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Moment of truth-adding carboplatin to neoadjuvant/adjuvant chemotherapy in triple negative breast cancer improves overall survival: An individual participant data and trial-level Meta-analysis

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ABSTRACT

Importance: Carboplatin increases the pathological complete remission (pCR) rate in triple negative breast cancer (TNBC) when added to neoadjuvant chemotherapy, however, evidence on its effect on survival outcomes is controversial.

Methods: The study was prospectively registered at PROSPERO (CRD42021228386).

We systematically searched PubMed, Embase, Cochrane Central Register of Clinical Trials, and conference proceedings from January 1, 2004 to January 30, 2022 for relevant randomized clinical trials (RCTs) of (neo) adjuvant chemotherapy in TNBC patients, with carboplatin in the intervention arm and standard anthracycline taxane (AT) in the control arm. PRISMA guidelines were used for this review. Data were pooled using fixed and random effects models as appropriate on extracted hazard ratios (HR). Individual patient data (IPD)for disease free survival (DFS) and overall survival (OS) were extracted from published survival curves of included RCTs; DFS and OS curves for each trial and the combined population were reconstructed, and HR estimated. The primary outcome was DFS; OS, pCR, and toxicity were secondary outcomes.

Results: Eight trials with 2425 patients were included. Carboplatin improved DFS (HR 0.60; 95% CI 0.47 to 0.78; I^2 45%, $p < 0.001$) compared with AT at trial level and IPD level (HR 0.66; 95%CI, 0.55 to 0.80, $p < 0.001$) analysis. The OS also improved with carboplatin at both trial level (HR 0.69, 95%CI 0.50 to 0.95, I^2 41%, $p = 0.02$) and IPD level (HR 0.68; 95%CI, 0.54 to 0.87, $p = 0.002$) analysis. The pCR as expected, was better in the carboplatin arm (OR 2.11; 95% CI = 1.44–3.08; I^2 67%, $p = 0.009$). Anaemia and thrombocytopaenia were higher in the carboplatin arm.

Conclusion: and relevance: Carboplatin added to (neo)adjuvant chemotherapy in TNBC improves survival, as shown in both trial level and IPD analysis.

Abbreviations: ASCO, American Society of Clinical Oncology; AT, anthracycline-taxane; DFS, disease free survival; ESMO, European Society of Medical Oncology; EFS, event free survival; HR, hazard ratio; OR, Odds ratio; OS, overall survival; pCR, pathological complete remission; PFS, Progression free survival; PRISMA, Preferred items for Systematic Review and Meta-analysis; RCT, randomized controlled trial; RFS, relapse free survival; SABCS, San Antonio Breast Cancer Symposium; SOC, standard of care; TNBC, triple negative breast cancer.

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1. Introduction

Triple negative breast cancer (TNBC), defined as those not expressing estrogen receptor, progesterone receptor, and lacking overexpression of human epidermal growth factor receptor 2 (HER2), constitutes about 10–20% of all breast cancers [1]. TNBC is typically diagnosed at a younger age and is associated with an aggressive biology [2]. The standard of care (SOC) for (neo)adjuvant chemotherapy in the treatment of breast cancer is sequential administration of anthracycline and a taxane (AT) [3].

Increased susceptibility of TNBC cells to DNA damaging agents has been demonstrated previously as a result of somatic/germline mutations in the DNA damage repair pathways seen in these patients [4,5]. This forms the scientific basis of "synthetic lethality" [4,6,7]. Platinum drugs have been shown to increase the rates of pathologic complete response (pCR; i.e., absence of residual invasive or in situ disease in primary tumour and axillary lymph node) in TNBC patients as compared to SOC neoadjuvant chemotherapy; however, this comes at the cost of increased toxicity [8,9].

Prior meta-analyses [10,11] have demonstrated higher pCR rates with the addition of platins in the neoadjuvant setting, but whether this improves survival outcomes is unclear [12,13]. We designed this systematic review to analyse if carboplatin in addition to neoadjuvant or adjuvant therapy in TNBC leads to better DFS and OS in patients compared to standard AT chemotherapy.

2. Materials and methods

2.1. Objectives

The primary objective of this meta-analysis is to assess the effect of adding carboplatin to neoadjuvant or adjuvant chemotherapy vs AT based treatment in TNBC patients on disease free survival (DFS). Secondary objectives included the effect on pCR, OS, and toxicity.

2.2. Methods

This study was conducted in accordance with the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14], and the protocol was prospectively registered at PROSPERO (CRD42021228386). Qualitative and quantitative analyses of randomized controlled trials (RCTs) were performed. As per protocol, our completion date was June 30, 2021 (data extraction till April 28, 2021); however, in light of two critical studies [15,16] that published their updates in November 2021(GeparOcto-GBG 84, Schneeweiss et al. [17]) and January 2022(BrighTNess, Geyer et al. [18]), during our peer review, we extended our cut off till January 30, 2022 to include them in our analysis.

2.3. Selection criteria

Participants: The study population comprised those with non-metastatic TNBC.

Intervention: Neoadjuvant/adjuvant chemotherapy with carboplatin as a part of combination therapy.

Comparison arm: Anthracycline-taxane (AT).

Outcomes: disease free survival/event free survival and/or relapse free survival.

The time point for outcome assessment: As most events for TNBC patients occur within the first three years from diagnosis, survival data of at least three years was sought.

Criteria for study selection: All phase 2/3 RCTs reporting long-term outcomes were eligible for the meta-analysis. Studies were excluded if they were not RCTs or were single-arm studies, met inclusion criteria but were available only in abstract form, ongoing studies with results not yet published, included TNBC in addition to other subtypes but did not provide data for this subset separately; control arm did not have AT based chemotherapy, platinum other than carboplatin as an experimental drug.

2.4. Search strategy

A literature search was conducted in Medline (via PubMed), Embase, and Cochrane library with the cut-off date of April 28, 2021. We extended our cut-off date to January 30, 2022 to include two important updates to prior publications of GeparOcto-GBG84 [17] and BrighTNess [18] studies. In addition, the annual conference presentations and abstracts were hand-searched from 2004 to 2020 for the following pertinent oncology conferences: the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO) congress, and the San Antonio Breast Cancer Symposium (SABCS). Cross-referencing of selected studies was done to confirm that all relevant studies were identified.

Keywords used in searching these databases were: 'Triple negative', 'Breast cancer', 'chemotherapy', and 'carboplatin'. Search terms were combined with Boolean operators. The studies obtained from these sources were stored in a bibliography management software (Zotero®), and duplicates were removed. Two authors (NP and AS) independently conducted a systematic literature search and screened the titles and abstracts. Any discordance was resolved by discussion with a third author (AB).

2.5. Data retrieval

Two authors (NP and AS) independently extracted data on the study name, year of publication, the number of participants in each arm, details regarding regimens and their toxicities, DFS or equivalent marker of long term outcome (time from randomization to local/locoregional or distant recurrence or death), OS (time from randomization to death due to any cause), and pCR (defined as no residual invasive or in situ tumour at the time of surgery in both breast and axilla, *i.e.* ypT0/Tis ypN0) for neoadjuvant studies. For studies that included other subtypes of breast cancer, or other arms of therapy, subgroup data for TNBC patients and for carboplatin vs no carboplatin therapy were extracted, respectively. AB resolved any differences in opinion.

2.6. Risk of bias assessment

Eligible RCTs was assessed using the Cochrane Collaboration Risk of Bias Tool [19] under five headings: selection bias, performance bias, detection bias, attrition bias, and reporting bias. Studies were graded as low, high or unclear risk of bias by AS and NP. Any discrepancies were resolved with a discussion with AB until a consensus was reached. Publication bias was assessed by funnel plot.

2.7. Statistical analysis

For assessment of survival time, data such as DFS and OS, hazard ratios (HR) were retrieved from the concerned studies. For studies that had not provided the HR, we derived it from the available data using the methods described by Tierney et al. [20]. The pooled HR was calculated by the generic inverse variance method using the random-effects model. Odds ratio (OR) and 95% CI were used for calculating pCR and grade $\geq$3 adverse events. Fixed effect model of pooled OR was estimated using Mantel–Haenzel method. Pooled OR and HR were considered statistically significant when 95% CI excluded 1, and two sided p-value was <0.05. Higgins I^2 coefficient was used to quantify statistical heterogeneity. Publication bias was assessed by visual inspection of the funnel plot. Sensitivity analysis was done by 'one out' sequential algorithm by excluding each study one by one and performing n number of meta-analyses for n number of studies included. A new set of n-1 studies is created with the least value of I^2 [21]. Review manager (Revman®)

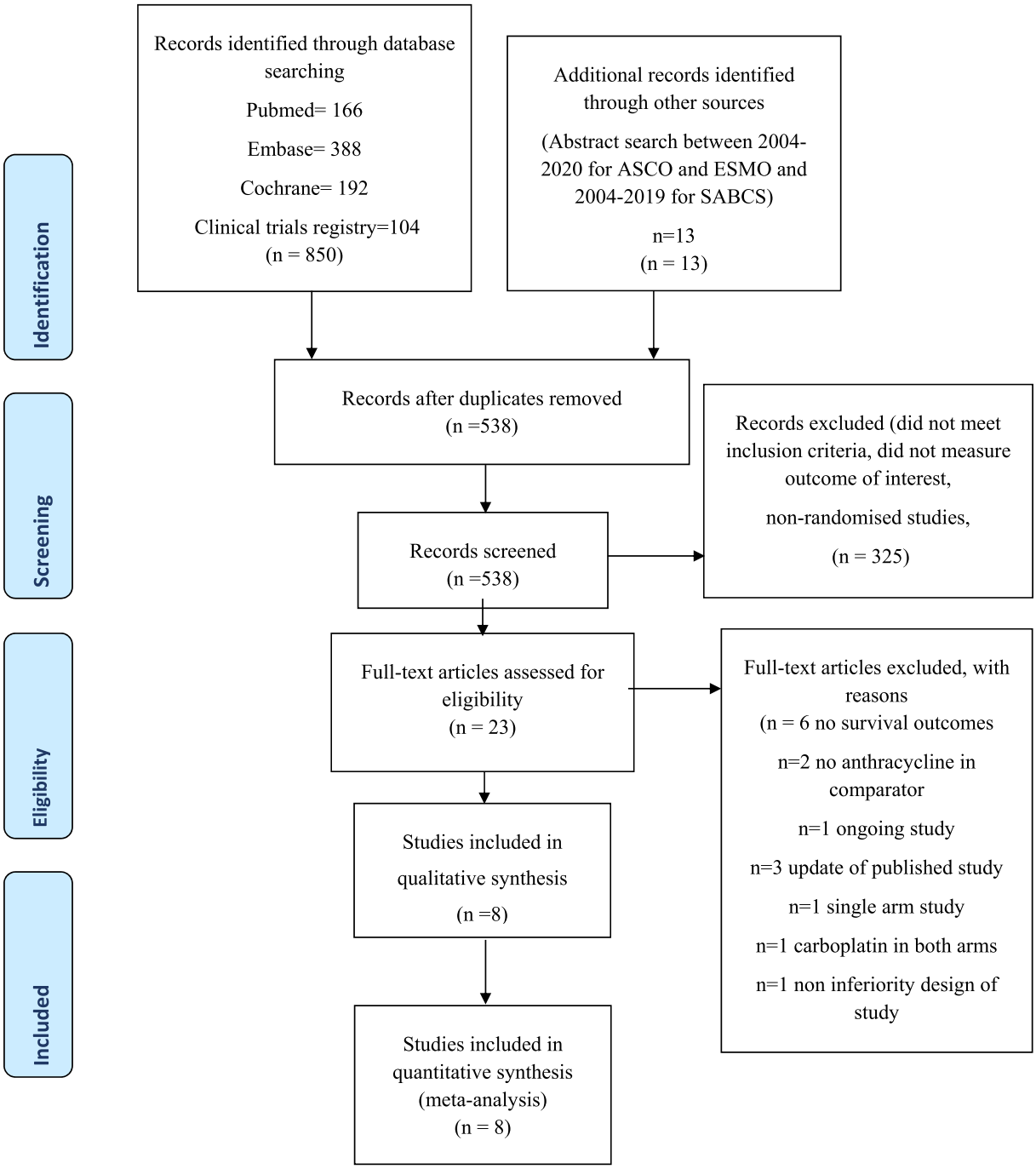


Fig. 1. PRISMA diagram of search results and study selection.

5.4 software (Cochrane Collaboration) was used for meta-analysis.

Exploratory individual patient data (IPD) analyses were performed for DFS and OS using WebPlotDigitizer® software [22] by extracting data from published Kaplan-Meier curves. The WebPlotDigitizer® provided the X and Y coordinates at several points on the curve, which were transformed to survival data using IPD from the KM package in R statistical software. The HR and 95%CI thus obtained were compared to those documented in each trial. The graphs were reconstructed from the data extracted.

3. Results

3.1. Study selection

A total of 863 studies were identified in the literature search, of which 23 studies were selected for full text review after screening the titles and abstracts. Of these, eight studies [8,9,15–18,23–29] fulfilled the eligibility criteria and were included for qualitative synthesis and meta-analysis, with a total of 2425 patients. (Fig. 1). In the case of several publications from the same study, DFS was taken from the most recent follow up. Authors were contacted for two studies with 3-year DFS via email; however, we did not get a response [23,28]. One study, Feng du et al. [30], met our inclusion criteria, however, it was excluded from the analysis as it had a non-inferiority design, which was

Table 1
Study characteristics.

Study (year)	Phase	Treatment arms	TNBC patients, n	Primary end point	Relevant Secondary end points
Neoadjuvant studies					
Loibl et al. [8,23] (2018)	III	wkP + PM + bevacizumab + carboplatin wkP + PM + bevacizumab	158 157	pCR (ypT0/isN0)	DFS,OS
Sikov et al. [9,24] (2016,2022 update)	II	wkP + Carboplatin→ddAC ± bevacizumab wkP→ddAC ± bevacizumab	221 212	pCR (ypT0/isNany).	5 year EFS, OS, toxicity, pCR (ypT0/isN0), which was used this analysis for pCR
Zhang et al. [25] (2016)	II	TP ET	47 44	pCR (ypT0/isN0)	RFS, OS, safety
Iwase et al. [26] (2019)	II	CEF + Paclitaxel + carboplatin CEF + Paclitaxel	37 38	pCR (ypT0/isN0)	DFS, safety
Schneeweiss et al., 2022 [16,17]	III	wkPMwkP→ wkCb iddE→iddP→iddC	203 200	pCR (ypT0/isN0)	iDFS, dDFS, LRRFI, OS,safety
Geyer et al., 2022[a] [15,18]	III	wkP + Cb→AC wkP→ AC	160 158	pCR pCR (ypT0/isN0)	EFS,OS
Adjuvant studies					
Ke Da Yu et al. (2020)	III	PCb CEF-T	325 322	5 yr DFS	RFS, dDFS, OS, toxicity
Qing li et al.(2020)	III	ddPC ddEC→ddP	70 73	3 yr DFS	OS, safety

Abbreviations: PM: non-pegylated liposomal doxorubicin, wkPM: weekly non-pegylated liposomal doxorubicin, wkP: weekly paclitaxel, (dd)AC: (dose dense) doxorubicin and cyclophosphamide, TP: paclitaxel plus carboplatin, ET; epirubicin plus paclitaxel, CEF: cyclophosphamide, epirubicin, and 5-fluorouracil,CEF-T: CEF plus docetaxel, Pcb: weekly paclitaxel and weekly carboplatin, EC→T: epirubicin, cyclophosphamide, docetaxel, ddPC: dose dense paclitaxel and carboplatin, ddEC dose dense epirubicin and cyclophosphamide, iddE: dose dense epirubicin, iddC: dose dense cyclophosphamide, (i)ddP: dose dense paclitaxel, RFS relapse free survival, DFS disease free survival, iDFS: invasive DFS, dDFS: distant disease free survival, OS overall survival, pCR pathological complete remission, LLRFI: loco-regional invasive recurrence-free interval.

[a] This study was a 3 arm study, Veliparib arm details not shown.

considered inconsistent with our hypothesis to determine the presence/absence of survival benefit of carboplatin over AT.

3.2. Study characteristics

Each study had AT based control arm and carboplatin in the comparator arm. Bevacizumab was a component in two studies. GeparSixto study included HER2 positive and TNBC patients, the study by Iwase et al. included hormone receptor-positive and TNBC patients and Schneeweiss et al. included all three subtypes: hormone-positive Her 2 negative, Her 2 positive, and TNBC. Only TNBC subsets were included from these studies in our analysis. The study by Sikov et al. used a 2*2 factorial design with the patients randomized to carboplatin and then to bevacizumab; carboplatin vs non-carboplatin comparison data was used. All studies but one, Sikov et al. included in our review, defined pCR as ypT0/isN0. The definition used by Sikov et al. for pCR for the primary endpoint was the absence of invasive breast cancer in the breast only (ypT0/isNany) for the primary endpoint, and the more accepted definition of absence of invasive breast cancer in breast and axilla as a secondary endpoint (ypT0/isN0. For this study, we selected the data from the secondary endpoint pCR (ypT0/isN0) definition for consistency with the remaining studies.

The characteristics of the included studies are shown in Table 1.

3.3. Quality and risk of bias

All studies were open-label RCTs with serious performance and detection bias risks. The random sequence generation method was clearly mentioned in only three studies. There was a low risk of reporting and other biases. One study (Iwase et al.) suffered from attrition bias, while attrition was unclear in the other two studies. Most of the studies included were open-label trials, except Geyer et al. which had quadruple blinding. The studies included in the review seemed to have a low to moderate risk of bias (Fig. 2a and b).

3.4. Pooled estimates for efficacy

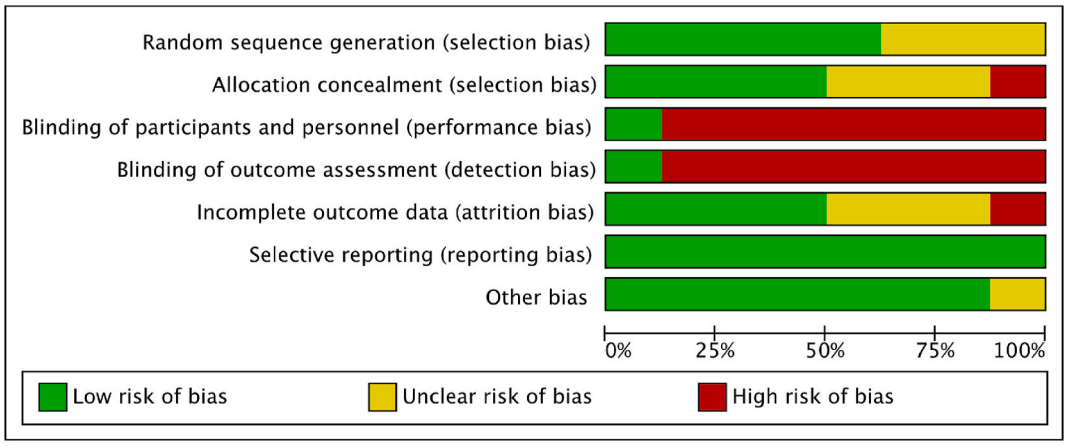
3.4.1. Disease free survival

The endpoints of these studies were variably defined as DFS, distant DFS, event free survival (EFS) and relapse free survival (RFS) (Table 2). Five of the studies reported DFS as an endpoint. Schneeweiss et al. reported invasive DFS(iDFS). One study (Zhang et al.) used RFS, Geyer et al. used EFS, while Sikov et al. used EFS and RFS. For Sikov et al. EFS data was chosen to resemble more closely to DFS definition. They were considered to retain enough contextual homogeneity to extract meaningful benefit.

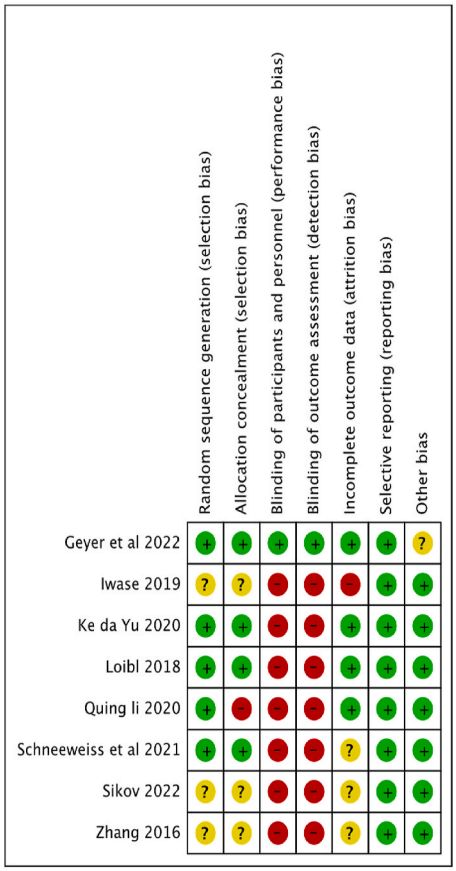
The addition of carboplatin to neoadjuvant/adjuvant chemotherapy significantly improved DFS by 40% in TNBC (HR 0.60; 95% CI 0.47 to 0.78; I^2 45%, $p < 0.0001$). Sensitivity analysis yielded consistent values for the hazard ratio for pooled DFS effect (Fig. 3a-random-effects model, Fig. 3b-fixed effects model). Three studies out of eight included in our analysis had standard dose-dense anthracycline + cyclophosphamide + taxane chemotherapy in their control arm: Sikov et al. Schneeweiss et al. and Qing li et al. One study, Geyer et al. gave the option of including either 2 weekly (dose-dense) or 3 weekly chemotherapy, for which difference in events for DFS and OS for paclitaxel + carboplatin vs paclitaxel were not specified, as this was a post hoc analysis. This study was therefore excluded from subgroup analysis. Evaluating DFS in two subgroups of dose-dense chemotherapy (ddCT) vs non-ddCT, the DFS results are as follows: for ddCT control arm studies HR 0.66; 95%CI 0.39 to 1.11, I^2 71% $p = 0.12$, and for non-ddCT HR 0.56; 95%CI 0.42 to 0.74, I^2 0% $p < 0.0001$ (Fig. 4a and b). The funnel plot for DFS suggests asymmetry among studies, thus raising the possibility of publication bias (Fig. 5). Exploratory IPD analysis by WebPlotDigitizer® software estimated pooled HR to be 0.66 (95% CI 0.55 to 0.80,$p < 0.001$) with 3-year and 5-year DFS as 84.3% and 81.2% (carboplatin arm) vs 77.4% and 73% (SOC arm), respectively (Fig. 6).

3.4.2. Overall survival

The pooled HR for OS was 0.69 (95%CI, 0.50–0.95; I^2 41%, $p = 0.02$) (Fig. 7a). Sensitivity analysis via random vs fixed effects model (Fig. 7b)



(a)



(b)

Fig. 2. a and b Risk of bias assessment.

and by excluding each study by turn (data not shown) revealed consistent results. Evaluating OS in two subgroups ddCT vs non-ddCT, the OS results are as follows: for ddCT control arm studies HR 0.69; 95%CI 0.34 to 1.42, I^2 71% p = 0.32 and for non-ddCT HR 0.65; 95%CI 0.45 to 0.94, I^2 0% p = 0.02 (Fig. 8a and b). Geyer et al. was excluded from this subgroup analysis as explained previously.

An exploratory IPD analysis of OS data (Fig. 6) from all eight studies was done using WebPlotDigitizer® software, and similar results were obtained with an HR of 0.68 (95%CI 0.54–0.87, p = 0.002).

3.4.3. *Pathological complete remission (ypT0/isN0)*

Neoadjuvant studies are shown in Tables 1 and 2; six of the eight studies included are neoadjuvant studies. Sikov et al. reported breast only pCR as the primary endpoint and breast and axilla pCR (ypT0/isN0)

Table 2
Definition of endpoints and individual result summary.

Study	Outcome measure (DFS)	Result (Carboplatin vs SOC)	OS(Carboplatin vs SOC)	pCR
Loibl 2018 [23] GeparSixto	DFS was defined as time in months from randomization until any invasive locoregional (ipsilateral breast, local/regional lymph nodes) recurrence of disease, any invasive contralateral breast cancer, any distant recurrence of disease, any secondary malignant neoplasm, or death from any cause, whichever occurs first. Disease progression under therapy was not considered as an event for DFS.	3 year DFS 85.8% vs 76.1%, HR 0.56 [95%CI 0.34–0.93]; p = 0.024	3 yr OS 91.9% vs 86.0%, HR 0.6, [95%CI 0.32–1.12], p = 0.109	84/158 (53·2%, 54·4–60·9) *vs* 58/157 (36·9%, 29·4–44·5) OR: 1·94 (1·24–3·04) p = 0.005
Sikov (2016, 2022) CALGB 40603 [9, 29]	EFS is measured from study entry to ipsilateral invasive breast or locoregional recurrence, distant recurrence or death from any cause RFS in protocol From definitive surgery to first instance of ipsilateral invasive breast tumour recurrence, local/regional invasive breast cancer recurrence, distant recurrence, or death from any cause. Number of Participants who Died Due to Any Cause or had a recurrence.	5yr EFS HR 0.99 [95% CI 0.70–1.40), p = 0.36	3 yr 85.5% vs. 80.9%, HR 1.15 [95%CI 0.74–1.79], p = 0.53	41% (35%–48%) 54% (48%–61%) OR: 1.71, p = 0.0029
Zhang 2016 [25]	RFS was calculated from the date of randomization to the date of the first local or distant recurrence.	5-year RFS 77.6% and 56.2%, p = 0.043	5 yr OS 83.3% vs 70.7%, p = 0.350	38.6% vs. 14.0%, 17/47 vs 6/44, p = 0.014
Iwase 2019 [26]	DFS was defined as the time from randomization to the first appearance of any recurrence of breast cancer (local, regional, or distant), or any cause of death.	HR 0.22 [95% CI 0.06–0.82], p = 0.024	93.9% vs 68.7%, HR 0.12 [95%CI 0.01–0.96] p = 0.046	23/37 vs 10/38
Ke Da Yu PATTERN [27]	DFS: Time from random assignment to first relapse (local, regional and distant), contralateral breast cancer, second primary cancer (other than sqcc or basal cell ca of skin melanoma in situ or ca in situ) or death due to any cause.	5-year DFS, 86.5% vs 80.3%, HR 0.65 [95% CI, 0.44–0.96], p = 0.03	OS, 93.4% vs 89.8%, HR 0.71 [95% CI 0.42–1.22], p = 0.22	–
Geyer et al., 2018, 2022 [15,18]	Event free survival (EFS) was defined as the time from randomization to documentation of the first of the following events: failure to reach potential curative surgery; local, regional, or distant invasive recurrence of breast cancer following curative surgery; a new breast cancer or secondary malignancy; or death from any cause.	4 year EFS 79.3% vs 68.5%, HR 0.57 [95% CI 0.36–0.91], p = 0.02	16/160 (10%) deaths vs 22/158 (14%) deaths, HR 0.63 [95%CI 0.33–1.21], p = 0.17	92/160 (58%) vs 49/158 (31%), p < 0.0001
Schneeweiss et al., 2018, 2022 [16, 17]	iDFS was defined as time from randomization to event: any invasive locoregional (ipsilateral breast, locoregional lymph nodes) recurrence of disease, any invasive contralateral BC, any distant recurrence of disease, any secondary malignancy, or death as a result of any cause, whichever occurred first.	4 year iDFS 80.3% v 73.7%, HR 0.73 [95%CI 0.47–1.13], P = 0.156	4 year OS 88.3% v 82.9% HR0.66 [95%CI 0.38–1.15], p = 0.141	105/203 (51.7% vs 97/200 (48.5%), p = 0.584
Qing li 2020 [28]	DFS, which was calculated from the date of randomization to the date of the first local/distant recurrence (in the absence of other primary malignancies).	3-year DFS 93.9% vs. 79.1%, HR 0.310 [95%CI 0.137–0.704], p = 0.005	3 yr OS 98.5% vs. 92.9%, HR 0.142, [95% CI 0.06–0.82], p = 0.028	–

Abbreviations: DFS: disease free survival, EFS: event free survival, HR: hazard ratio, OS: overall survival, RFS: relapse free survival, sqcc: squamous cell carcinoma, Yr: year.

as a secondary endpoint; the latter was included in the analysis to allow equal comparison. The remaining five studies defined pCR similarly. A total of 1635 patients were analysed, with 826 in the intervention and 809 patients in the control arm. The odds ratio for achieving pCR (Fig. 9) was significantly higher with the addition of carboplatin in neoadjuvant chemotherapy in TNBC patients. (OR, 2.11; 95% CI = 1.44 to 3.08; p = 0.0001). Heterogeneity among these studies was high (I^2 = 67%). On excluding the 2 studies (Schneeweiss et al. Sikov et al. with ddCT, the OR for pCR is 2.71; 95%CI 1.55 to 34.74, I^2 36%, p < 0.0005 in favour of carboplatin (Fig. 10). As explained previously, Geyer et al. was excluded as the study had both ddCT and 3-weekly chemotherapy.

3.4.4. Pooled estimates for toxicity and safety

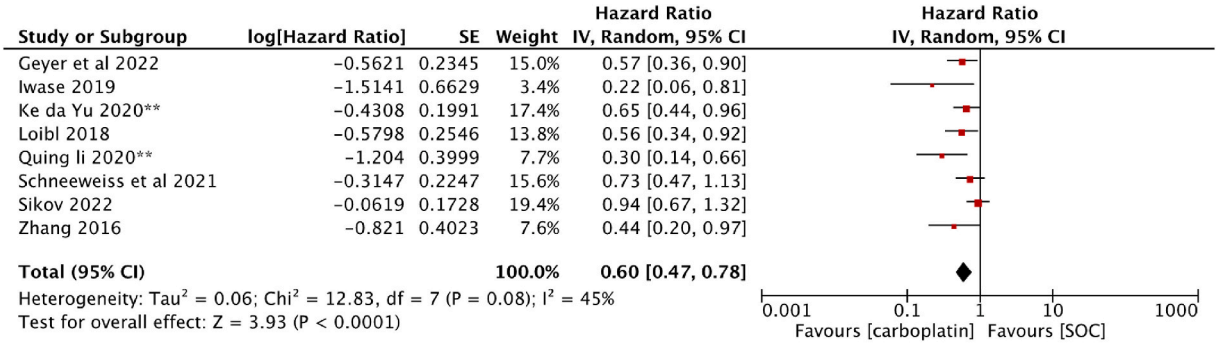
Significant toxicities of common terminology criteria for adverse events (CTCAE) grade 3 or more were evaluated. For Geyer et al. only the arms with paclitaxel and carboplatin vs paclitaxel alone were considered as veliparib has overlapping toxicities that would have confounded the effect. For the study by Schneeweiss et al. all patients, regardless of ER, PR or Her 2 status, were included in the analysis as separate information for TNBC patients was not provided in the paper. It was assumed there would be no difference in toxicity among these groups. Anaemia (OR, 6.14; 95% CI, 1.11–33.91; p = 0.04; I^2, 90%) and thrombocytopaenia (OR, 5.17; 95% CI, 1.13–23.59; p < 0.0001; I^2, 89%) were higher in carboplatin arm vs those of control arm (Fig. 11).

Schneeweiss et al. Qing li et al. and Zhang et al. found no grade 3/4 cardiotoxicity in either arm in their study. Loibl et al. documented one grade 5 cardiac event in the control arm and two grade 3 events in carboplatin containing arm.

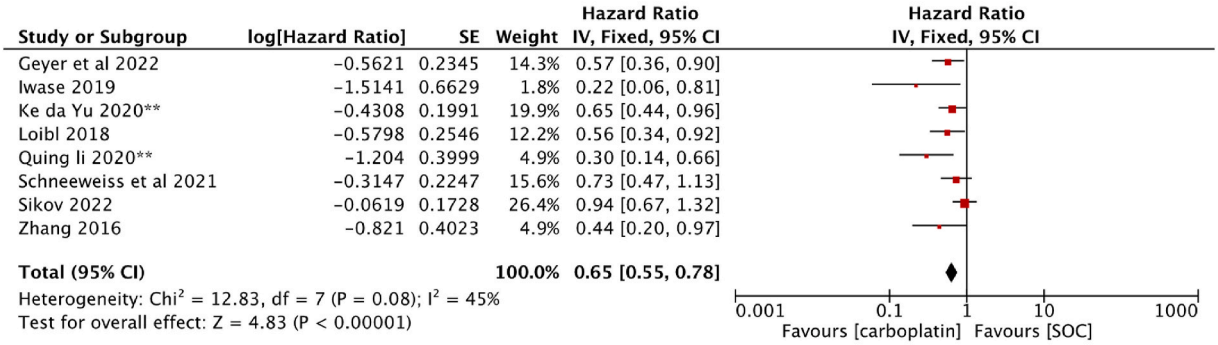
4. Discussion

This meta-analysis resolves the controversy of the benefit of platinum in TNBC patients treated with curative intent. We observed that adding carboplatin to (neo)adjuvant therapy resulted in a definite DFS and OS benefit by trial level and IPD analysis in 2425 patients. As the most updated meta-analysis in this area, ours is the only study to include Schneeweiss et al. and the CALGB 40603 2022 update.

Similar to our results, Bian et al. (HR 0.70; 95% CI: 0.58 to 0.84) and Saleh et al. (HR 0.70; 95%CI 0.56 to 0.89) demonstrated a DFS benefit with the use of platinum agents in early TNBC [12,31]. Both included the RCT by Feng Du et al. [30], which we excluded as it was a non-inferiority RCT. Saleh et al. included early TNBC patients from trial and non-trial (retrospective) studies and depicted better pooled DFS with the addition of cisplatin/carboplatin. Unlike our study, which specified anthracycline-taxane as the control arm and carboplatin as the interventional agent to be evaluated, both these analyses did not select any particular inclusion criteria for the control arm and included all platinum-based compounds. Our choice in this regard was made to



(a)



(b)

Fig. 3. a (random effects model) and b (fixed effects model).

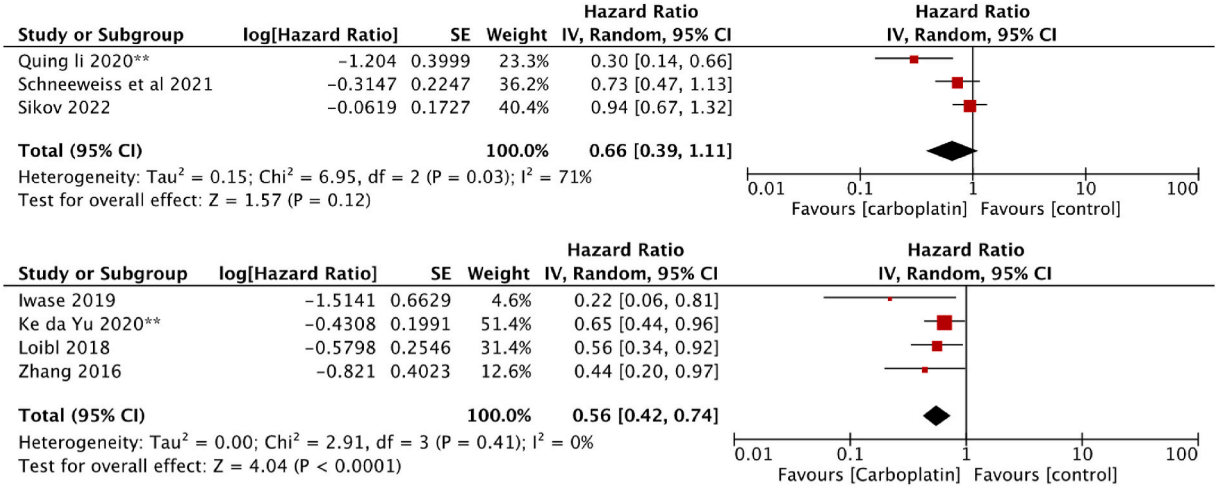


Fig. 4. a: Forest plot of DFS subgroup: studies with ddCT in the control arm and b: Forest plot of DFS subgroup: studies non-ddCT in the control arm.

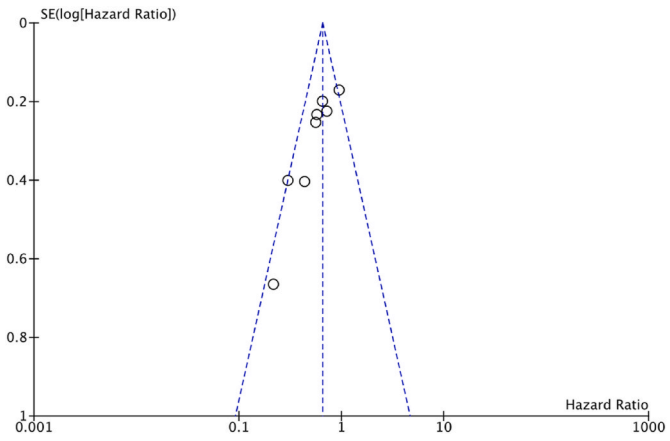


Fig. 5. Funnel plot for DFS.

reflect the standard of care in (neo)adjuvant chemotherapy for TNBC and achieve greater homogeneity in the studies included. The preference for carboplatin in recent studies [24,27] is likely related to ease of administration and better side effect profile. It is unclear whether the choice of a specific platinum compound impacts outcomes in TNBC patients. A retrospective study compared cisplatin and carboplatin in breast cancer and found that the use of cisplatin was associated with better PFS and OS [32]. Another study evaluating neoadjuvant therapy in a similar setting found no difference between cisplatin and carboplatin in pCR, PFS or OS [33].

In their study, Feng et al. found a pooled OS benefit of three studies [9,25,26] included herein, with moderate heterogeneity (HR = 0.56; 95% CI, 0.15–0.96, I^2 69.4% p < 0.001). Ours is the first study to demonstrate a durable OS benefit with the addition of carboplatin. Most of the studies incorporated in our analysis (and the above studies) are underpowered to assess survival outcomes; most had pCR as the primary endpoint. Two studies had DFS and none OS. Moreover, the number of events for OS in these studies is limited, even with updated follow-ups included in the current analysis. This could account for the lack of overall survival benefit not seen previously. Similarly, an older meta-analysis by Poggio et al. [10] did not demonstrate an EFS benefit due to a dearth of events (only two studies [8,9] had published survival data) to extract meaningful difference. Their November 2021 update demonstrated EFS benefit with carboplatin [34].

We were able to confirm our results in survival analysis through IPD analysis, which adds to the robustness of our results.

Dose-dense chemotherapy has shown benefit in high risk breast cancer patients in terms of pCR and overall survival in previous studies [35,36]. During our analysis, we found 3 out of 8 studies [9,16,28] to have used dose-dense anthracycline + cyclophosphamide + taxane in the control arm. In contrast, BrighTNness [15] had both, with data not available for the subgroup of dose-dense receiving patients in paclitaxel + carboplatin vs paclitaxel events as it was a post-doc analysis. We conducted an exploratory subgroup analysis (excluding BrighTNess). We found that pooled DFS benefit was not seen for studies with dose-dense chemotherapy of these three drugs. In the remaining studies, the heterogeneity decreased significantly ($I^2 = 0\%$). Similar results were seen with OS.

Thus, the benefit of carboplatin addition to (neo)adjuvant chemotherapy in TNBC seems to be abrogated in the face of appropriate standard 3 drug dose-dense therapy, as shown by our analysis. This adds an interesting facet to the existing (neo)adjuvant therapy options in TNBC.

Our results pertaining to pCR and toxicities are in keeping with published systematic reviews, with platinum increasing pCR as compared to standard at the cost of increased toxicity, especially anaemia and thrombocytopaenia [10–12].

Our study has certain limitations. The studies included were not powered to evaluate survival benefit and mainly focussed on the surrogate endpoint of pCR. Moreover, we utilised extracted rather than actual individual patient records for IPD analysis. Although we tried to standardise included studies by allowing only those with anthracycline-taxane in the control arm in our analysis, various studies have used different regimens, doses, additional drugs such as bevacizumab, or lack cyclophosphamide in the regimen, which may confound the results in unknown ways. Notably, two studies [23,25], did not include cyclophosphamide in their regimens, which could overestimate the impact of carboplatin in such patients [37,38].

TNBC is a heterogeneous entity, and this is known to impact response

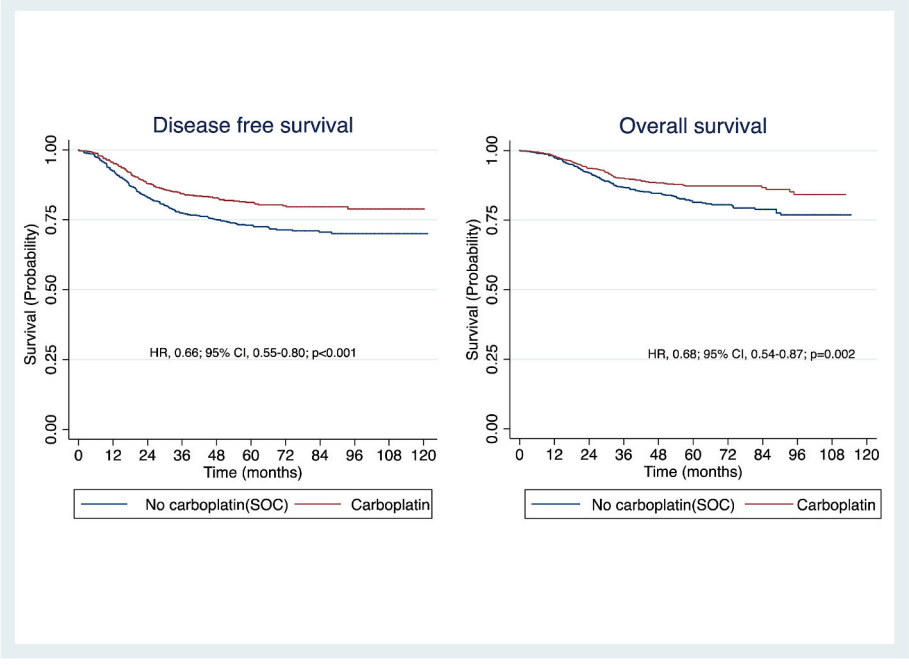


Fig. 6. Kaplan Meier graph of DFS and OS of carboplatin vs AT (SOC), IPD analysis.

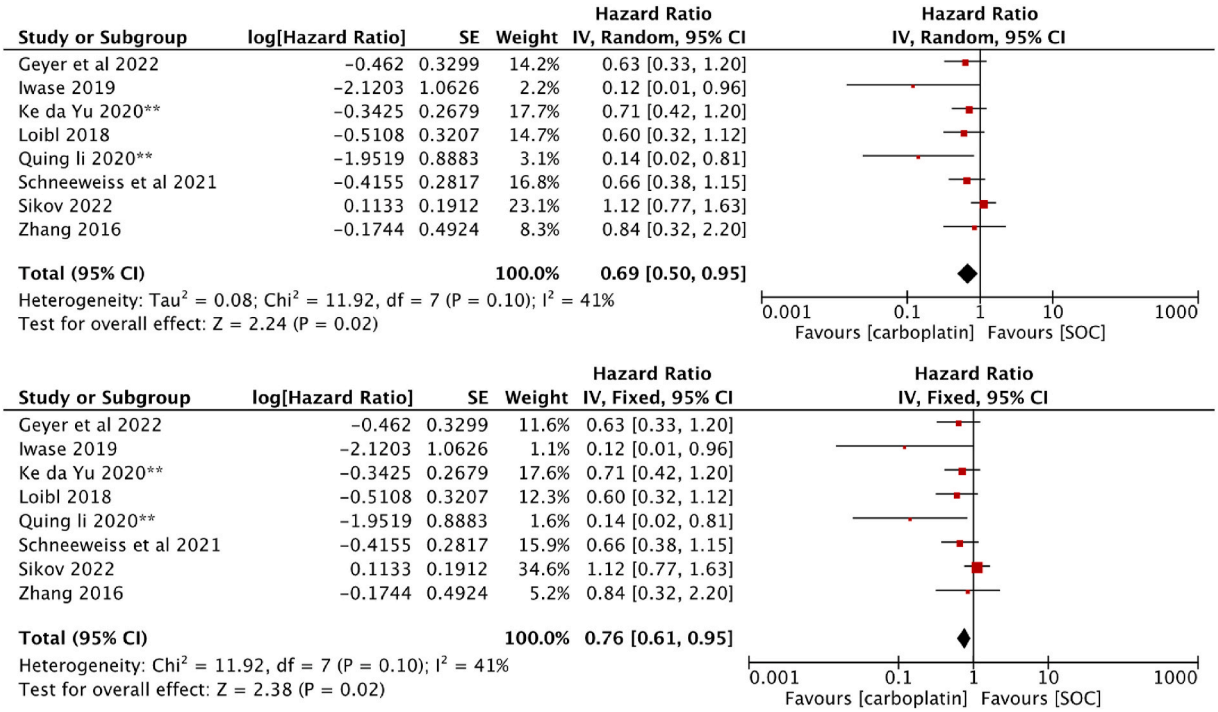


Fig. 7. (a) Forest plot for pooled OS for carboplatin vs SOC(random-effects model) and (b) Forest plot for pooled OS for carboplatin vs SOC(fixed-effects model).

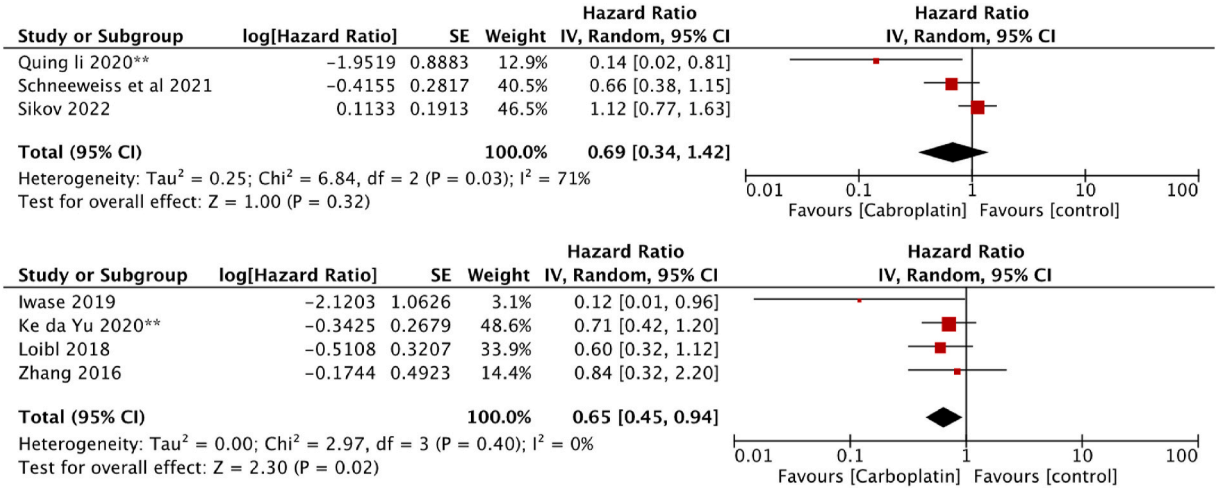


Fig. 8. (a) Forest plot of OS subgroup ddCT as the control arm and (b) Forest plot of OS subgroup non-ddCT as the control arm.

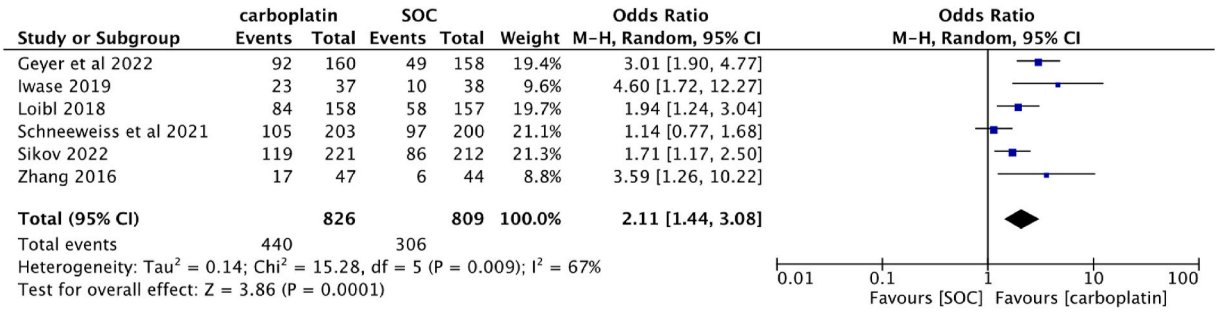


Fig. 9. Forest plot for pCR for Carboplatin vs SOC in NACT.

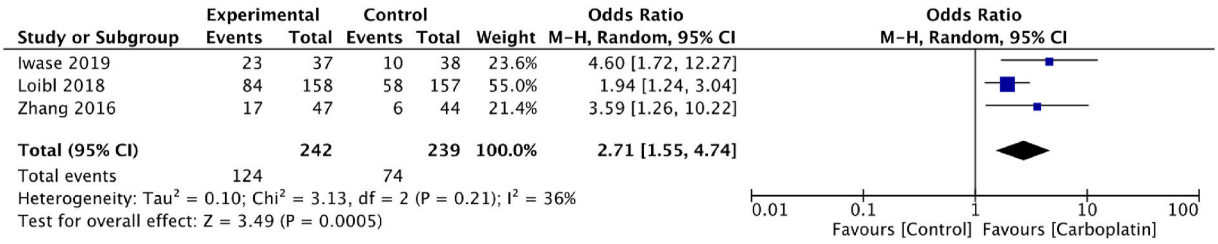


Fig. 10. Forest plot of pCR excluding ddCT studies.

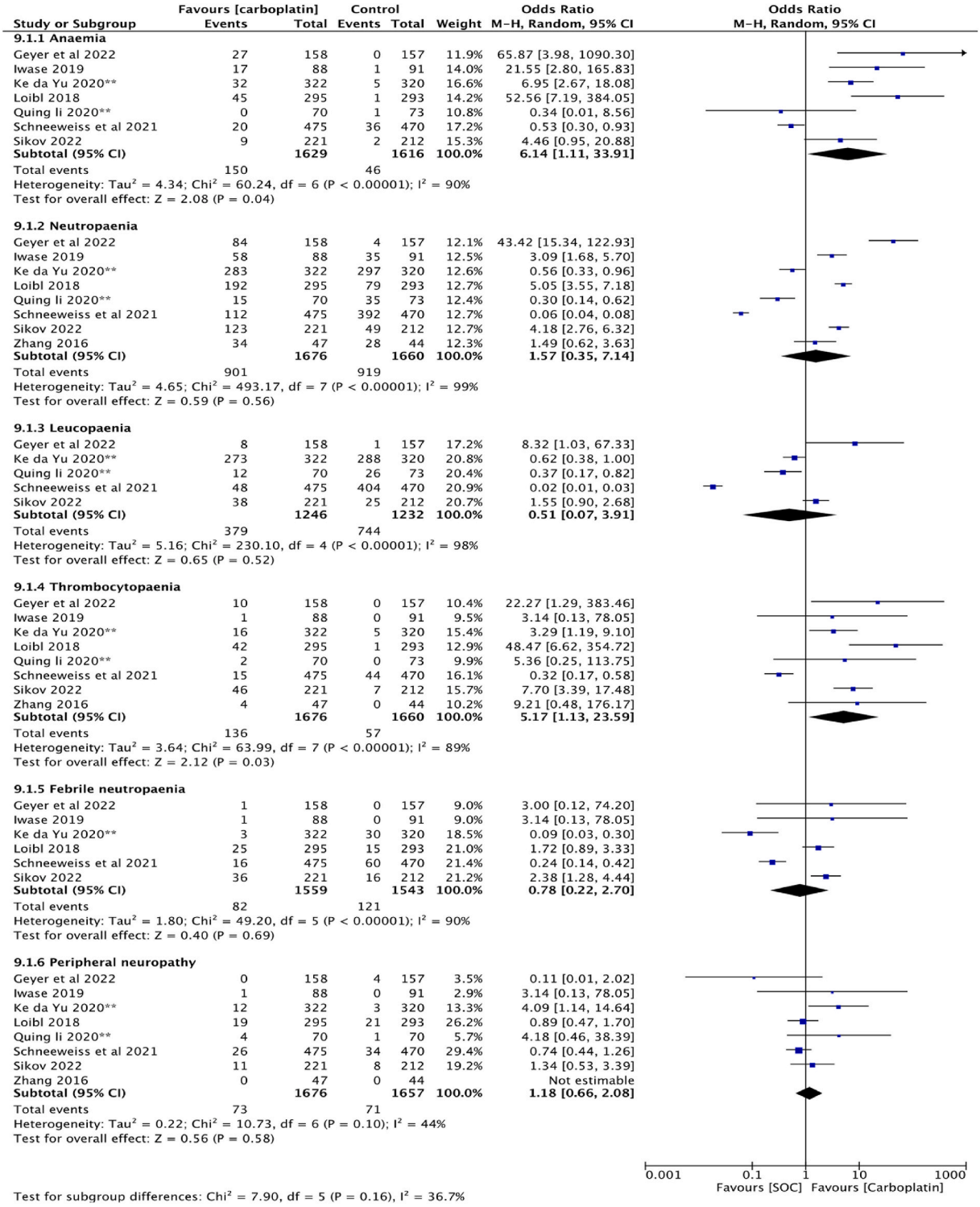


Fig. 11. Forest plot of Adverse events of carboplatin vs SOC** Indicate adjuvant chemotherapy studies; rest are neoadjuvant studies.

to the therapy [4]. Prognosis and response to different chemotherapeutics and targeted agents vary amongst these subtypes [39,40]. We recommend further studies to identify the subpopulations that will benefit from platinum compounds in neoadjuvant/adjuvant therapy.

In conclusion, this study is the first and most updated meta-analysis to demonstrate a significant survival benefit of carboplatin in terms of DFS and OS in non-metastatic TNBC patients by trial-based and IPD analysis.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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