version of the same trials, and (d) studies with full-text unavailable. The quality of included studies was assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB2 tool) by two independent reviews (FP and CS).

The primary outcome was OS; secondary endpoint was DFS. Heterogeneity between studies was assessed using the Q test and I^2 statistics. Fixed effect or random effect model was chosen based on the I^2 value (<50% or >50%, respectively). The results from fixed- and random-effects models were consistent, with only wider 95% credible intervals (CrIs) noted for the random-effects models, so we used a fixed effect model to provide results.

NMA was performed under the Bayesian framework using the "gemtc" package (https://gemtc.drugis.org). Noninformative priors were set, and posterior distributions were obtained using 60,000 and 75,000 iterations for OS and DFS, and a thinning interval of 10. The NMA results were reported as HRs with 95% CrIs for OS and DFS. The probability of each treatment regarding survival outcomes was ranked according to the HRs and the posterior probabilities. Overall ranks of treatments were estimated by SUCRA P-scores which were based solely on the point estimates and standard errors of the network estimates. Treatments with the highest and lowest p-scores are considered the best and worst ones, respectively. Two-sided $p < .05$ indicates statistical significance.

3. Results

A total of 27 randomized trials were included (Fig. 1; Table 1, Supplementary files). Twelve and fourteen different arms were compared and provided data for OS and DFS, respectively. Only 2 trials had high risk of bias according to the Cochrane scale.

Ordered from the most to the least effective, treatments with significantly improved OS in randomized controlled trials when compared to anthracyclines alone included only the anthracyclines/taxanes plus capecitabine combinations (HR, 0.56; 95% CI, 0.36–0.87) (P for ranking the first = 29%). Treatments associated with significantly improved DFS included carboplatin/paclitaxel (HR = 0.51; 95%CI 0.3–0.86), anthracyclines/taxanes plus capecitabine combinations (HR = 0.56; 95%CI 0.38–0.81), anthracyclines followed by high dose CT (HR = 0.6; 95%CI 0.42–0.86), bevacizumab-based combinations (HR = 0.6; 95%CI 0.38–0.95), anthracyclines plus ixabepilone (HR = 0.6; 95% CI 0.36–0.99), anthracyclines/taxanes followed by maintenance metronomic methotrexate/cyclophosphamide (HR = 0.62; 95%CI
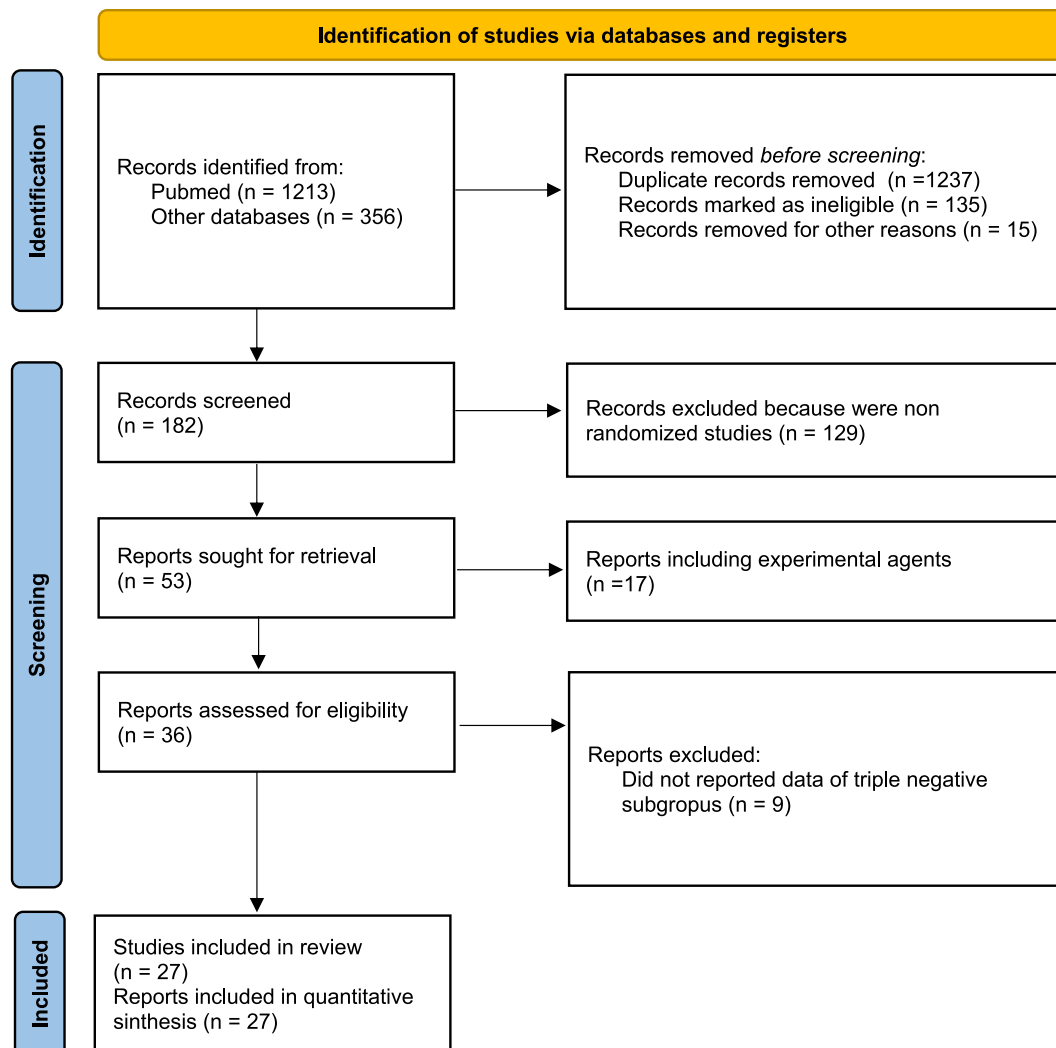

Fig. 1. Flow diagram of included studies.

Table 1

Characteristics of included studies.

Author/year	Type of study	N° pts	Stage	Control arm	Experimental arm	HR OS (95% CI)	HR DFS (95% CI)	Bias
Bell R et al., 2017	Phase III R	2591	T1b–T3 or T1a with ipsilateral axillary node involvement N pos N neg	Adj CHT ≥4 cycles→ observation	Adj CHT ≥4 cyles + bevacizumab followed by bevacizumab for 1 year	HR 0.93 (0.74–1.17)	IDFS HR 0.87 (0.72–1.07)	Moderate
Cheang MCU et al., 2012	Phase III R	94	T1-T3 N pos	CMF 6 cycles	CEF 6 cycles	HR 1.32 (0.71–2.46)	RFS HR 1.12 (0.60–2.08)	Low
Colleoni M et al., 2016	Phase III R	814	any nodal status, T1-3 disease, or pT4 with minimal dermal invasion	AdjCHT →Observation for 1 year	AdjCHT→CM maintenance for 1 year		HR 0.80 (0.60–1.06)	High
De Gregorio A et al., 2019	Phase III R	1279	T1 - T4 N pos N neg with at least one risk factor	EC 4 cycles→T 4 cycles FEC 3 cycles-→ T 3 cycles	TC 6 cycles	HR 1.080 (0.762–1.533)	HR 0.992 (0.759–1.297)	Low
Eiermann W et al., 2011	Phase III R	604	T1-3, clinically N0-1, M0	AC 4 cycles→ T 4 cycles	TAC 6 cycles	HR 1.00 (0.75–1.32)	HR 0.535 (0.453–0.632)	Low
Gluz O et al., 2008	Phase III R	66	T1-4 N pos N neg	EC 4 cycles→dd CMF 3 cycles	HD EC 2 cycles→ECT HD 2 cycles		EFS HR 0.31 (0.15–0.65)	Uncertain
Campone M et al., 2018	Phase III R	586	T1-T3 N pos N neg M0	FEC 3 cycles→ DOC 3 cyles	FEC 3 cycles→ ixabepilone 3 cycles	HR 0.88 (0.58–1.35)	HR 0.77 (0.53–1.11) DMFS HR 0.58 (0.37–0.90)	Low
Earl HM et al., 2017	Phase III R	726	excised invasive early breast cancer of any nodal	EC 4 cycles→P 4 cycles	EC 4 cyles→ GP 4 cyles	HR 1.00 (0.72–1.40)	HR 0.95 (0.70–1.31)	Low
Joennsu H et al., 2022	Phase III R	202	pT1-pT4 pN0 pN pos	T 3 cycles→ CEF 3 cycles	TX 3 cycles→ CEX 3 cycles	HR 0.59 (0.36–0.97)		Low
Blum Jl et al., 2017	Phase III R	1288	pT1-3 N pos pN1 Mi For pN0, one of the following criteria: (ER) and (PgR) neg, tumor size >2.0 cm, or if T1c and ER or PgR positive GIII	TAC 6 cycles	TC 6 cycles		IDFS HR 1.42 (1.04–1.94)	Low
Mackey GR et al., 2013	Phase III R	192	T ≤ 2 cm->5 cm N neg or N pos	FAC 6 cycles	TAC 6 cycles	HR 0.81 (0.51–1.27)	HR 0.84 (0.56–1.25)	Low
Li J et al., 2020	Phase III R	585	T1a-b,T2,T3 N0-3	T 3 cycles→ FEC 3 cycles	TX 3 cycles→CEX 3 cycles	HR 0.67 (0.37–1.22)	HR 0.66 (0.44–0.99)	Moderate
Martin M et al., 2010 (geicam 9906)	Phase III R	209	Stage II-III	FEC 6 cycles	FEC 4 cyles→ P 8 cycles		HR 0.58 (0.35–0.94)	Moderate
Martin M et al., 2010 (geicam)	Phase III R	170	T1, T2, T3 N0	FAC 6 cycles	TAC 6 cycles		HR 0.59 (0.32–1.07)	Low
Lluch A et al., 2020	Phase III R	876	Stage I-III N neg if T measured 1 cm or greater in diameter.	(Neo)adjCHT 6–8 cycles→Observation	(Neo) adjCHT 6–8 cycles→X 8 cycles	HR 0.92 (0.66–1.28)	HR 0.82 (0.63–1.06)	Low
Martin M et al., 2015	Phase III R	166	T1-3 N1-3	EC 4 cyles→T 4 cycles	ET 4 cyles→X 4 cycles		IDFS HR 1.19 (0.70–2.04)	Low
Mavroudis D et al., 2016	Phase III R	74	lumpectomy or modified radical mastectomy with clear margins, N pos	dd FEC 4 cycles→ T 4 cyles	TC 6 cycles		HR 1.06 (0.47–2.40)	Uncertain
Mobus V et al., 2017	Phase III R	421	T1-T4 N0–N3	iddEPC 3 cycles	ddEC 4 cycles→ PX 4 cycles	HR 0.805 (0.539–1.20)	HR 0.97 (0.682–1.38)	Moderate
Miller KD et al., 2018	Phase III R	1796	T ≤ 2 cm->5 cm N neg or N pos	ARM A AC every 14 or 21 days + placebo for 4 cycles→ P for 12 cycles + placebo for 4 cycles	ARM B AC every 14 ore 21 days + bevacizumab for 4 cycles→P for 12 cycles + bevacizumab for 4 cycles ARM C AC every 14 ore 21 days + bevacizumab for 4 cycles→	ARM A HR 0.77 (0.53–1.12) ARM B HR 0.99 (0.69–1.41) ARM C HR 0.79 (0.58–1.06)	IDFS ARM A HR 0.77 (0.58–1.03) ARM B HR 1.00 (0.76–1.33) ARM C	Low

Table 1 (*continued*)

Author/year	Type of study	N° pts	Stage	Control arm	Experimental arm	HR OS (95% CI)	HR DFS (95% CI)	Bias
Muss HB et al., 2019	Phase III R	154	T ≤ 2 cm->5 cm N neg N pos	CMF for 6 cycles or AC for 4 cyles	P for 12 cycles + bevacizumab for 10 cycles X for 6 cycles	HR 0.82 (0.53–1.25)	HR 0.77 (0.61–0.98) RFS HR 0.67 (0.44–1.00) BCSS HR 0.70 (0.34–1.43)	High
O'Shaughnessy J et al., 2015	Phase III R	780	T1–3, N1–2, M0; or T > 2 cm, N0, M0; or T > 1 cm, N0, M0	AC 4 cyles→T 4 cycles	AC 4 cycles→ TX 4 cycles	HR 0.62 (0.41–0.94)	HR 0.81 (0.57–1.15)	Low
Rhodenhuis S et al., 2006	Phase III R	119	T1,T2, T3 at least 4 N pos	FEC 5 cycles	FEC 4 cycles + HD (cyclophosphamide, thiotepa and carboplatin) 1 cycles		HR 0.73	Moderate
Steenbruggen GT et al., 2020	Phase III R	140	stage II or III N ≥ 4	FEC 5 cycles	FEC 4 cyles-→HDCT 1 cycle (C-thiotepa-CBDCA) supported with autologous hematopoietic stem cell transplant.	HR 0.67 (0.42–1.05)		Moderate
Wang X et al., 2020	Phase III R	443	T1b-3 N0-3 cM0	Standard adj CHT→ observation	Standard adj CHT→ low dose X for 1 year	HR 0.75 (0.47–1.19)	HR 0.64 (0.42–0.95)	High
Yu KD et al., 2020	Phase III R	647	T1-T3 N pos N neg	FEC 3 cycles-→ T 3 cycles	P + CBDCA for 6 cycles	HR 0.71 (0.42–1.22)	DFS HR 0.65 (0.44–0.96)	Low
Van Rossum AGJ et al., 2020	Phase III R	108	pT1-3, pN0-3	TAC 6 cycles	dd AC 6 cycles	HR 0.91 (0.41–1.99)	RFS HR 1.78 (0.75–4.22)	Low
Yu KD et al., 2021	Phase III R	112	pT1–3 and pN+ pT2–3N0 with at least one risk factors (grade II/III, lymphovascular invasion, ≤35 years of age or hormone-receptor negative)	EC 4 cycles → P for 12 weeks	CT 6 cycles or FEC 3 cycles-→ T 3 cycles		CT vs EC-P HR 1.76 (0.78–4.52) FEC-T vs EC-P HR 0.91 (0.35–2.38)	Low

AC: doxorubicin-cyclophosphamide; ADJ: adjuvant; BCSS: breast cancer specific survival; CBDCA: carboplatin; DCIS: ductal carcinoma in situ; DDFS: distant disease free survival; DMFS: distant metastases free survival; IDFS: invasive disease free survival; C: cyclophosphamide; CEX: cyclophosphamide-epirubicin-capecitabine; CHT chemotherapy; CMF: clophosphamide-docetaxel; -metotrexate-fluorouracil; dd: dose dense; CT: ciEC epirubicin cyclophosphamide; EC-T: epirubicin-cyclophosphamide-→docetaxel; ECT: epirubicin-cyclophosphamide-tiothepa; EFS: event free survival; EPC: epirubicin-taxolo-cyclophosphamide; FAC: fluorouracil-doxorubicin-cyclophosphamide; FEC fluorouracil-epirubicine cyclophosphamide; GP: gemcitabine-taxolo; HDCT: high dose chemotherapy; HD: high dose; HRR: homologous recombination repair (HRR)–related genes; idd: intense-dose dense; M: metastases; N: nodes; P: taxolo; R randomized; RFI: recurrence free interval; RFS: recurrence free survival; TAC: docetaxel-doxorubicin-cyclophosphamide; TC: docetaxel-cyclophosphamide; X: capecitabine;

0.39–0.98), and concomitant anthracyclines/taxanes schedule (HR = 0.65; 95%CI 0.49–0.88) (Fig. 2a and b and 3a-b). A league table presenting the HRs for all possible pairwise comparisons between treatments is available in eTables 1 and 3 in the Supplement.

Treatment ranking probabilities suggested that anthracyclines/taxanes plus capecitabine had the highest probability of being the best treatment for optimizing OS (29%, i.e., based on the available randomized controlled trial evidence, there is a 29% probability that this is the best treatment for patients with TNBC regarding OS) and carboplatin/paclitaxel had the highest probability of being the best treatment
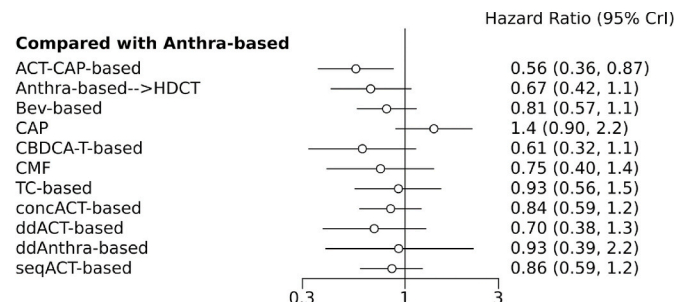

Compared with Anthra-based		Hazard Ratio (95% CrI)
ACT-CAP-based		0.56 (0.36, 0.87)
Anthra-based-->HDCT		0.67 (0.42, 1.1)
Bev-based		0.81 (0.57, 1.1)
CAP		1.4 (0.90, 2.2)
CBDCA-T-based		0.61 (0.32, 1.1)
CMF		0.75 (0.40, 1.4)
TC-based		0.93 (0.56, 1.5)
concACT-based		0.84 (0.59, 1.2)
ddACT-based		0.70 (0.38, 1.3)
ddAnthra-based		0.93 (0.39, 2.2)
seqACT-based		0.86 (0.59, 1.2)

Fig. 2a. Treatment ranking and relative effect for overall survival of various modern regimens compared to anthracycline-based chemotherapy.

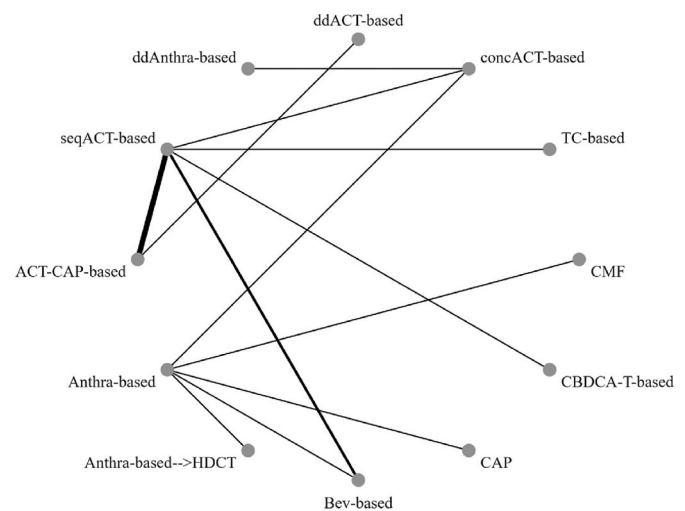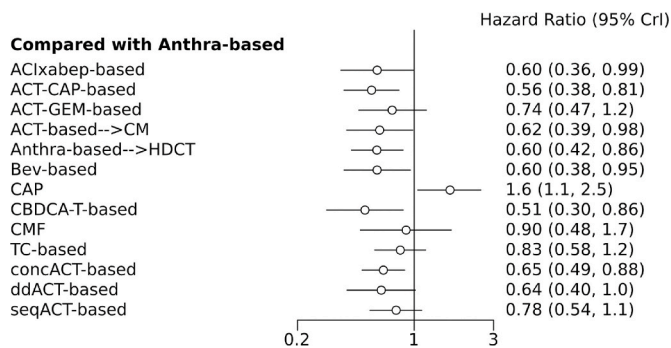**Fig. 2b.** Network diagram of overall survival comparison.

Hazard Ratio (95% CrI)

Compared with Anthra-based

	Hazard Ratio (95% CrI)
ACIxabep-based	0.60 (0.36, 0.99)
ACT-CAP-based	0.56 (0.38, 0.81)
ACT-GEM-based	0.74 (0.47, 1.2)
ACT-based-->CM	0.62 (0.39, 0.98)
Anthra-based-->HDCT	0.60 (0.42, 0.86)
Bev-based	0.60 (0.38, 0.95)
CAP	1.6 (1.1, 2.5)
CBDCA-T-based	0.51 (0.30, 0.86)
CMF	0.90 (0.48, 1.7)
TC-based	0.83 (0.58, 1.2)
concACT-based	0.65 (0.49, 0.88)
ddACT-based	0.64 (0.40, 1.0)
seqACT-based	0.78 (0.54, 1.1)

0.2   1   3

Fig. 3a. Treatment ranking and relative effect for disease-free survival of various modern regimens compared to anthracycline-based chemotherapy.
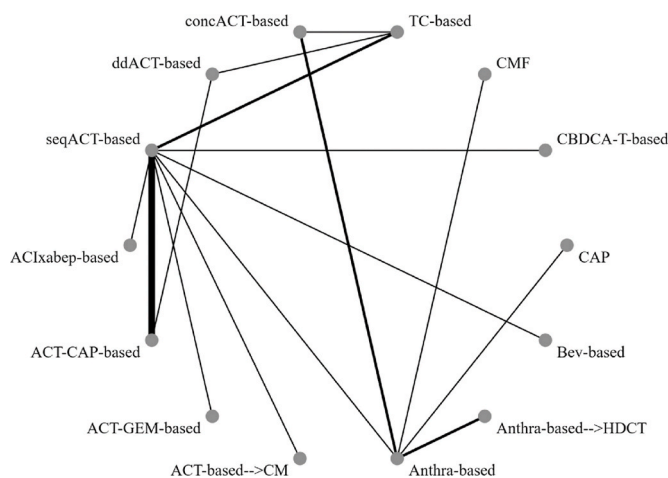
Fig. 3b. network diagram of disease-free survival comparison.

regarding DFS (41%) (eTables 2 and 4 in the Supplement).

4. Discussion

To the best of our knowledge this is the first systematic review and NMA including patients with resected early-stage TNBC that compared different adjuvant treatment regimens, revealing that the best impact on OS was associated with anthracycline-/taxane-/capecitabine-based CT (moderate level of evidence for lack of sufficient comparisons with modern regimens). The latest 2021 Saint Gallen Consensus guidelines suggest the administration of docetaxel-cyclophosphamide (TC) or anthracycline cyclophosphamide/taxane CT in the resected TNBC stage I adjuvant setting [4] and adding capecitabine to standard adjuvant chemotherapy could be a valuable option for fit patients.

The 5 studies where capecitabine was administered with anthracyclines and taxanes employed various dose and treatment schedules (concomitant with taxanes in most of the cases, and concomitant with anthracyclines or sequential with different doses and length of the treatment for capecitabine in a few cases). Indeed, neither concomitant capecitabine-based regimens nor extended adjuvant capecitabine are currently the standard of care. This heterogeneity should be further explored to understand which schedule is optimal in terms of safety, tolerability and outcomes.

This NMA suggests that CT doublets based on taxane and carboplatin retained similar efficacy in DFS (and a positive trend in OS) as anthracycline/taxane/capecitabine-based regimens. Although the level of evidence is low due to the paucity of trials and lack of direct comparisons with other regimens, an adjuvant taxane/carboplatin doublet may be a reasonable alternative to TC for patients who cannot receive

anthracyclines, such as the elderly and patients with cardiac disease. The result is potentially important because it might result in superior outcomes over the current standards (e.g sequential anthracyclines/taxanes and TC combinations). A significant caveat is that carboplatin was administered in doses that were not used in clinical practice, and it was not part of a high-dose regimen in these trials. Notably, adding carboplatin to taxanes and anthracyclines in the neoadjuvant setting increases the pCR rate [5,6], consistently highlighting the activity of carboplatin in TNBC. In comparison with carboplatin/taxane schedules (median follow-up 62 months), capecitabine schedules may have a higher OS rank due to a longer median follow-up (up to 15 years).

Limitations of our work include: 1) limited applicability in routine clinical practice, considering that a neoadjuvant approach is much more frequent in early-stage TNBC, and considering that the new standard for most TNBC patients treated in the neoadjuvant setting includes ICIs; 2) the heterogeneity of the patient populations (some studies included mostly Asian patients); 3) the lack of information about the germline *BRCA* status. Strengths of our work are: 1) the number of patients involved; 2) the number of trials included; 3) the consistent effect observed for the capecitabine/anthracycline/taxane-based triplet in terms of DFS, OS, and of ranking with respect to other schedules.

5. Conclusion

To summarize, this NMA provides evidence that adjuvant treatment strategies for resected, early-stage TNBC can be further optimized. We found that including capecitabine in classic anthracycline-/taxane-based combinations improved DFS and OS outcomes relative to anthracyclines alone and possibly to sequential standard regimens including anthracyclines and taxanes. Only one study was conducted that evaluated an anthracycline-free regimen as carboplatin/paclitaxel, so this analysis was unable to detect significant differences between anthracycline-free and anthracycline-based regimens due to the limited number of patients evaluated. Despite this limitation, a trend toward better survival was observed**.** Dose dense CT is another option that can improve DFS in the adjuvant setting [6], but toxicity may limit its use in some patients and a clear OS benefit is not observed. In the end, it is important to individualize the treatment strategy according to patient fitness. Adding capecitabine to standard therapy may be warranted in very fit patients, and anthracycline-free regimens (i.e., carboplatin/paclitaxel) may represent a helpful choice in patients who are less fit.

Declaration of competing interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.12.004.

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