REVIEW ARTICLE
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# Integrative review of clinical trials and meta-analysis of the main studies of neoadjuvant chemotherapy in the treatment of breast cancer in the past 30 years

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## ABSTRACT

Neoadjuvant chemotherapy (NAC) has become a common treatment strategy for early-stage breast cancer. In this study, we conducted a systematic research in the PubMed database using the following terms: breast cancer, neoadjuvant chemotherapy, randomized clinical trials, complete pathological response, overall survival, and disease-free survival. The research has been limited to articles published in the past 30 years (1993–2023). We included only randomized clinical trials that evaluated the use of NAC in breast cancer and data on PCR rates and survival outcomes. Our research resulted in a total of 13 randomized clinical trials and two meta-analyses. The PCR rates ranged from 13% to 58%, with higher rates observed in patients with triple-negative breast cancer (TNBC) and human epidermal growth factor 2 (HER-2+) disease. Several trials reveal a significant association between PCR and better survival results, including overall survival and disease-free survival. However, the impact of PCR on survival results was less consistent in patients with hormone receptor-positive breast cancer. The use of taxanes in combination with anthracyclines has been the most common NAC scheme evaluated in these trials. The PCR rates have been associated with better survival outcomes, in patients with TNBC and HER-2+ disease. However, the impact of PCR on survival outcomes in patients with hormone receptor-positive breast cancer is less clear. Additional studies are needed to determine the optimal NAC regimen for each subtype of breast cancer and to identify biomarkers that can predict the NAC response.

KEYWORDS: breast neoplasms; neoadjuvant therapy; chemotherapy.

## INTRODUCTION

Breast cancer (CM) is the most common type of cancer and the leading cause of cancer death among women worldwide[1]. Treatment of breast cancer is complex and depends on several factors, such as stage, degree, status of hormone receptors, and human epidermal growth factor 2 (HER-2). Neoadjuvant chemotherapy (NAC) is the standard treatment for locally advanced breast cancer and is increasingly used for early-stage breast cancer[2]. It has been shown to improve the chances of conservative breast surgery, reduce the risk of involvement of lymph nodes, and increase the possibility of achieving a complete pathological response (PCR)[3].

The PCR is defined as the absence of any invasive or *in situ* cancer in the breast and axillary lymph nodes after completion of NAC[4]. The PCR has been suggested as a substitute outcome for long-term survival outcomes, such as global survival (SG) and disease-free survival (SLD)[5]. However, the relationship between the PCR and survival outcomes is still controversial, and many studies have conflicting results.

In recent years, several randomized clinical trials (ECRs) and meta-analyses have investigated the effectiveness of NAC in breast cancer and its relationship with PCR and survival outcomes. The aim of this integrative review is to synthesize the evidence of ECRs and meta-analysis published over the past 30 years on NAC in breast cancer, with a particular focus on the association between PCR, SG, and SLD.

## METHODS

This is a non-systematic integrative review that aims to synthesize evidence on NAC for the treatment of breast cancer, specifically

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in relation to its impact on PCR and overall survival and disease-free survival. The search was carried out in the PubMed database using the following MeSH terms: "Breast Neoplasms"[Mesh] AND "Antineoplastic Combined Chemotherapy Protocols"(Mesh) AND "Neoadjuvant Therapy" (Mesh), AND "Randomized Controlled Trials as Topic"(Mesh), and "Meta-Analysis as Topics" (Mesh). The search was limited to studies published in the past 30 years (January 1993 to December 2022) in English. In addition, manual searches were carried out in the reference lists of relevant studies to identify additional articles.

The inclusion criteria were as follows:

1. Randomized clinical trials and meta-analyses that assessed the effectiveness of NAC in breast cancer;
2. Studies that reported the rates of PCR, SG, and/or SLD;
3. Studies that were published in English.

Exclusion criteria were as follows:

1. Studies that did not evaluate NAC;
2. Studies that did not report the rates of PCR, SG, and/or SLD;
3. Studies that were not published in English.

The data synthesis was carried out using a narrative approach, and a summary table was created to present the main features of the studies included. The results were summarized separately for subtypes and all subtypes. Studies that did not report PCR or survival outcomes were excluded from the synthesis.

The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed throughout the review process. The initial search identified a total of 1,276 studies, of which 1,129 were found on PubMed, 127 on EMBASE, and 20 on ClinicalTrials.gov. After the removal of duplicate studies, the total number of studies was reduced to 1,116. The sorting of titles and summaries led to the exclusion of 1,077 studies. Full-text articles were obtained for the remaining 39 studies, of which 33 were clinical trials and 5 were meta-analyses. After the inclusion and exclusion criteria were applied, a total of 15 studies were included in the final synthesis (Figure 1).

## Integrative review

### *Treatment of breast cancer*

Treatments for non-metastatic CM are surgical resection, systemic therapy (chemotherapy, endocrinotherapy, and target therapies), and radiotherapy. Systemic treatment prior to definitive surgical treatment, called neoadjuvant treatment, is recommended for almost all patients diagnosed with locally advanced breast cancer. The primary objective of this approach is to reduce the volume of the tumor and allow the realization of surgical treatment with better aesthetic results not only in those patients considered inoperable to the diagnosis but also in those with operable tumors and who wish to be subjected to conservative surgery[2]. Moreover, neoadjuvant treatment allows direct observation of response to treatment, with the potential to provide data that can be used with predictive and prognostic intent[6]. From studies in adjuvant treatment (the one that is administered after surgery), we can obtain information regarding the outcomes of SLD and SG, but such studies require the inclusion of a large number of patients and that they are followed for a long period, which generates a high cost. On the contrary, studies in neoadjuvant treatment can be conducted with fewer patients and at a shorter time interval, as well as provide information on intermediate outcomes, such as PCR and clinical response, which could predict the benefit in terms of long-term outcomes at a lower cost. These advantages have stimulated the expansion of the number of studies in NAC in recent years, including those for the inclusion of new drugs[6,7].

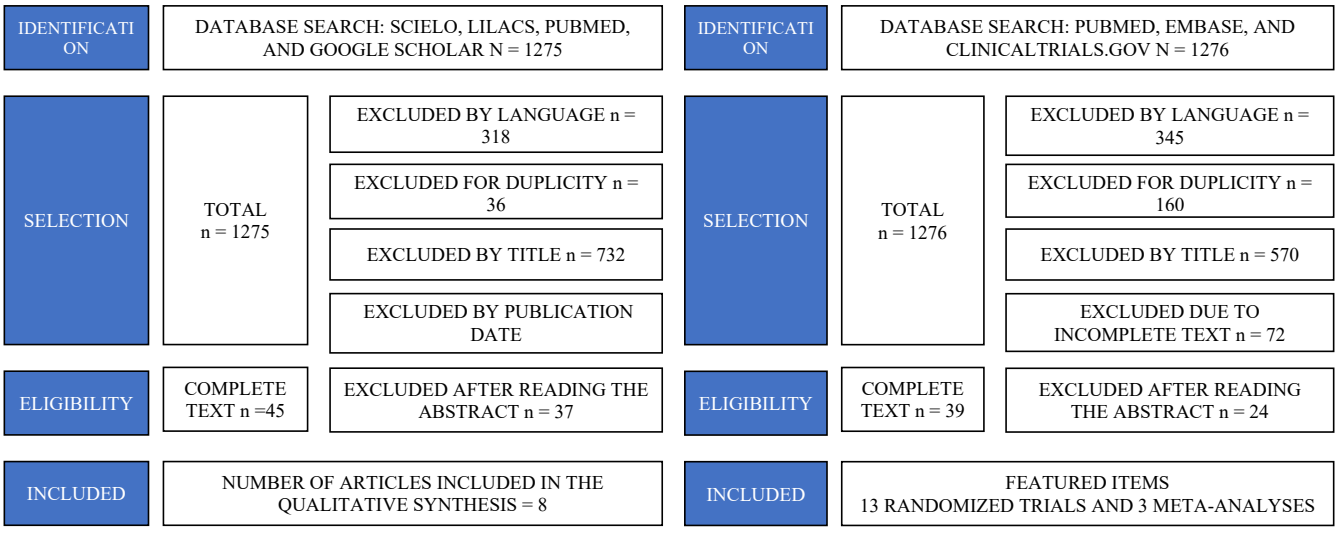



**Figure 1.** Database search flowchart.

While historically surgery followed by adjuvant chemotherapy has been considered the first and primary treatment, neoadjuvant chemotherapy (administration of chemotherapy before surgery) has emerged as the recommended approach in patients with locally advanced disease, or whose "tumor size/mother" ratio is unfavorable for conservative surgery, or for those with aggressive tumor biology (triple-negative breast cancer (TNBC) and HER-2 positive (HER-2+))[8]. The NAC approach offers multiple advantages as it offers the opportunity to reduce surgical management based on the response, provides response information that is prognostic and is used to guide adjuvant treatment recommendations, serves as a platform to advance in drug development, and enables time gains until the outcome of the genetic panel for hereditary breast cancer[9].

In Table 1, we find the main current schemes for NAC established by the National Comprehensive Cancer Network Guideline updated in February 2023[2].

## Complete pathological response rates

One of the pioneering studies on NAC in breast cancer was conducted by Bonadonna et al. and published in 1976[10]. This study, conducted at the National Cancer Institute of Milan, evaluated the use of chemotherapy with CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) before surgery in women with operable breast cancer. The results of this study showed that NAC reduced the size of the tumor and increased the rate of conservative resection of the breast[10].

After two decades of studies comparing adjuvant versus neoadjuvant strategies, such as the National Surgical Adjuvant Bowel and Breast Project (NSAPB) B-18[11], which randomized 1,523 women with operable CM for doxorubicin (Adriamycin) and cyclophosphamide (AC) in the neoadjuvant or adjuvant treatment, the rate of PCR in this initial study was only 13%, which is much lower than that currently seen. This study was carried out before the routine tests for RH or HER-2 to guide the selection of systemic therapy[11].

The NSABP B-27 study evaluated the addition of paclitaxel (T) to the combination of AC in the neoadjuvant or adjuvant scenario and clearly demonstrated the benefit of adding the taxane, with improved PCR rates (26.1%), thus indicating a factor of better prognosis[12].

The GeparDuo study was conducted to determine the rate of PCR between administrations of dense-dose AC chemotherapy (ACdd) every 14 days, compared with conventional scheme every 21 days. The PCR rate was significantly higher in the ACdd group (14.3% versus 7.0%)[13].

A meta-analysis that included nine randomized clinical trials (RC) with a total of 3,274 patients, who received dense-dose NAC schemes, did not observe an increase in PCR (OR 1.18) in all patients; however, when evaluating patients with low hormone receptor expression (HR), there was a significant increase in PCR (OR 1.36)[14].

Over the past few years, several studies have shown different rates of PCR, which vary, in a general way, from 3.3 to 40.9%, without assessing the molecular profile[15]. A meta-analysis with eight EC and eight retrospective studies (RS) showed a PCR of 22.4%. Thus, PCR rates are discordant between different subtypes, and the prognostic effects of PCR are not applicable to all molecular subtypes of CM[15].

The rate of PCR is higher in TNBC and HER-2-positive patients than in HR+/HER-2-negative patients[15]. According to the results of the CTNeoBC meta-analysis, which analyzed 12 EC on the association of PCR with long-term results, patients with highly aggressive subtypes, such as TNBC or HER2+, who achieved PCR, showed better results than patients with luminal subtypes A[16].

Spring et al.[17] conducted a meta-analysis of 52 studies and 27,895 patients, of whom 14,254 (51.1%) came from ECRs, 1,709 patients (6.1%) from non-randomized clinical trials, and 11,932

**Table 1.** Main current schemes for neoadjuvant chemotherapy of National Comprehensive Cancer Network version 4.2023[6].

| Subtype of Breast Cancer | Main NAC Scheme | Associated Target Therapies | Main indications |
|---|---|---|---|
| RH+ HER-2 - | AC-T sequential | | Conservative Surgery Wish T>5.0 cm or N+ <40 years, G3 |
| | TC | | Cardiotoxicity risk |
| HER-2 + | AC – T sequential | Trastuzumab + Pertuzumab (1 year) | T>2.0 cm or qqT N+ |
| | T Carboplatin | | |
| TNBC | AC + T Carboplatin | Pembrolizumab (T>2,0 cm) | T>1.0 cm qqN |

NAC: neoadjuvant chemotherapy; HER-2+: human epidermal growth factor 2; TNBC: triple-negative breast cancer; AC: Adriblastine + Cyclophosphamide; T: Taxanes; TC: Taxane + Cyclophosphamide; ACdd: Adriblastine + Cyclophosphamide dose dense, qq: any, N+ - armpit with involved lymph nodes, G3 histological grade.

patients (42.8%) from retrospective cohort studies. CTNeoBC[16] meta-analysis data were included in a single study, showing that the PCR was 21% (range: 10.1%–74.2%), with the highest rate of PCR observed in HER2+ tumors at 36.4% (range: 17.5%–74.2%) and TN tumors at 32.6% (range: 20.3%–62.2%), while HR+/HER2-negative tumors had the lowest rate at 9.3% (interval: 5.5%–31.3%)[17].

## Full pathological response rate in HER-2+ patients

In general, superexpression of the HER-2 protein and/or the amplified HER-2 gene is found in about 20%–25% of CM cases. It is known that CM HER-2+ has a more aggressive phenotype, with a higher rate of relapses and mortality when left untreated; however, HER-2 blockage with anti-HER therapies demonstrated a significantly better prognosis[18].

The first major study was conducted at the MD Anderson Cancer Center, comparing the effect of NAC with or without Trastuzumab in 42 patients with operable HER-2+ disease. They were randomly assigned to paclitaxel followed by 5-FU + Epirubicin + cyclophosphamide (FEC) for four cycles, or to the same Trastuzumab chemotherapy regimen. The rates of PCR were 25% in the chemotherapy-only group and 66.7% in the chemo + Trastuzumab group (p=0.02). Despite the small sample size, the study showed that adding Trastuzumab to chemotherapy improves PCR[18].

The TRYPHAENA study is an open phase II study, in which patients with operable, locally advanced, or inflammatory HER-2+ disease were randomized into three groups: FEC + trastuzumab + pertuzumab followed by taxane + trastuzumab + pertuzumab (arm A), FEC followed by taxane + trastuzumab + pertuzumab (arm B), and FEC followed by taxane and carboplatin + trastuzumab & pertuzumab (arm C). The PCR was 61.6% in arm A, 57.3% in arm B, and 66.2% in arm C[19].

The NeoSphere study also evaluated the effectiveness of pertuzumab use in neoadjuvant treatment. Patients were randomized to receive trastuzumab + taxane (group A), pertuzumab + trastuzumab + taxane (group B), pertuzumab + trastuzumab (group C), or pertuzumab + taxane (group D). Patients in group B had significantly higher response, with a PCR of 45.8% compared with patients in group A, with a PCR of 29.0%. The PCR in group C was 16.8%, and in group D, it was 24%. According to the study, the best option for NAC is the taxane scheme associated with double block HER-2[20].

The TRAIN-2 study assessed the effect of omitting the use of anthracyclines in patients with HER-2+ breast cancer. In the study, 438 patients were randomized to receive anthracyclines or not, and there was no difference in PCR rates between the groups. The group that received anthracyclines showed a PCR rate of 67%, while, in the group that did not receive them, the rate was 68% (p=0.95). These results suggest that omitting anthracyclines may be a viable treatment option in patients with HER-2+ breast cancer, without compromising the effectiveness of treatment[21].

## Full pathological response rate in triple-negative patients

Patients with TNBC account for 13–20% of cases and respond significantly better to NAC compared with luminal subtype, probably because they are more proliferative. Three major studies, namely, BrighTNess[22], GeparSixto[23], and CALGB 40603[24], have shown that the addition of platinum to a NAC regimen leads to higher PCR rates. However, enthusiasm for increased PCR rates is accompanied by additional toxicity, often requiring dose reductions or cycle eliminations, with results that do not always improve long-term survival rates[22-24].

The addition of platinum derivatives to NAC in TNBC patients has shown an increase in PCR rates. A meta-analysis was performed with nine ECs, totaling 2,109 patients with a PCR in the group that received a platinum scheme of 52.1% compared with 37.0% in the non-platinum group[25].

Recent successes in immunotherapy have been able to incorporate it into NAC for CM. The interaction between the programmed cell death receptor 1 (PD-1) and the programmable cell death ligand 1 (DP-L1) constitutes a key immune control point that negatively regulates T-cell activity and is exploited by tumors to escape immunological surveillance. Inhibition of the interaction between PD-1 and PD-L1 has been successfully used in several tumors to restore or enhance the endogenous antitumoral immune response. The three most important studies evaluating the addition of immunotherapy to NAC are I-SPY2, KEYNOTE-522, and IMpassion031[26-28].

I-SPY2 is an open, multicenter, randomized neoadjuvant phase II clinical trial that evaluated the addition of Pembrolizumab with paclitaxel in NAC. The addition of Pembrolizumab tripled the estimated PCR rates in TNBC, 22% with placebo and 60% with Pembrolizumab[26].

KEYNOTE-522 was designed to determine whether Pembrolizumab added to standard NAC improved the PCR and SLD rates in patients with operable TNBC. This study was randomized, phase III, and placebo-controlled. The PCR rates were improved with Pembrolizumab: 64.8% in the study group and 51.2% in the placebo group. The positive subgroup for PD-L1 showed overall higher PCR rates, but the benefit was observed independently of the expression of PD-L1[27].

IMpassion031 is a minor phase III study with a design similar to KEYNOTE-522(28), but it evaluated Atezolizumab as the immunotherapy agent. The study PCR rates for the PD-L1 positive subgroup achieved overall higher PCR (68.8% with Atezolizumab versus 49.3% with placebo), but the benefit was observed independently of PD-L1 expression, with a PCR of 57.6% with Atezolizumab versus 41.1% with the placebo[28].

The addition of NAC-specific immunotherapy in patients is independent of PD-L1 expression and is currently the new treatment scheme for patients with NBC[2].

In Table 2, we find a summary of the main studies of NAC and its receptive rates of PCR and NAC scheme.

## Causes of complete pathological response failures

Failure to PCR is related to unfavorable prognosis in TNBC and HER-2+ tumors, but not in most luminal patients[29]. In fact, studies have indicated that luminal patients tend to present a favorable prognosis, although they are less responsive to chemotherapy, with relatively lower chances of achieving PCR, thus reflecting the uncertain correlation between PCR and long-term outcomes in luminal patients[16].

Although estimated PCR rates have increased after the addition of new drugs to routine chemotherapy, many patients cannot PCR after NAC, and not all patients with PCR have a good prognosis[17].

Factors related to the highest probability of PCR include TNBC tumors, HER-2+, high rate of cell proliferation (Ki67), and high degree of nuclear and ductal histology. Usually, patients with positive hormone receptor (RH+) have worse rates of PCR[12,29,30].

**Table 2.** Pathological complete response rates in neoadjuvant treatment for breast cancer.

| Study | Year | Subtype | NAC Scheme | PCR (%) |
|---|---|---|---|---|
| Fisher et al.[11]<br>NSABP-B18 | 1997 | All | AC | 13.0 |
| Bear et al.[12]<br>NSABP B27 | 2003 | All | AC + T | 26.1 |
| von Minckwitz et al.[13]<br>GeparDuo | 2005 | All | ddAC<br>AC | 14.3<br>7.0 |
| Spring et al.[17] | 2020 | All | Various schemes<br>PCR vs. non-PCR | 21.1 |
| von Minckwitz et al.[23]<br>GeparSixto | 2014 | TNBC | A+T Carboplatin + Bev<br>A+T + Bev | 53<br>43 |
| Sikov et al.[24]<br>CALGB 40603 | 2015 | TNBC | TCarbo+AC + Bev<br>T + AC + Bev | 54<br>41 |
| Geyer et al.[22]<br>BrigTNess | 2020 | TNBC | T + Veliparib + Carbo<br>T + Veliparib + AC | 58<br>31 |
| Poggio et al.[25] | 2018 | TNBC | Scheme with Platinum<br>Non-Platinum Scheme | 51<br>37 |
| Mittendorf et al.[28]<br>IMpassion031 | 2020 | TNBC | Atezolizumab + Nab-P □ Atezolizumab + ddAC Nab-P □ ddAC | 58<br>41 |
| Nanda et al.[26]<br>I-SPY2 | 2020 | TNBC | Pembrolizumab +T + AC<br>AC + T | 60<br>22 |
| Schmid et al.[27]<br>KEYNOTE-522 | 2020 | TNBC | PCarbo + AC ou EC + Pembrolizumab<br>PCarbo + AC ou EC + Placebo | 64.8<br>51.2 |
| Spring et al.[17] | 2020 | TNBC | Various schemes<br>PCR vs. non-PCR | 32.6 |
| Budzar et al.[18] | 2005 | HER-2+ | AC -T + Placebo<br>AC - T + Trastuzumab | 25<br>66.7 |
| Scheeweiss et al.[19]<br>TRYPHAENA | 2013 | HER-2+ | FECHP + THP<br>FEC + THP<br>TCHP | 61.6<br>57.3<br>66.2 |
| Gianni et al.[20]<br>NeoSphere | 2012 | HER-2+ | T+Trastuzumab<br>T+Trastuzumab + Pertuzumab<br>Trastuzumab + Pertuzumab<br>Taxane + Pertuzumab | 29.0<br>45.8<br>16.8<br>24 |
| van Ramshorst et al.[21]<br>TRAIN-2 | 2018 | HER-2 + | 3FEC + HP + 6TCarboHP<br>9TCarboHP | 67<br>68 |
| Spring et al.[17] | 2020 | HER-2 + | Various schemes<br>PCR vs. non-PCR | 36.4 |

AC: Adriblastine + Cyclophosphamide; T: Taxanes; TC: Taxane + Cyclophosphamide; ddAC: Adriblastin dose dense + Cyclophosphamide; Carb: Carboplatin; Bev: Bevacizumab; TNBC: triple-negative breast cancer; Nab-P: Nab-paclitaxel; P: Paclitaxel; EC: Epirubicin + Cyclophosphamide; FEC: 5FU + Epirubicin + Cyclophosphamide; H: Trastuzumab; HP: Trastuzumab + Pertuzumab; PCR: polymerase chain reaction.

Currently, the rates of PCR are higher in TNBC patients, reaching 64.8% due to the use of immunotherapy with Pembrolizumab combined with chemotherapy[27], and in HER-2+ due to double blockage with trastuzumab and pertuzumab associated with chemotherapy[20] (Table 3).

## Complete pathological response relation and prognosis

Several studies have shown that NAC is an effective treatment option in patients with breast cancer. In addition to reducing the tumor size, NAC has been associated with a significant influence on the extent of surgery. In addition, PCR after NAC has been shown to be an important prognostic factor in patients with breast cancer. This observation highlights the relevance of PCR as a prognostic marker and reinforces the importance of the use of NAC in the treatment of patients with CM[16,31,32].

The initial study comparing adjuvant versus neoadjuvant treatment was NSAPB B-18[11]. The aim was only to assess the PCR rates. These patients continued to be followed in a new study to define the prognosis of the disease. Their follow-up showed that patients who performed NAC showed an SG of 81% and those who did in adjuvance showed an SG of 80%; the SLD was 55% versus 53%, respectively, with no significant difference for the two outcomes. Patients with PCR after NAC had an SLD of 75% versus 58%, while SG was 85% versus 73%, showing that PCR has an impact on long-term prognosis[33].

The NSABP B-27 study, which evaluated the addition of paclitaxel (T) to the combination of AC in the neoadjuvant or adjuvant scenario, demonstrated that there was no modification in GH with the addition of taxane. However, when patients were evaluated for PCR, there was an improvement in GHS (89% versus 74%), showing a reduction in rates of mastectomy and smaller local relapses. This study clearly demonstrates the benefit of adding the taxane with improved rates of PCR (26.1%) and thus a better prognosis[12,34].

The findings of NSABP B-18 were corroborated in a joint analysis of 12 ECs, including 12,000 patients, which showed that those who achieved PCR had improved survival, in TNBC and HER-2+[35].

In the TRYPHAENA study, in the evaluation of SLD over 3 years, the results were found to be 87%, 88%, and 90% in groups A to C, respectively. Progression-free survival rates were found to be 89%, 89%, and 87%. The risk rate for SLD was 0.27 in comparison between PCR and non-PCR[19].

In the NeoSphere study, the addition of Pertuzumab showed that PCR can be considered a long-term prognosis improvement factor. Patients were randomized to receive trastuzumab + taxane

**Table 3.** Main randomized clinical trials and meta-analysis of randomized clinical trials, in neoadjuvant chemotherapy and polymerase chain reaction relationship and prognosis.

| Study | Year | Subtype | NAC Scheme | SLD (%) | SG (%) |
|---|---|---|---|---|---|
| Wolmark et al.[35] NSABP-B18 | 2001 | All | AC | 75 x 58 | 85 x 73 |
| Rastogiet al.[34] NSABP B27 | 2008 | All | AC + T | | 89 x 73 |
| Spring et al.[17] | 2020 | All | Various schemes PCR vs. non-PCR | 88 x 67 | 94 x 75 |
| Poggio et al.[25] | 2018 | TNBC | Scheme with Platinum Non-Platinum Scheme | No difference | No difference |
| Nanda et al.[26] I-SPY2 | 2020 | TNBC | Pembrolizumab +T + AC AC + T | 95 81 | |
| Spring et al.[17] | 2020 | TNBC | Various schemes PCR vs. non-PCR | 90 x 47 | 84 x 57 |
| Schneeweiss et al.[19] TRYPHAENA | 2013 | HER-2+ | FECHP + TTP FEC + TTP TCTP | 87 88 90 | |
| Gianni et al.[20] NeoSphere | 2012 | HER-2+ | T+Trastuzumab T + TP TP TP | 81 84 80 75 | |
| van der Voort et al.[36] TRAIN-2 | 2021 | HER-2+ | 3FEC + HP + 6TCarboHP 9TCarboHP | 92.7 93.6 | 97.7 98.2 42 |
| Spring et al.[17] | 2020 | HER-2+ | Various schemes PCR vs. non-PCR | 86 x 63 | 95 x 76 |

AC: Adriblastine + Cyclophosphamide; T: Taxanes; PCR: polymerase chain reaction; TNBC: triple-negative breast cancer; HER-2+: human epidermal growth factor 2; FECHP: 5-fluorouracil, epirubicin, cyclophosphamide, trastuzumab, pertuzumab; TTP: docetaxel, docetaxel, pertuzumab; TCTP: docetaxel, cyclophosphamide, docetaxel, pertuzumab; TP: docetaxel, pertuzumab; FEC: 5-fluorouracil, epirubicin, cyclophosphamide; 5FU + Epirubicin + Cyclophosphamide; HP: Trastuzumab + Pertuzumab.

(group A), pertuzumab + trastuzumab + taxane (group B), pertuzumab + trastuzumab (group C), or pertuzumab plus docetaxel (group D). Patients in group B had SLD of 84% in 5 years compared with 81% in patients in group A. Group C showed an SLD of 80%, and group D showed an SLD of 75%[20].

In the TRAIN-2 study, the 3-year follow-up analysis noted that the use of anthracyclines in the treatment of patients with HER-2+ CM showed no improvement in SLD (92.7% versus 93.6%) and SG (97.7% versus 98.2%). In the evaluation of patients with PCR alone, SG was 42% (p=0.006)[36].

The addition of platinum derivatives in NAC in TNBC patients was studied in a meta-analysis with nine ECs, totaling 2,109 patients, and an increase in PCR rates was found, but there was no significant improvement in SG and SLD (OR 1.17, 95%CI 0.51–2.67, p=0.711)[25].

In the publication of I-SPY2, EC for the use of Pembrolizumab in NAC, in the ratio of PCR and SLD, a 95% SLD was observed in patients with PCR, while, in patients without PCR, an 81.9% SLD was observed in 3 years of follow-up[37].

The meta-analysis of 52 studies by Spring et al., totaling 27,895 patients, showed that patients with PCR after NAC had significantly better SLD (88%×67%), TNBC (90%×47%), and HER-2+ (86%×63%). Similarly, PCR was associated with better SG (94%×75%), TNBC (84%×57%), and HER-2+ (95%×76%). The association of the improvement of SG and SLD occurred only when the retrospective studies and the EC were evaluated separately, and in retrospective studies, there was no such observation[17].

The association of the improvement of SG and SLD with PCR in HER-2+ patients was confirmed in a meta-analysis of 78 studies (retrospective and EC), totaling 25,150 patients, which showed that PCR improves SLD (91.6%×79.0%) and SG (93.8%×80.3%) as well[38].

A growing number of studies have investigated the prognostic value of PCR and whether there is a relationship with age. Although BC in young women tends to be more aggressive, with a relatively unfavorable prognosis, reports show that patients ≤40 years of age can also obtain significant survival benefits when achieving PCR after NAC. As a prognostic indicator, PCR has the advantage of reflecting chemo-sensitivity shortly after NAC, which highlights the need for subsequent adjuvant treatment after surgery[39].

Although several studies have suggested a correlation between PCR and better prognosis, a small group of people have recurrence of the disease and metastasis in the short term, even reaching PCR after NAC. Studies point out that factors such as HER-2+, axillary lymph nodal metastases, premenopausal patients, and advanced clinical stage (IIIA–C) may increase the rates of recurrence or metastasis in patients who have achieved PCR[34-40].

The presence of PCR has emerged as a powerful prognosis predictor for patients undergoing NAC, especially TNBC and HER-2+; thus, in these patients, it has been used as a prognostic outcome. As such, PCR has entered as a criterion to accelerate the approval of medicines by the Food and Drug Administration (FDA)[41,42].

In Table 3, we find the main EC and meta-analysis of EC, in NAC and PCR ratio and prognosis.

## CONCLUSIONS

NAC has become a common treatment strategy for early-stage breast cancer, and several randomized clinical trials have evaluated its effectiveness over the past 30 years. The use of taxane in combination with anthracyclines has been the most common NAC scheme evaluated in these trials. The addition of HER blocking (preferably double – trastuzumab and pertuzumab) has been indicated in HER2+ patients, while the addition of immunotherapy has been preferential in triple-negative diseases. The PCR rates have been associated with better survival outcomes in patients with TNBC and HER-2+ disease. However, the impact of PCR on survival outcomes in patients with hormone receptor-positive breast cancer is less clear. Additional studies are needed to determine the optimal NAC regimen for each subtype of breast cancer and to identify biomarkers that can predict the NAC response.

## AUTHORS' CONTRIBUTION

MA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft. AM: Formal Analysis, Investigation, Methodology, Writing – original draft. GDP: Formal Analysis, Investigation, Methodology, Writing – original draft. LHG: Supervision, Validation, Visualization. OF: Supervision, Validation, Visualization. RGCL: Supervision, Validation, Visualization. JMR: Supervision, Validation, Visualization.

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