

# Pathological complete response following cisplatin or carboplatin-based neoadjuvant chemotherapy for triple-negative breast cancer: A systematic review and meta-analysis

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**Abstract.** The addition of platinum compounds to standard neoadjuvant chemotherapy (NACT) for triple-negative breast cancer (TNBC) is highly controversial. Platinum agents, such as cisplatin and carboplatin, are DNA-damaging agents which exhibit activity in breast cancer, particularly in the TNBC subgroup. In order to assess the efficacy of each most representative platinum agent (cisplatin and carboplatin) in patients with TNBC treated with NACT, the present study performed a systematic review and meta-analysis of all available published studies on TNBC. A search of PubMed was performed to identify studies that investigated platinum-based NACT in patients with TNBC. The primary endpoints were the pooled rate of the pathological complete response (pCR) between cisplatin vs. carboplatin-based NACT. A total of 24 studies were selected (17 studies for carboplatin and 6 studies for cisplatin and 1 study with both carboplatin and cisplatin, with 20 prospective studies) for the analysis of 1,711 patients with TNBC. Overall, the pooled rate of pCR in patients treated with platinum-based NACT was 48%. No significant differences were observed between the rates of pCR obtained under carboplatin vs cisplatin treatment. The carboplatin pCR rate was 0.470 [95% confidence interval (CI), 0.401-0.539], while the cisplatin pCR rate was 0.473 (95% CI, 0.379-0.568). The

comparison between these two categories revealed no significant differences ( $P=0.959$ ). In the whole, the present study demonstrates that neoadjuvant platinum-based chemotherapy improves the pCR rate in patients with TNBC, regardless of the platinum agent used. Carboplatin may thus represent a viable option due to its more favorable toxicity profile.

## Introduction

Triple-negative breast cancer (TNBC) is a term that defines breast cancers with a lack of expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (Her2). It accounts for 10-20% of all breast tumors (1) and exhibits a more aggressive behavior than other molecular subtypes of breast cancer. Unlike other breast cancer subtypes (i.e., ER<sup>+</sup>/PR<sup>+</sup>; Her2<sup>+</sup> breast cancers), there is currently no targeted therapy available for TNBC, although immunotherapy is available for advanced TNBC that expresses programmed cell death ligand 1 (PD-L1); however, this performed in combination with chemotherapy.

High-risk early-stage breast cancer is frequently associated with a high recurrence rate (2). Neoadjuvant chemotherapy (NACT) is the gold standard treatment in this setting (3-5).

In addition, the patients with pathological complete response (pCR) following NACT have longer disease-free and overall survival rates (6-9). The pCR has a strong prognostic value and is a surrogate endpoint for clinical trials testing neoadjuvant treatment in patients with early-stage breast cancer, including TNBC (7,10).

Despite its aggressive behavior, TNBC is particularly sensitive to cytotoxic chemotherapy (known as the 'triple-negative paradox') (11). The pCR is achieved in ~30-40% of TNBC cases following standard anthracycline plus cyclophosphamide- and taxane-based NACT (12).

At the molecular level, TNBC is a heterogeneous disease based on transcriptional and mutational heterogeneity. The biology of TNBC is characterized by an increased

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immunological infiltrate, a basal-like and mesenchymal phenotype, as well as a deficiency in homologous recombination (13).

Genomic instability in the homologous recombination repair genes (i.e., BRCA1 and BRCA2) provides specific therapeutic opportunities for the use of DNA double-strand break-inducing agents: Platinum salts, anthracyclines, cyclophosphamide and poly-ADP-ribose polymerase (PARP) inhibitors (14-16). Platinum agents, such as carboplatin and cisplatin are cytotoxic DNA-damaging compounds which lead to cell apoptosis (17).

Several trials have investigated the benefits of the addition of platinum agents to NACT regimens for TNBC with proven activity, efficacy and safety. In patients with TNBC, the addition of platinum agents is associated with significantly increased pCR rates; however, event-free and overall survival data remain inconclusive (18). To the best of our knowledge, to date, there is currently no available meta-analysis comparing the pCR following NACT with the two principal and most commonly used platinum representatives, cisplatin and carboplatin.

The present study conducted a systematic review and meta-analysis of clinical trials in order to elucidate the differences and benefits of the addition of carboplatin or cisplatin to NACT for patients with TNBC.

## Data and methods

**Search strategy.** A PubMed and Cochrane Register of Controlled Trials search was conducted for published studies evaluating the pCR following platinum-based NACT for patients with TNBC from 1990 to November, 2020. The key medical terms used were: (breast cancer) AND breast cancer [MeSH Terms] AND ['1990/01/01'(Pdat): '2020/06/30'(Pdat)] AND Humans [Mesh] AND English [lang] AND triple-negative AND [cisplatin (MeSH Terms)] OR carboplatin [MeSH Terms] OR platinum [MeSH Terms] AND [neoadjuvant therapy (MeSH Terms)] OR neoadjuvant treatment [MeSH Terms] AND breast cancer [MeSH Terms]. Only studies in the English language were selected.

**Selection criteria.** The eligibility criteria included prospective (randomized and open-label studies) and retrospective studies evaluating the pCR (both in the breast and axilla; ypT0N0) in patients with TNBC treated with cisplatin or carboplatin-based NACT. The reference lists of the included studies were examined in order to identify additional relevant articles. A flow-chart of the literature search is presented in Fig. 1.

From this analysis, studies with <20 patients, phase 1 studies and platinum single-agent studies were excluded. Data selection and extraction were performed by AN, AV and ST independently and data entry was performed by RV. The results were reviewed by the coordinating author (TC).

The primary endpoint of the present meta-analysis was the pooled pCR for the comparison of cisplatin vs. carboplatin-based NACT in TNBC.

**Data extraction.** The following information was extracted from each study/article: The first author and the year of publication, study design, the number of patients included, the neoadjuvant treatment by type (carboplatin or cisplatin), the number of cycles and the percentage of pCRs in the patients with TNBC.

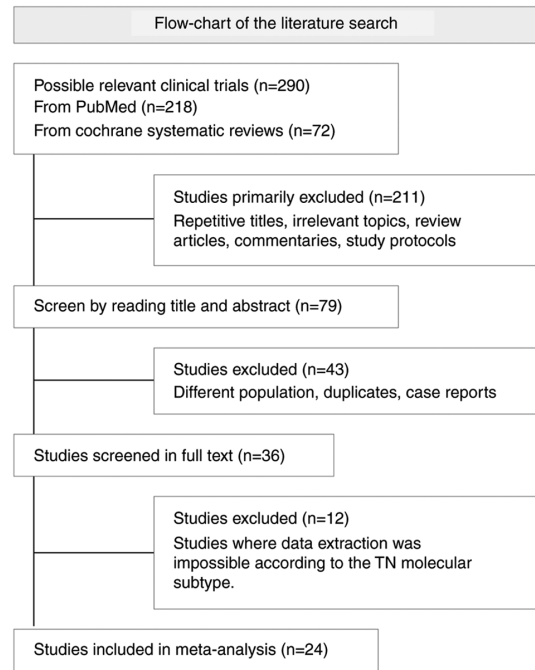


Figure 1. Selection of publications included in the current meta-analysis.

**Statistical analysis.** The analysis was conducted using the Comprehensive Meta-Analysis software, version 2 (<https://www.meta-analysis.com>). As an indicator of the effect size, the event rate (the rate of pCR) was used. Publication bias analysis was performed computing the Begg and Mazumdar rank correlation test. This test computes the rank order correlation (Kendall's tau-b) between the effect size and the standard error (which is driven primarily by the sample size). This determines whether large studies tend to be included in the analysis, regardless of their effect size, whereas small studies are more likely to be included when they exhibit a relatively large effect size. For the moderation analysis, statistical comparisons were performed between the categories of each moderator (the case of categorical moderators) and meta-regressions for continuous moderators. The confidence intervals for the effect sizes were constructed in a parametric manner, for a probability of 95%, by adding on each side of the effect size, the product between its standard error and the critical Z-value 1.96.

## Results

**Identification of relevant studies.** Upon an initial search, 290 relevant articles were identified for evaluation. Based on the inclusion and exclusion criteria, 266 articles were excluded. Case reports, clinical reports and clinical trials that did not provide pCR rates were excluded. Additionally, studies in which data extraction was impossible according to the triple-negative molecular subtype were also excluded. Ultimately, 24 studies were selected for analysis, comprising 1,711 patients with TNBC (19-42). In total, 20 studies were prospective studies and five were retrospective studies. There were 6 studies with cisplatin (5 prospective and 2 retrospective studies, including one arm from a retrospective study with both arms) with a total of 325 patients with TNBC. The remaining studies (18 studies) were with carboplatin (15 prospective studies and 3 retrospective studies, including one arm from a

Table I. Characteristics of the studies included in the current meta-analysis.

Authors/(Refs.), year	Type of study	NLTN/not TNBCs	Protocol	pCR TNBCs with platinum (%)	pCR TNBCs without platinum (%)	pCR not TNBCs with (%)	ORRs TNBCs with vs. without platinum (%)	BCS (%)	DFS/OS (%)	DFS/OS pCR vs. no pCR pts (%)	Median FU (months)
Fraci <i>et al</i> (40), 2009	Prospective series	74/0	wCDDP + wEPI + wPAC	62	-	-	98.3	-	76/89	90/95.6	41
Torrise <i>et al</i> (33), 2008	Prospective series	30/0	EPI d1-2 + CDDP d1 + 5-FU ci d1 (q21d) x 4 -> PAC d1,8,15 (q28d) x 3	40	-	-	86	86	-	-	17
Chen <i>et al</i> (38), 2010	Phase 2	24/71	wPAC + wCBDCA d1, 8,15 (q28d)	33	-	-	-	-	-	-	-
Gogas <i>et al</i> (42), 2010	Phase 2	46	PAC -> CBDCA AUC6	9.5	-	-	60	-	-66	-	45
Chang <i>et al</i> (37), 2010	Prospective series	11/63	CBDCA AUC6 d1 (q21d) + 3wDOC d1 (q21d) x 4	54.6	-	20.9	-	-	-	-	22.8
Silver <i>et al</i> (32), 2010	Phase 2	28	CDDP 75 mg/m <sup>2</sup> (q21d)	21	-	-	-	-	-	-	-
Alba <i>et al</i> (20), 2012	Phase 2 randomized	93	EC d1 q 21 x 4 + 3wDOC ± CBDCA AUC5 d1 (q21d) x 4	30	35	-	77 vs. 70	72 vs. 67	-	-	-
Hurley <i>et al</i> (22), 2013	Retrospective series	144	CBDCA AUC5 or wCBDCA or 3wCDDP + 3wDOC or wDOC x 4 ± AC x 4	31	-	-	-	7.6	55/61	81 vs.44/78 vs.51	48
Roy <i>et al</i> (26), 2013	Phase 2	9/48	DOC d1 (q14d) + CBDCA AUC6 d2 (q14d) x 4	44	-	11.9	-	34	-	-	38
Sikov <i>et al</i> (31), 2015	Phase 2 randomized	443	wPAC x 12 -> AC d1 (q14d) X 4 ± wCBDCA ± bevacizumab (10 mg/kg) d1 (q14d) x 9	54 vs. 41 <sup>b</sup>	-	-	-	57 vs. 40	-	-	-
Ando <i>et al</i> (30), 2014	Phase 2 Randomized	181	wCBDCA AUC5 + wPAC -> (CEF) CTX + EPI + 5-FU	61.2	26.3	-	84.1 vs 70.3	NR	-	-	-
Kern <i>et al</i> (25), 2016	Prospective series	30	CBDCA AUC6 + DOC d1 (q21d)	50	-	-	-	100	-	-	-

Table I. Continued.

Authors/(Refs.), year	Type of study	NLTN/not TNBCs	Protocol	pCR TNBCs with platinum (%)	pCR TNBCs without platinum (%)	pCR not TNBCs with (%)	ORRs TNBCs with vs. without platinum (%)	BCS (%)	DFS/OS (%)	DFS/OS pCR vs. no pCR pts (%)	Median FU (months)
Zhu <i>et al</i> (35), 2016	Phase 2	14/96	CBDCA AUC 5 + PAC ± trastuzumab (6 mg/mg), bi-weekly	57.14	-	-	-	-	-	-	-
AL-Tweigeri <i>et al</i> (19), 2016	Phase 2	51/29	(FEC100) EPI + CTX + 5-FU d1 (q21d) → CDDP + DOC ± trastuzumab d1 (q21d)	36	-	-	-	NR	67/86	96/95 vs 57/82	43
Canello <i>et al</i> (36), 2015	Phase 2	34	EPI + CDDP + 5-FU d1 (q21d) → PAC d1,8,15 (q28d) + CTX 50 mg/day for 12 weeks	56	-	-	-	-	-	-	27
Shinde <i>et al</i> (29), 2015	Retrospective series	10/29	CBDCA AUC6 + wPAC	60	-	31	-	-	-	-	-
Zhang <i>et al</i> (34), 2016	Phase 2 randomized	91	EPI + PAC d1/2 (q21d) vs. PAC + CBDCA AUC5 d2/1 (q21d)	38.6 vs. 14	-	-	89.4 vs. 79.5	-	71.1 vs. 52.8/70.1 vs. 72.5	-	55
De Iulius <i>et al</i> (23), 2017		24/37	CBDCA AUC2 + PAC ± trastuzumab	83	-	-	61,39	57	-	-	48
Sharma <i>et al</i> (28), 2017	Phase 2	190	CBDCA AUC6 + DOC + MGFS (q21d)	55	-	-	-	-	-	-	-
Gluz <i>et al</i> (41), 2018	Randomized trial	336	Arm A: PAC + GEM d1,8 (q3w) Arm B: PAC + CBDCA AUC2 d1,8 (q3w)	45.9	28.7	-	-	-	-	-	-
Hahnen <i>et al</i> (21), 2017	Randomized Clinical Trial	291	Arm A: PAC + NPLD + bevacizumab + CBDCA AUC2 Arm B: PAC + NPLD + bevacizumab	56.8	41.4	-	-	-	85.3/-	-	35
Jovanovic <i>et al</i> (24), 2017	Phase 2	145	CDDP + PAC ± everolimus	40	-	-	-	-	-	-	42

Table I. Continued.

Authors/(Refs.), year	Type of study	NLTN/not TNBCs	Protocol	pCR TNBCs with platinum (%)	pCR TNBCs without platinum (%)	pCR not TNBCs with (%)	ORRs TNBCs with vs. without platinum (%)	BCS (%)	DFS/OS (%)	DFS/OS pCR vs. no pCR pts (%)	Median FU (months)
Fontaine <i>et al</i> (39), 2019	Prospective phase 2	63	wPAC + CBDCA AUC2 -> EPI + CTX + MGFS	54	-	-	-	-	-	-	22
Schmid <i>et al</i> (27), 2020	Randomized double-blind trial	1174	PAC + CBDCA + pembrolizumab; PAC + CBDCA + pembro placebo -> DOC/EPI + CTX	68.9/54.9	-	-	-	-	-	-	15,5

W, weekly; d, day; - not available; TNBC, triple-negative breast cancer; pCR, pathologic complete response; NR, not reported; BCS, breast-conserving surgery; ORR, overall response rate; DFS, disease free survival; OS, overall survival; FU, follow up; CBDCA, carboplatin; CDDP, cisplatin; PAC, paclitaxel; DOC, docetaxel; EPI, epirubicin; 5-FU, 5-fluorouracil; NPLD, non-pegylated liposomal doxorubicin; ADM, adriamycin; AUC, area under the curve; AC, adriamycin + cyclophosphamide; EC, epirubicin + cyclophosphamide; FEC, 5-fluorouracil + epirubicin + cyclophosphamide; NAB-PAC, nab-paclitaxel; GEM, gemcitabine; CTX, cyclophosphamide; MGFS, myeloid growth factor support; ->, followed.



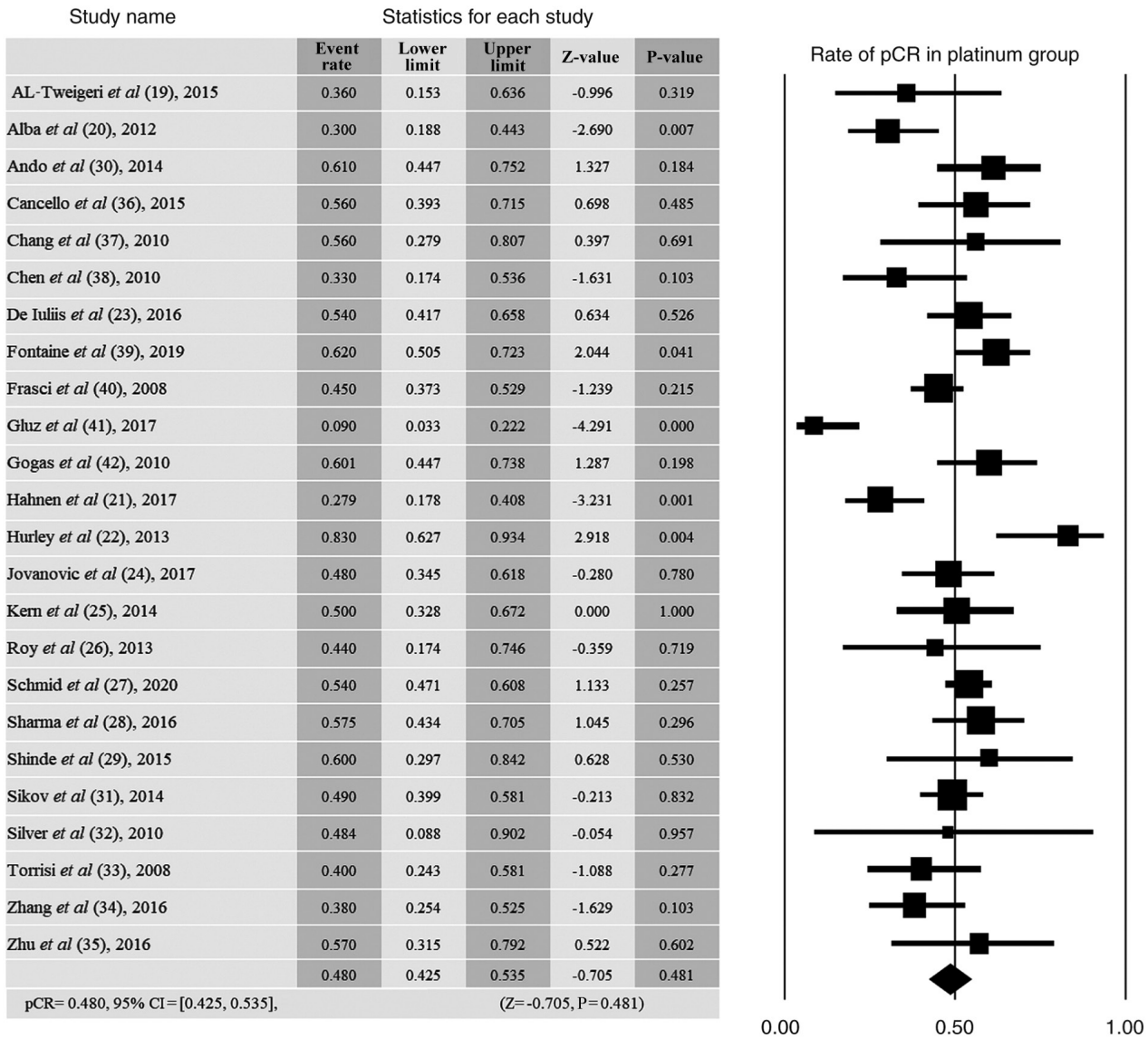


Figure 2. Forest plot of the overall pCR rate in the platinum group. The results indicate a non-significant overall rate of pCR=0.480; (95% CI, 0.425-0.535), compared with the pCR rate obtained under random conditions (Z=-0.705; P=0.481). pCR, pathological complete response.

retrospective study with both cisplatin and carboplatin arms) with a total of 1,386 patients with TNBC (one study included cisplatin and carboplatin as well). The characteristics of the included trials are presented in Table I.

**Heterogeneity of the included studies.** The distribution of effects proved to be significantly heterogeneous,  $Q(24)=65.13$ ,  $P<0.001$ , which indicates that it would be reasonable to test several possible moderators of pCR rate variability. The heterogeneity test investigates whether the effect sizes from each study are sufficiently enough to consider that they come from different populations. In other words, the data upon which the analysis was performed is the distribution of the effect sizes from each study, which is represented in the forest plot (Fig. 2).

**Publication bias.** The risk of publication bias was calculated using the Begg and Mazumdar rank correlation test. This test computes the rank order correlation (Kendall's tau-b) between

the rate of pCR obtained in each study and the standard error (which is primarily driven by the sample size) to identify whether large studies tend to be included in the analysis regardless of their pCR rate, whereas small studies would be more likely to be included when they exhibit a relatively large pCR rate. The rank order correlation (Kendall's tau-b) analysis between the pCR rate and the standard error did not reveal any significant differences, which indicated no publication bias (tau-b=-0.090,  $P=0.528$ ).

The present study performed a meta-analysis of published trials, which included both prospective and retrospective studies, representing a mixed population of patients with early-stage TNBC with different prognoses and responses to NACT. The NACT protocols were very heterogeneous, and platinum agents were associated with very different regimens (conventional and non-conventional combinations).

Overall, the pooled weighted pCR rate in patients with TNBC treated with platinum-based NACT was 48.0%. The results revealed a non-significant overall rate of pCR=0.480,

Table II. Analysis of the pCR rate as a function of treatment (carboplatin vs cisplatin).

Treatment	No. of studies	pCR rate	Inf (95% CI%)	Sup (95% CI%)	Z value	P-value	Heterogeneity between categories		
							Q-value	df	P-value
Carboplatin	18	0.470	0.401	0.539	-0.859	0.390	0.003	1	0.959
Cisplatin	7	0.473	0.379	0.568	-0.559	0.576			

pCR, pathological complete response; df, degrees of freedom; inf, confidence interval lower limit; sup, confidence interval upper limit.

Table III. Analysis of the pCR rate as a function of BRCA (only 4 studies reported results separately, positive vs. negative).

Treatment	No. of studies	pCR rate	Inf (95% CI%)	Sup (95% CI%)	Z value	P-value	Heterogeneity between categories		
							Q-value	df	P-value
Negative	3	0.452	0.294	0.621	-0.547	0.584	2.534	1	0.111
Positive	3	0.626	0.495	0.740	1.892	0.059			

pCR, pathological complete response; df, degrees of freedom; inf, confidence interval lower limit; sup, confidence interval upper limit.

(95% CI, 0.425-0.535), compared with the rate of pCR obtained in random conditions ( $Z=-0.705$ ,  $P=0.481$ ; Fig. 2).

According to the type of platinum agent used, the analysis of the pCR rate revealed no significant differences between the rate of pCR obtained with carboplatin vs. cisplatin treatment (Table II). In addition, no significant differences were observed between the rates of pCR obtained under carboplatin vs. cisplatin treatment. The effect sizes for both categories of the moderator did not differ significantly (carboplatin: pCR rate, 0.470; 95% CI, 0.401-0.539; cisplatin: pCR rate, 0.473; 95% CI, 0.379-0.568) (Table II). The comparison between these two categories revealed no significant differences [ $Q(1)=0.003$ ;  $P=0.959$ ]. Thus, as shown in Table II, no significant differences were observed between the rates of pCR obtained under carboplatin vs. cisplatin treatment.

According to the BRCA status, there was a slightly higher pCR rate for BRCA-positive patients, although no statistically significant differences were observed in comparison to the rate obtained for BRCA-negative patients. This analysis is perhaps as rather inconclusive due to the low number of studies that reported separate results for BRCA-positive and -negative in patients with TNBC (Table III). The pCR rate for BRCA-positive patients observed was 62.6% and that for BRCA-negative patients was 45.2%.

**Discussion**

The present meta-analysis aimed to complement previous systematic review and meta-analysis studies (18,43,44) that analyzed the effects of platinum agents in TNBC as a class, without differentiation between the agents used (carboplatin and cisplatin) in this setting.

The data of the present study demonstrated a pCR rate of 48.0% (pCR, 0.480; 95% CI, 0.425-0.535) in patients with TNBC treated with platinum-based NACT. The current analyses confirmed that the addition of platinum agents confers a higher response rate in TNBC, 48.0 vs. 30-40% without addition of platinum agents, as previously observed by Petrelli *et al* (43). In the present study, the pooled pCR rate is similar that obtained in the study by Poggio *et al* (18) and Petrelli *et al* (43), with pCR rates of 51 and 45%, respectively.

In the meta-analysis by Petrelli *et al*, the pooled pCR rate for 1,598 patients with TNBC treated with platinum-based NACT was 45% (43). Poggio *et al* (18) also observed a significantly increased pCR rate (51%) in patients with TNBC treated with platinum-based NACT. In the present study, according to the type of platinum agent used, the analysis of the pCR rate did not reveal any significant differences between that obtained with carboplatin vs. cisplatin treatment (47.0 vs. 47.3%).

Poggio *et al* (18) reported a significant incidence of grade 3 and 4 hematological adverse events (AEs), and no increased risk of grade 3 and 4 neuropathy with platinum-based NACT. Given the lack of available data, the selection of the most effective platinum agent to be added to the neoadjuvant setting remains unclear, and the decision is guided by the patient characteristics and the decision made by the respective physician. Both carboplatin and cisplatin demonstrate toxicity consistent with their known safety profiles, with AEs occurring as anticipated for these well-known chemotherapy drugs (45).

BRCA mutations can be found in around 15-25% of patients with TNBC (46). It has been demonstrated that BRCA DNA repair defects determine a sensitivity to DNA-damaging agents, such as platinum salts and PARP inhibitors (16). The present study found that patients with TNBC who harbored a BRCA mutation had higher pCR rates compared to patients

who were negative for BRCA mutations; however, the differences were not statistically significant.

These results are in accordance with the results of the meta-analysis by Caramelo *et al* (46), where a pCR rate of 58.4% was achieved in BRCA-positive patients with TNBC who received platinum-based NACT vs. one of 50.7% for BRCA-negative patients; their results did not reach statistical significance either. However, not all studies have found the same positive response to neoadjuvant platinum-based chemotherapy in BRCA-positive patients with TNBC. The GeparSixto trial demonstrated that the addition of platinum agents did not improve the pCR rate in BRCA-positive patients vs. those without BRCA mutations (36.4 vs. 55%) (21). Another meta-analysis confirmed the results from GeparSixto trial and suggested that the addition of platinum agents did not statistically improve the pCR rate (43.4 vs. 33.9%; OR, 1.340; 95% CI, 0.677-2.653; P=0.400) (47). The benefits of the addition of platinum agents to the neoadjuvant setting in BRCA-positive patients with TNBC still needs to be evaluated, considering the limited number of patients with BRCA mutations.

In a retrospective analysis of 144 patients with locally advanced TNBC, Hurley *et al* (22) evaluated the use of carboplatin and cisplatin. In the cisplatin-based NACT group (97 patients) a pCR rate of 35 (36.1%; HR, 0.32; P=0.009) was observed, vs. one of 10 (21.3%; HR, 0.40; P=0.002) in the carboplatin-based NACT group (47 patients), suggesting that cisplatin was superior to carboplatin, although with a different toxicity profile.

In conclusion, the present meta-analysis of published studies included both prospective and retrospective studies, representing a mixed population of early-stage TNBC with different prognoses and responses to NACT. The NACT protocols were very heterogeneous and the platinum agents were associated with markedly different regimens. To the best of our knowledge, the present study performed the first meta-analysis that investigated the efficacy of carboplatin and cisplatin as different chemotherapy agents in the neoadjuvant treatment of patients with TNBC. The results revealed that NACT improved the pCR rate in TNBC, regardless of the platinum agent used. Carboplatin represents a viable option in terms of accessibility, affordability and a more favorable toxicity profile.

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#### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

#### Authors' contributions

AN, AV and ST performed the data selection and data extraction independently. RV performed data entry. SP and AD

performed the statistical analysis. RV and TC, the coordinating author, were involved in the conception and the design of the study and reviewed the final results. RV, AN and TC confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

#### Ethics approval and consent to participate

Not applicable.

#### Patient consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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