REVIEW

Editorial Process: Submission:07/07/2025 Acceptance:02/25/2026 Published:03/06/2026

Pertuzumab and Pathological Complete Response in Early HER2+ Breast Cancer: A Systematic Review and Meta-analysis of Real-World Studies

Silvio Matsas[1]*, Julita Zembala[2], Anderson Ruiz Simões[3], Luiza Giuliani Schmitt[4], Yara Abdou[5], Auro Del Giglio[6]

Abstract

Background: Human epidermal growth factor receptor 2-positive (HER2+) breast cancer (BC) is an aggressive subtype that is associated with poorer outcomes. Neoadjuvant chemotherapy combined with trastuzumab has significantly improved prognosis, and the addition of pertuzumab has further enhanced the treatment response. Pathological complete response (pCR) is a reliable surrogate marker of long-term outcomes, and its achievement can inform surgical and adjuvant therapy decisions. While randomized controlled trials (RCTs) have demonstrated the benefits of dual HER2 blockade, real-world evidence (RWE) is critical for assessing treatment effectiveness in broader, more diverse populations. **Objective:** To evaluate the impact of dual HER2 blockade with pertuzumab and trastuzumab compared to single-agent trastuzumab on pCR rates in early-stage HER2+ breast cancer using real-world data. **Methods:** A systematic review and meta-analysis were conducted using the PubMed, Embase, and Scopus databases from inception to February 28, 2025. Eligible studies were retrospective or prospective real-world investigations comparing neoadjuvant chemotherapy with trastuzumab alone versus trastuzumab plus pertuzumab. Data were extracted independently by two reviewers. Pooled odds ratios (ORs) for pCR, along with 95% confidence intervals (CIs), were calculated. The risk of bias was assessed using the Newcastle-Ottawa Scale. **Results:** Eighteen studies involving 8,651 patients met the inclusion criteria. The pooled odds ratio (OR) showed significantly higher pCR rates with dual HER2 blockade (OR: 1.81; 95% CI: 1.56–2.09), with no observed heterogeneity ($I^2 = 0\%$). Subgroup analyses confirmed consistent findings across geographic regions and study characteristics. Publication bias was low, as supported by Egger's test ($p = 0.37$). **Conclusion:** In real-world settings, adding pertuzumab to neoadjuvant therapy significantly improves pCR rates in early-stage HER2+ breast cancer, aligning with RCT evidence. These findings support the broader adoption of dual HER2 blockade and highlight the need for further prospective real-world studies to refine treatment strategies for specific patient subgroups.

Keywords: breast cancer- pathological complete response- pertuzumab- dual HER2 blockade- meta-analysis

Asian Pac J Cancer Prev, **27 (3)**, 813-821

Introduction

Breast cancer (BC) is one of the most prevalent malignancies among women and remains a significant global health concern [1]. Over the past decades, its incidence has steadily increased, with more than 1 million new cases diagnosed annually worldwide [2]. Overexpression of Human epidermal growth factor receptor 2 (HER2)-positive constitutes an aggressive subtype of disease and is associated with poor prognosis [3]. A high molecular heterogeneity adds complexity for the management of this malignancy [4].

Trastuzumab (Herceptin), a humanized monoclonal antibody, was the first FDA-approved anti-HER2 therapy. When combined with chemotherapy, trastuzumab significantly improves overall response rate and survival compared to chemotherapy alone. This breakthrough established neoadjuvant chemotherapy combined with trastuzumab as the standard treatment for early HER2+ BC [5, 6]. The emergence of novel targeted therapies changed the treatment landscape. Among these, pertuzumab introduced improvements in disease-free survival (DFS) when used in conjunction with neoadjuvant trastuzumab and chemotherapy, as demonstrated by the

*[1]Center for Studies and Research in Hematology and Oncology (CEPHO), Santo André, SP, Brazil. [2]First Department of Obstetrics and Gynecology, Medical University of Warsaw, Starynkiewicza 1/3, 02-015 Warsaw, Poland. [3]Department of Internal Medicine, Escola Paulista de Medicina, São Paulo, SP, Brazil. [4]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA. [5]University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA. [6]Department of Oncology and Hematology, ABC Medical School, Santo André, SP, Brazil. *For Correspondence: silviom08@hotmail.com*

phase II NEOSPHERE trial [7]. Moreover, the adjuvant use of pertuzumab was shown to improve the rates of invasive-disease-free-survival by the APHINITY trial [8]. Achievement of pathological complete response (pCR) is a reliable predictor of prognosis and plays an important role in management decision-making [9, 10]. For instance, achievement of pCR in the breast and axilla often guides the choice of breast conserving surgery and omission of axillary lymph node dissection, respectively [11]. Major clinical trials have shown higher pCR rates with the use of dual HER2 blockade with pertuzumab and trastuzumab compared to single blockade with trastuzumab [7, 12, 13].

Real-world evidence (RWE) is the scientific evidence based on routine healthcare data, which includes electronic health records [14]. While randomized clinical trials (RCTs) remain the gold standard evidence for the assessment of drugs efficacy and safety, inherent limitations of these studies often do not reflect outcomes in the routine healthcare setting. In this context, RWE has gained attention as a useful tool to complement data from RCTs and reveal clinical outcomes in diverse populations [15]. In Oncology, RWE has begun to be incorporated in frameworks to support approval of drugs by regulatory agencies [16]. Numerous BC studies were conducted using RWE and some results vary considerably to those of RCTs [17–19].

Here we aim to conduct a systematic review and meta-analysis of real-world studies to compare pCR rates between neoadjuvant regimens using single-agent HER2 blockade with trastuzumab and dual HER2 blockade with pertuzumab and trastuzumab in patients with early-stage HER2+ BC.

Materials and Methods

A systematic search of articles published up to 28 February 2025 was carried out in PubMed, Embase and Scopus databases. The search strategy encompassed key terms, Boolean operators and characters as follows: (“pathological complete response” OR “pathological response” OR “pathologic complete response” OR “pathologic response”) AND “breast” AND (“prospective” OR “retrospective” OR “real-world” OR “phase IV”) AND (“pertuzumab”). A list of results was downloaded from each database and subsequently exported to Rayyan software where one investigator removed duplicates manually, with the assistance of the duplicate recognition tool [20]. On Rayyan, two independent investigators screened the resulting list of studies, using the Blind mode. Divergences were resolved by a third investigator.

PICOS criteria

Our study design employed the following PICOS criteria: 1) Population: female patients with early-stage HER2+ BC; 2) Intervention: patients treated with neoadjuvant chemotherapy plus dual HER2 blockade with trastuzumab and pertuzumab; 3) Control: patients treated with neoadjuvant chemotherapy plus single-agent HER2 blockade with trastuzumab; 4) Outcome: pCR rates; 5) Study design: real-world prospective or retrospective studies comparing pCR rates of single agent vs. dual HER2 blockade.

Selection criteria

We included studies with the following criteria: 1) early HER2+ BC patients treated with neoadjuvant chemotherapy plus single agent or dualHER2 blockade; 2) explored the predictive significance of single vs. dual HER2 blockade in relation to pCR; 3) provided an Odds Ratio (OR) and 95% Confidence interval (CI); 4) Study written in English; 5) Full text manuscripts or conference abstracts. The exclusion criteria were: 1) Studies with lack of data for pCR; 2) Studies exploring reporting pCR rates with a measure of association other than HR; 3) reviews, expert opinions, case reports and studies with animals.

Data extraction

Data extraction was independently performed by two reviewers, encompassing the first author’s surname, year of publication, country of origin, early HER2+ BC stage included, period of patients treatment, neoadjuvant therapy, number of participants, fashion of institution (single institution/multicentric), endpoints, follow-up period and OR analysis. The extracted data were subsequently entered into Microsoft Excel (2019 version). Any discrepancies were reviewed and resolved by a third reviewer.

Risk of bias assessment

Since all studies in our analysis were observational and retrospective, Newcastle-Ottawa scale was employed to evaluate risk of bias. Each study was assigned ratings by two independent investigators. Disagreements were resolved by a third reviewer. Studies with a score of 7 or greater were considered as having a low risk of bias.

Statistical analysis

All statistical analyses were made using the R system for statistical computing (version 4.4.2; R core team, Vienna, Austria). A significance level of $p < 0.05$ was adopted.

PROSPERO registration

This work has been registered in the PROSPERO network under the registration number CRD420251087018.

Results

1012 articles were retrieved from the three databases. After the removal of 462 duplicates, 550 studies were screened by two investigators based on titles and abstracts, of which 525 were excluded. Subsequently, an accurate full-text appraisal of the remaining 25 articles was conducted and this resulted in the elimination of 7 articles. The total number of included studies was 18 [21–38]. The details can be seen in Figure 1.

Study characteristics

The included studies represent a diverse patient population across three continents: Asia, Europe and North America. Most studies focused on patients with stage I–III HER2-positive breast cancer, although a few excluded

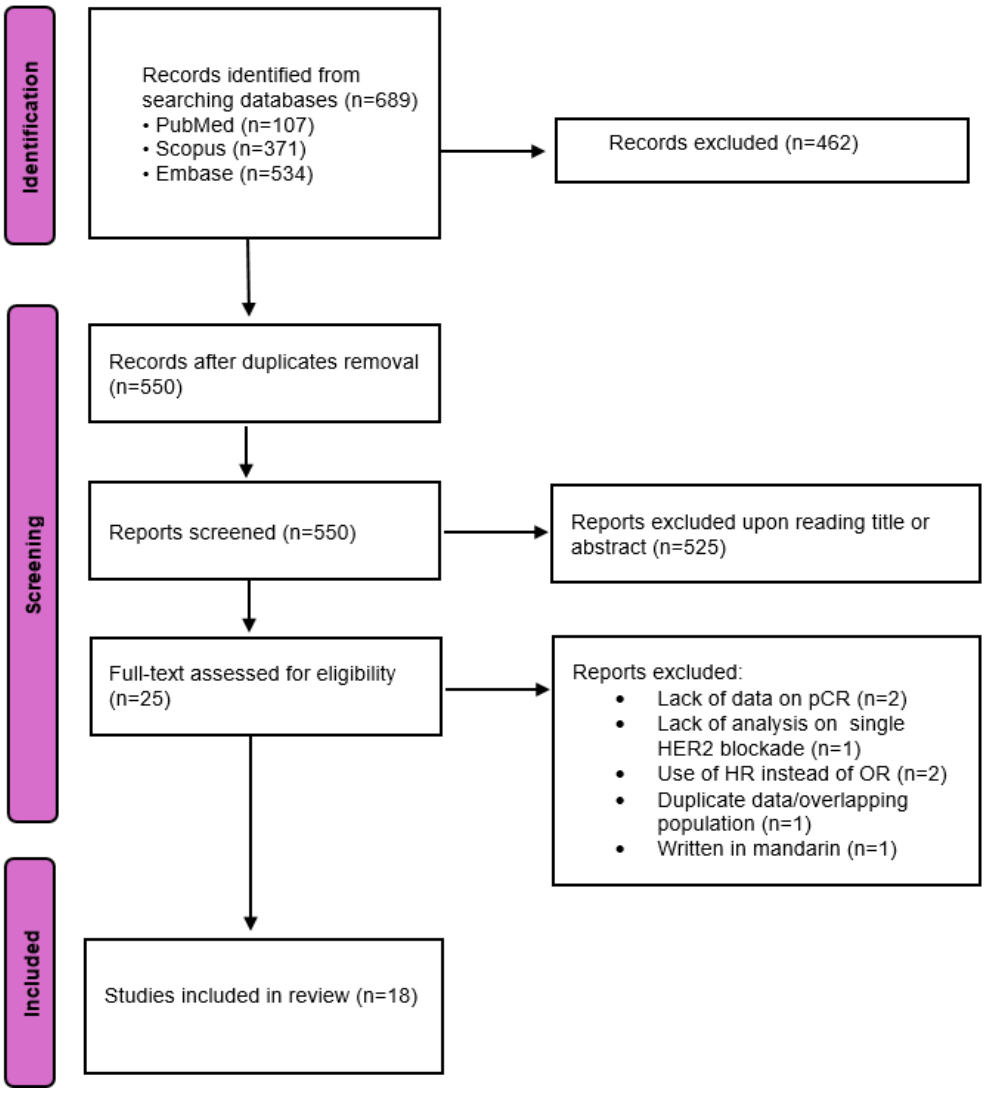

Figure 1. PRISMA Flowchart for Study Selection

stage I disease. All studies were retrospective in design. Sixteen studies evaluated breast pCR, three examined axillary pCR, and one assessed both breast and axillary pCR. A variety of neoadjuvant chemotherapy regimens were used across studies. Fasching et al. [26] analyzed dual HER2 blockade using pertuzumab in combination with trastuzumab or a trastuzumab analogue; however, it was the only study that did not clearly report whether a univariate or multivariate approach was used [26]. Two Chinese studies investigated dual versus single HER2 blockade in early HER2-positive breast cance. The first, Chen (I) et al. 34], focused on differences in estrogen and progesterone receptor expression, while the second, Chen (II) et al. [35], did not address hormone receptor status. The full details of the studies can be seen in Supplementary Table 1.

Analysis

This meta-analysis evaluated the differences in pCR rates between single-agent HER2 blockade with trastuzumab and dual HER2 blockade with trastuzumab plus pertuzumab in early-stage HER2-positive breast cancer. We pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) from the included studies, prioritizing multivariate-adjusted estimates whenever available.

Among the studies, Fifty percent reported a statistically significant benefit in pCR rates with dual HER2 blockade, while the remaining half showed no significant difference. Notably, Cha et al. [29] was the only study that trended in favor of single agent blockade, although this finding was not statistically significant.

The overall pooled analysis demonstrated a significant benefit with dual blockade, with an OR of 1.81 (95% CI: 1.56–2.09), favoring pertuzumab plus trastuzumab. Heterogeneity across studies was minimal ($I^2 = 0\%$).

Subgroup analysis

Despite the low heterogeneity observed, the included studies encompassed a diverse range of ethnic populations, warranting a subgroup analysis based on geographical location. additional subgroup analyses were conducted based on institutional model, sample size (≥250 vs. <250 patients), follow-up duration, type of pCR reported (breast vs. axillary), and use of multivariate analysis. Unfortunately, due to limited and inconsistent reporting

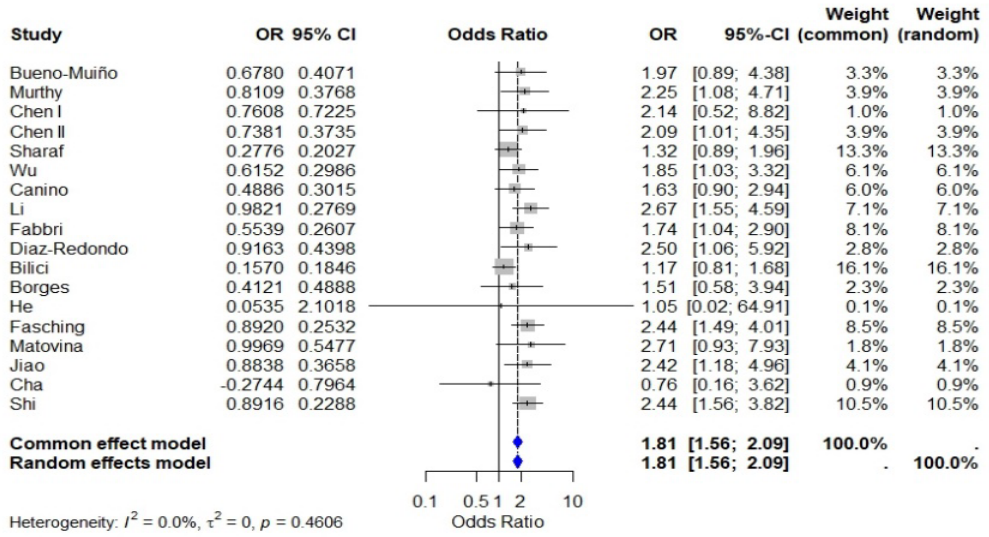

Figure 2. Forest Plot of Included Studies; OR = odds ratio; CI = confidence interval.

of specific chemotherapy regimens, subgroup analysis by chemotherapy type could not be performed. The results of these subgroup analysis are presented in Table 1.

Risk of bias

Given that all included studies were retrospective and observational, the Newcastle-Ottawa scale was used to evaluate risk of bias. Results are shown in Table 2. Sixteen [21–25, 27–30, 32–38] out of eighteen studies scored 7 or higher, indicating a low risk of bias, while two studies [26, 31] scored below 7 and were considered to have a high risk of bias (Figure 2).

As expected, all studies lost one point in the selection domain due to the retrospective design and the inability to confirm that the outcome of interest was not present at the start of the study. Additionally, several studies did not clearly report the source of medical data collection, leading to a further one-point deduction in the outcome domain.

Publication bias

To evaluate the risk of publication bias, we performed

Table 1. The Results of Subgroup Analysis

Subgroups	number of studies	OR	Heterogeneity	
			I²%	p
Single institution	10	1.96 (1.59-2.42)	0%	0.65
Multicentric	8	1.73 (1.36-2.19)	21.8%	0.01
>250 patients	13	1.85 (1.53-2.23)	25.5%	0.18
<250 patients	5	1.90 (1.28-2.81)	0%	0.94
Europe	7	1.74 (1.38-2.21)	12%	0.33
Spain	2	2.20 (1.22-3.95)	0%	0.69
Germany	2	2.49 (1.58-3.90)	0%	0.86
Portugal	1	1.51 (0.58–3.94)		
Italy	2	1.69 (1.15-2.49)	0%	0.87
Turkey	1	1.17 (0.81-1.67)		
Asia	9	1.68 (1.33-2.13)	25.3%	0.21
China	6	2.21 (1.66-2.94)	0%	0.98
Korea	1	0.76 (0.16-3.63)		
Jordan	1	1.32 (0.89-1.97)		
Turkey	1	1.17 (0.81-1.67)		
Median FU >12m	6	1.82 (1.35-2.47)	0%	0.47
Median FU unclear	12	1.85 (1.52-2.26)	10.6%	0.34
Axillary pCR	3	1.92 (1.12-3.26)	20.4%	0.28
Breast pCR	16	1.76 (1.51-2.05)	0%	0.53
Multivariate	17	1.70 (1.45-2.00)	0%	0.60
Unclear	1	2.44 (1.49-4.02)		

Table 2. Results of Evaluate Risk of Bias

Study	Selection	Comparability	Outcome	Total score
Bueno-Muiño	***	**	**	7
Murthy	***	**	***	8
Chen (I)	***	**	***	8
Chen (II)	***	**	**	7
Sharaf	***	**	***	8
Wu	***	**	***	8
Canino	***	**	***	8
Li	**	**	**	6
Fabbri	***	**	***	8
Diaz-Redondo	***	**	***	8
Bilici	***	**	***	8
Borges	***	**	**	7
He	***	**	**	7
Fasching	***	*	**	6
Matovina	***	**	**	7
Shi	***	**	**	7
Cha	***	**	***	8
Jiao	***	**	***	8

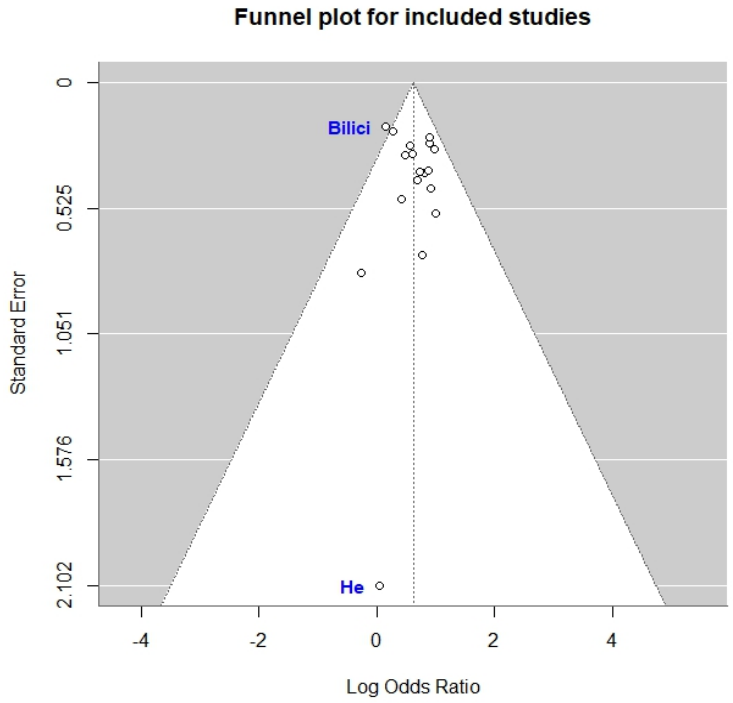

Figure 3. Funnel Plot for Included Studies

a visual assessment of the funnel plot (Figure 3). The plot showed slight asymmetry, primarily at the outer margins, with He et al. [25] positioned at the periphery; likely due to a small sample size and wide confidence intervals. Seventeen out of eighteen studies were located within the funnel's triangular region, with Bilici et al. [38] falling just outside, suggesting a potential outlier.

To further assess for publication bias, Egger's test was performed, yielding a p-value of 0.37. This result indicates no statistically significant evidence of publication bias across the included studies.

Other analyses

Although the following statistical assessments were not the primary endpoint of this study, we carried out these analyses based on questions that arose while this manuscript was being written.

Given the reported discrepancy of outcomes between HER2+/HR+ and HER2+/HR-, we decided to perform a meta-analysis comparing pCR rates between both groups. Of note, the comparisons of pCR between HER2+/HR+ and HER2+/HR− groups did not consider the type of HER2-targeted therapy administered. A total of 15 studies(21–30,32,34–36,38) provided ORs for this comparison. The pooled results indicate a resulting OR of 0.52 (0.42-0.64) in favor of hormone receptor negative status, with hormone receptor positive status having significantly lower rates of achievement of pCR. A heterogeneity of 71.1% was observed.

Our included studies didn't provide data for comparison of pCR rates associated with single vs. dual HER2 blockades in relation to specific chemotherapy regimens. However, some studies provided comparisons between neoadjuvant regimens containing anthracyclines vs. those without anthracyclines. These comparisons were irrespective of single or dual HER2 blockade. Nonetheless, we performed a meta-analysis of 5 studies [21,27,30,34,35] to assess the possible influence of the presence of neoadjuvant anthracycline in pCR rates. The pooled result resulted in an inconclusive OR of 0.99 (0.65-1.53) with a heterogeneity of 50.2%.

Discussion

Our pooled analysis included 18 studies, aggregating 8651 patients. The results indicate with a high degree of confidence that neoadjuvant regimens using pertuzumab for early-stage HER2+ BC are associated with a significantly higher rate of pCR compared with regimens without pertuzumab. Heterogeneity was negligible and funnel plot analysis reveals a low risk of publication bias, with only one study falling marginally outside the funnel boundaries. Egger test confirmed low risk. To the best of our knowledge, this meta-analysis represents the first comprehensive synthesis of real-world evidence assessing the effect of pertuzumab-containing regimens on pCR rates in early-stage HER2-positive breast cancer. This work fills a notable gap in the literature by providing aggregated insights from observational studies, complementing findings from randomized clinical trials.

Although phase III randomized clinical trials (RCTs) serve as the basis for drug approval and marketing, real-world data plays an important role in the postmarketing assessment of drug's efficacy in broader populations, not entirely limited to the restrictions of phase III trials. An example of the discrepancy between RTCs and real-world data is a 2021 study which found a 14 month survival decrease for metastatic HER2+ BC patients as compared

to the phase III CLEOPATRA trial [13,39]. Therefore, it is imperative to investigate differences between RCTs and real-world evidence in various scenarios. With regard to early-stage HER2+ BC, the NEOSPHERE trial demonstrated a significantly higher pCR in the arm receiving neoadjuvant dual blockade with pertuzumab, trastuzumab and chemotherapy (45.8%) compared to the arm receiving pertuzumab and chemotherapy (29.0%) [7]. Subsequent trials reported pCR rates ranging from 57.3% to 68% in groups treated with dual blockade and different chemotherapy regimens [12, 13, 40]. In the real-world studies included, breast pCR rates ranged from 40.0% to 66.4% for dual HER2 blockade, with a median of 57%, and from 30.2% to 56.8% for single-agent blockade, with a median of 39.6%. These numbers are consistent with the pCR range of RCTs. A meta-analysis of 3 RCTs examining the effect of pertuzumab on pCR in early-stage HER2+ BC reported an OR of 2.10 (1.53-2.83) in favor of dual blockade with pertuzumab and trastuzumab [41]. This result is close to the one found by our meta-analysis, indicating that findings are similar, albeit with some variation and a narrower CI in our study.

The results have implications for clinical practice as achievement of pCR is associated with improved survival and lower incidence of disease recurrence. A number of studies have shown that even minimal residual disease, represented by lack of pCR, is associated with a significantly higher recurrence rate in HER2+ BC [10, 42, 43]. Moreover, pCR can aid surgical decision-making, as it is associated with increased rates of breast conserving surgery rather than mastectomy [22, 44]. Beyond surgical significance, pCR plays a critical role in guiding clinical treatment decisions. For patients who fail to achieve pCR, escalation of therapy may be warranted. The KATHERINE trial demonstrated that adjuvant ado-trastuzumab emtansine (T-DM1) significantly reduced recurrence risk compared to adjuvant trastuzumab alone [45].

However, it is crucial to personalize treatment according to other criteria. Heterogeneity within HER2+ BC is significant and despite advancements in management, approximately 15% of patients with early disease relapse [46]. A number of studies report worse outcomes for HR+/HER2+ in comparison to HR-/HER2+, including a lower pCR rate and higher recurrence rates [46, 47]. We confirmed this finding in our meta-analysis for the assessment of differences in pCR rates between HER2+/HR+ and HER2+/HR-, with HER2+/HR+ having significantly better pCR rates. Both real-world and RCTs have shown low pCR rates for early HR+/HER2+ BC even with the use of dual HER2 blockade [7, 33, 35, 48]. These patients may benefit from neoadjuvant T-DM1 regimen, with an associated clinically meaningful pCR rate as shown by the ADAPT trial [49]. Real-world data about HR+/HER2+ early BC treated with T-DM1 is scarce and studies investigating this population are needed. Significant differences in pCR rates have also been found between HER2 IHC 3+ and HER2 IHC 2+/FISH+. Both these classifications are deemed HER2+ by the 2018 ASCO guidelines [50], however HER2 IHC3+ exhibited higher pCR rates compared to HER2 IHC2+/FISH+ in several real-world studies when exposed to pertuzumab, trastuzumab and various chemotherapy regimens [24, 51, 52]. There are currently no recommendations for alternative treatments targeting HER2 ICH2+/FISH+ specifically.

While we were not able to perform a subgroup analysis based on different chemotherapy regimens, some studies provided data for differences in pCR rates between neoadjuvant regimens with anthracyclines and others without, irrespective of the use of single or dual HER2 blockade. We chose to perform a meta-analysis to examine the possible effect that anthracyclines may exert on achievement of pCR. Our result was not statistically significant and the influence of adjuvant anthracyclines remain inconclusive. More studies should be conducted to investigate this effect in patients treated with single and dual HER2 blockade.

Our study also included 3 articles that examined the differences of pCR rates between single and dual HER2 blockade in the axilla [23, 28, 29]. Axillary pCR has been less explored than the long-established breast pCR, which appears to be the strongest predictor for axillary pCR [28]. In the post-neoadjuvant setting, clinically positive node (cN+) patients who have axillary pCR may have omission of axillary surgery [53, 54]. Our pooled results suggest a significant association between dual HER2 blockade and higher achievement of pCR in early-stage HER2+ BC. Intriguingly, Cha et al. [29] in their multivariate analysis suggest that the use of trastuzumab plus chemotherapy may be more effective for achievement of pCR than dual HER2 blockade plus chemotherapy. A previous network meta-analysis with different inclusion criteria also explored axillary response to single and dual HER2 blockades, but failed to find a significant difference between groups [55]. Our results regarding the axilla should be carefully considered since the small number of studies make it challenging to reach a final conclusion.

A meta-analysis of survival outcomes was not feasible given the variability in survival endpoints reported. However, findings from individual studies vary substantially. Chen (I) et al. [34] report a significant association between the use of dual HER2 blockade and a higher OS, while Canino et al. [30] failed to find this association. Two studies [22,34] failed to find a significant association between the use of dual HER2 blockade and an improved DFS. More studies should be carried out with statistical assessments of OS and DFS before any conclusion is drawn. This study possesses a number of limitations. The first limitation is the inclusion of retrospective studies exclusively. Currently there is a lack of prospective real-world studies investigating the effect of single and dual HER2 blockades on pCR. The second limitation is the retrospective collection of data for this manuscript. The third limitation is the recruitment of patients over a large period of time, spanning from 2005 to 2022. This can potentially introduce selection bias, since patients enrolled at the beginning of the recruitment period were treated solely with trastuzumab and chemotherapy. A fourth limitation is the variety of backbone chemotherapy regimens, which may explain differences in studies' results. The lack of precise data

regarding chemotherapy in individual studies made a subgroup analysis for chemotherapy unfeasible.

However, this meta-analysis also has several notable strengths. The first strength is the large number of aggregated studies and patients, which provides reliability to our results. Remarkably, our analysis demonstrated no heterogeneity and a low risk of publication bias. Additionally, 17 of the included studies used a multivariate analysis, which allows the conclusion that use of pertuzumab in the dual HER2+ blockade is an independent prognostic factor for achievement of pCR. One included study didn't specify whether a multivariate or univariate analysis was employed [26]. A final strength is the selection of a majority of studies with a low risk of bias.

In conclusion, this systematic review and meta-analysis strongly suggests that the addition of pertuzumab to the neoadjuvant treatment of early-stage HER2+ BC can increase pCR rates in the real-world setting to a similar degree to RCTs. Patients should be individualized as some subtypes of disease have a decreased benefit. Prospective real-world studies should be conducted in the future to validate our findings.

Author Contribution Statement

Conceptualization: Silvio Matsas; Methodology: Silvio Matsas; Investigation: Silvio Matsas, Anderson Ruiz Simões, Julita Zembala; Data curation: Silvio Matsas, Anderson Ruiz Simões, Julita Zembala; Writing - original draft: Silvio Matsas, Julita Zembala; Software: Silvio Matsas, Julita Zembala; Writing – review and editing: Yara Abdou, Luiza Giuliani Schmitt, Auro del Giglio; Validation: Yara Abdou, Auro del Giglio; Visualization: Silvio Matsas; Supervision: Auro del Giglio; Funding acquisition: Auro del Giglio; Resources: Auro del Giglio.

Acknowledgements

The authors gratefully acknowledge the support provided by the Centro de Estudos de Hematologia e Oncologia (CEPHO) in the development of this project.

Competing interests

Silvio Matsas: no competing interests; Julita Zembala: no competing interests; Anderson Ruiz Simões: no competing interests; Luiza Giuliani Schmitt: no competing interests; Yara Abdou: Consultant for AstraZeneca and Pfizer; Auro del Giglio: no competing interests.

Funding statement

This study did not receive any funding. The publication fee was paid by Centro de Estudos de Hematologia e Oncologia (CEPHO).

Availability of data

All collected data for this study was publicly available in published articles.

Statement of registration

This work has been registered in the PROSPERO network under the registration number CRD420251087018.

Ethics approval and consent to participate

As this study is a systematic review, using previously published data, no Ethics approval or consent to participate were required.

Consent for publication

As this study is a systematic review, using previously published data, no consent for publication was needed.

References

1. Woolston C. Breast cancer. Nature. 2015;527(7578):S101. https://doi.org/10.1038/527S101a.
2. Waks AG, Winer EP. Breast cancer treatment. Jama. 2019;321(3):316. https://doi.org/10.1001/jama.2018.20751.
3. Asif HM, Sultana S, Ahmed S, Akhtar N, Tariq M. Her-2 positive breast cancer - a mini-review. Asian Pac J Cancer Prev. 2016;17(4):1609-15. https://doi.org/10.7314/apjcp.2016.17.4.1609.
4. Roulot A, Héquet D, Guinebretière JM, Vincent-Salomon A, Lerebours F, Dubot C, et al. Tumoral heterogeneity of breast cancer. Ann Biol Clin (Paris). 2016;74(6):653-60. https://doi.org/10.1684/abc.2016.1192.
5. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against her2 for metastatic breast cancer that overexpresses her2. N Engl J Med. 2001;344(11):783-92. https://doi.org/10.1056/nejm200103153441101.
6. Giordano SH, Franzoi MAB, Temin S, Anders CK, Chandarlapaty S, Crews JR, et al. Systemic therapy for advanced human epidermal growth factor receptor 2-positive breast cancer: Asco guideline update. J Clin Oncol. 2022;40(23):2612-35. https://doi.org/10.1200/jco.22.00519.
7. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early her2-positive breast cancer (neosphere): A randomised multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13(1):25-32. https://doi.org/10.1016/s1470-2045(11)70336-9.
8. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant pertuzumab and trastuzumab in early her2-positive breast cancer. N Engl J Med. 2017;377(2):122-31. https://doi.org/10.1056/NEJMoa1703643.
9. Berruti A, Amoroso V, Gallo F, Bertaglia V, Simoncini E, Pedersini R, et al. Pathologic complete response as a potential surrogate for the clinical outcome in patients with breast cancer after neoadjuvant therapy: A meta-regression of 29 randomized prospective studies. J Clin Oncol. 2014;32(34):3883-91. https://doi.org/10.1200/jco.2014.55.2836.
10. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: The ctneobc pooled analysis. Lancet. 2014;384(9938):164-72. https://doi.org/10.1016/s0140-6736(13)62422-8.
11. Zhou T, Yang M, Wang M, Han L, Chen H, Wu N, et al. Prediction of axillary lymph node pathological complete response to neoadjuvant therapy using nomogram and machine learning methods. Front Oncol. 2022;12:1046039. https://doi.org/10.3389/fonc.2022.1046039.
12. Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients

with her2-positive early breast cancer: A randomized phase ii cardiac safety study (tryphaena). Ann Oncol. 2013;24(9):2278-84. https://doi.org/10.1093/annonc/mdt182.
13. Swain SM, Ewer MS, Viale G, Delaloge S, Ferrero JM, Verrill M, et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with her2-positive localized breast cancer (berenice): A phase ii, open-label, multicenter, multinational cardiac safety study. Ann Oncol. 2018;29(3):646-53. https://doi.org/10.1093/annonc/mdx773.
14. Dang A. Real-world evidence: A primer. Pharmaceut Med. 2023;37(1):25-36. https://doi.org/10.1007/s40290-022-00456-6.
15. Thakur S. Real-world evidence studies in oncology therapeutics: Hope or hype? Indian J Surg Oncol. 2023;14(4):829-35. https://doi.org/10.1007/s13193-023-01784-y.
16. Aguiar PN, Matsas S, Dienstmann R, Ferreira CG. Challenges and opportunities in building a health economic framework for personalized medicine in oncology. Per Med. 2023;20(5):453-60. https://doi.org/10.2217/pme-2022-0008.
17. Lluch-Gómez J, Núñez-Álvarez V, de la Torre-Hita C, Bernal-Gómez M, Campini-Bermejo A, Perdomo-Zaldívar E, et al. Real world evidence of adjuvant trastuzumab in her2 positive early breast cancer. Sci Rep. 2023;13(1):7168. https://doi.org/10.1038/s41598-023-34429-9.
18. Rauthan A, Jain A, Singh M, Sendur MAN. Palbociclib in hr-positive, her2-negative advanced/metastatic breast cancer: A systematic scoping review of real-world evidence from countries outside of western regions that are underrepresented in clinical trials. Oncol Ther. 2024;12(3):395-418. https://doi.org/10.1007/s40487-024-00295-2.
19. Sánchez-Bayona R, Lopez de Sa A, Jerez Gilarranz Y, Sanchez de Torre A, Alva M, Echavarria I, et al. Everolimus plus endocrine therapy beyond cdk4/6 inhibitors progression for hr+/her2- advanced breast cancer: A real-world evidence cohort. Breast Cancer Res Treat. 2024;206(3):551-9. https://doi.org/10.1007/s10549-024-07324-8.
20. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210. https://doi.org/10.1186/s13643-016-0384-4.
21. Wu HY, Lin CY, Tzeng YD, Hung CC, Liu SI, Yin CH, et al. Preoperative systemic inflammation response index: Clinicopathologic predictor of pathological complete response in her2-positive breast cancer patients receiving neoadjuvant systemic therapy. J Chin Med Assoc. 2024;87(2):226-35. https://doi.org/10.1097/jcma.0000000000001034.
22. Sharaf B, Tamimi F, Al-Abdallat H, Khater S, Salama O, Zayed A, et al. Dual anti-her2 therapy vs trastuzumab alone with neoadjuvant anthracycline and taxane in her2-positive early-stage breast cancer: Real-world insights. Biologics. 2025;19:59-71. https://doi.org/10.2147/btt.S468650.
23. Borges A, Pereira F, Redondo P, Antunes L, Vieira C, Antunes P, et al. The addition of neoadjuvant pertuzumab for the treatment of her2+ breast cancer: A cost estimate with real-world data. Health Econ Rev. 2021;11(1):33. https://doi.org/10.1186/s13561-021-00332-0.
24. Jiao D, Li G, Dai H, Wang J, Zhang J, Hou Y, et al. Comparison of the response to neoadjuvant therapy between immunohistochemistry her2 (3+) and her2 (2+)/ish+ early-stage breast cancer: A retrospective multicenter cohort study. Oncologist. 2024;29(7):e877-e86. https://doi.org/10.1093/oncolo/oyae047.
25. He Q, Li JY, Ren QL. Efficacy of neoadjuvant single or dual anti-her-2 therapy combined with chemotherapy in patients with her-2-positive breast cancer: A single-center retrospective study. Asian Pac J Cancer Prev. 2021;22(5):1467-75. https://doi.org/10.31557/apjcp.2021.22.5.1467.
26. Fasching PA, Hartkopf AD, Gass P, Häberle L, Akpolat-Basci L, Hein A, et al. Efficacy of neoadjuvant pertuzumab in addition to chemotherapy and trastuzumab in routine clinical treatment of patients with primary breast cancer: A multicentric analysis. Breast Cancer Res Treat. 2019;173(2):319-28. https://doi.org/10.1007/s10549-018-5008-3.
27. Matovina S, Engler T, Volmer LL, Müller H, Grischke EM, Staebler A, et al. Comparison of biosimilar trastuzumab abp 980 with reference trastuzumab in neoadjuvant therapy for her2-positive breast cancer - an analysis of a large university breast cancer centre. Geburtshilfe Frauenheilkd. 2023;83(6):694-701. https://doi.org/10.1055/a-1963-7511.
28. Shi W, Huang X, Wang Y, Wan X, He J, Xu Y, et al. A novel nomogram containing efficacy indicators to predict axillary pathologic complete response after neoadjuvant systemic therapy in breast cancer. Front Endocrinol (Lausanne). 2022;13:1042394. https://doi.org/10.3389/fendo.2022.1042394.
29. Cha C, Ahn SG, Kim D, Lee J, Park S, Bae SJ, et al. Axillary response according to neoadjuvant single or dual human epidermal growth factor receptor 2 (her2) blockade in clinically node-positive, her2-positive breast cancer. Int J Cancer. 2021;149(8):1585-92. https://doi.org/10.1002/ijc.33726.
30. Canino F, Barbolini M, Giorgi U, Fontana T, Gaspari V, Gianni C, et al. Safety and efficacy analysis of neoadjuvant pertuzumab, trastuzumab and standard chemotherapy for her2–positive early breast cancer: Real–world data from neopower study. BMC Cancer. 2024;24. https://doi.org/10.1186/s12885-024-12506-0.
31. Li JJ, Li HC, Gao A, Syed SK, Unni N, Sadeghi N. Impact of dual anti-her2 therapy on pathologic complete response rate in breast cancer in a minority-enriched population. Journal of Clinical Oncology. 2019;37(15_suppl):e18111-e. https://doi.org/10.1200/JCO.2019.37.15_suppl.e18111.
32. Fabbri A, Nelli F, Botticelli A, Giannarelli D, Marrucci E, Fiore C, et al. Pathologic response and survival after neoadjuvant chemotherapy with or without pertuzumab in patients with her2-positive breast cancer: The neopearl nationwide collaborative study. Front Oncol. 2023;13:1177681. https://doi.org/10.3389/fonc.2023.1177681.
33. Díaz-Redondo T, Lavado-Valenzuela R, Jimenez B, Pascual T, Gálvez F, Falcón A, et al. Different pathological complete response rates according to pam50 subtype in her2+ breast cancer patients treated with neoadjuvant pertuzumab/trastuzumab vs. Trastuzumab plus standard chemotherapy: An analysis of real-world data. Frontiers in Oncology. 2019;Volume 9 - 2019. https://doi.org/10.3389/fonc.2019.01178.
34. Chen H, Gui X, Zhou Z, Su F, Gong C, Li S, et al. Distinct er and pr expression patterns significantly affect the clinical outcomes of early her2-positive breast cancer: A real-world analysis of 871 patients treated with neoadjuvant therapy. Breast. 2024;75:103733. https://doi.org/10.1016/j.breast.2024.103733.
35. Chen HL, Chen Q, Deng YC. Pathologic complete response to neoadjuvant anti-her2 therapy is associated with her2 immunohistochemistry score in her2-positive early breast cancer. Medicine (Baltimore). 2021;100(44):e27632. https://doi.org/10.1097/md.0000000000027632.
36. Bueno-Muiño C, Echavarría I, López-Tarruella S, Roche-Molina M, Del Monte-Millán M, Massarrah T, et al.

Assessment of a genomic assay in patients with erbb2-positive breast cancer following neoadjuvant trastuzumab-based chemotherapy with or without pertuzumab. JAMA Oncol. 2023;9(6):841-6. https://doi.org/10.1001/jamaoncol.2023.0187.
37. Murthy RK, Raghavendra AS, Hess KR, Fujii T, Lim B, Barcenas CH, et al. Neoadjuvant pertuzumab-containing regimens improve pathologic complete response rates in stage ii to iii her-2/neu-positive breast cancer: A retrospective, single institution experience. Clin Breast Cancer. 2018;18(6):e1283-e8. https://doi.org/10.1016/j.clbc.2018.07.008.
38. Bilici A, Olmez OF, Kaplan MA, Oksuzoglu B, Sezer A, Karadurmus N, et al. Impact of adding pertuzumab to trastuzumab plus chemotherapy in neoadjuvant treatment of her2 positive breast cancer patients: A multicenter real-life her2path study. Acta Oncol. 2023;62(4):381-90. https://doi.org/10.1080/0284186x.2023.2202330.
39. Ethier J-L, Desautels D, Robinson A, Amir E, Kong W, Booth CM. Practice patterns and outcomes of novel targeted agents for the treatment of erbb2-positive metastatic breast cancer. JAMA Oncology. 2021;7(9):e212140-e. https://doi.org/10.1001/jamaoncol.2021.2140.
40. Untch M, Jackisch C, Schneeweiss A, Conrad B, Aktas B, Denkert C, et al. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (geparsepto-gbg 69): A randomised, phase 3 trial. Lancet Oncol. 2016;17(3):345-56. https://doi.org/10.1016/s1470-2045(15)00542-2.
41. Fazal F, Bashir MN, Adil ML, Tanveer U, Ahmed M, Chaudhry TZ, et al. Pathologic complete response achieved in early-stage HER2-positive breast cancer after neoadjuvant therapy with trastuzumab and chemotherapy vs. trastuzumab, chemotherapy, and pertuzumab: a systematic review and meta-analysis of clinical trials. Cureus. 2023 May 31;15(5).
42. Symmans WF, Wei C, Gould R, Yu X, Zhang Y, Liu M, et al. Long-term prognostic risk after neoadjuvant chemotherapy associated with residual cancer burden and breast cancer subtype. J Clin Oncol. 2017;35(10):1049-60. https://doi.org/10.1200/jco.2015.63.1010.
43. Symmans WF, Peintinger F, Hatzis C, Rajan R, Kuerer H, Valero V, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. J Clin Oncol. 2007;25(28):4414-22. https://doi.org/10.1200/jco.2007.10.6823.
44. Nigam S, Hakim A, Cuffolo G, Winter L, Levitt N, Tuthill M, et al. P081: Dual anti-her-2 blockade with primary systemic therapy for her-2 positive non-metastatic breast cancer can increase breast conservation rates: Benefit beyond survival. European Journal of Surgical Oncology. 2020;46(6):e32. https://doi.org/10.1016/j.ejso.2020.03.120.
45. Geyer CE, Jr., Untch M, Huang CS, Mano MS, Mamounas EP, Wolmark N, et al. Survival with trastuzumab emtansine in residual her2-positive breast cancer. N Engl J Med. 2025;392(3):249-57. https://doi.org/10.1056/NEJMoa2406070.
46. Pernas S, Tolaney SM. Targeting her2 heterogeneity in early-stage breast cancer. Curr Opin Oncol. 2020;32(6):545-54. https://doi.org/10.1097/cco.0000000000000685.
47. Nitz UA, Gluz O, Christgen M, Grischke EM, Augustin D, Kuemmel S, et al. De-escalation strategies in her2-positive early breast cancer (ebc): Final analysis of the wsg-adapt her2+/hr- phase ii trial: Efficacy, safety, and predictive markers for 12 weeks of neoadjuvant dual blockade with trastuzumab and pertuzumab ± weekly paclitaxel. Ann Oncol. 2017;28(11):2768-72. https://doi.org/10.1093/annonc/mdx494.
48. Hurvitz SA, Martin M, Symmans WF, Jung KH, Huang CS, Thompson AM, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with her2-positive breast cancer (kristine): A randomised, open-label, multicentre, phase 3 trial. Lancet Oncol. 2018;19(1):115-26. https://doi.org/10.1016/s1470-2045(17)30716-7.
49. Harbeck N, Gluz O, Christgen M, Kates RE, Braun M, Küemmel S, et al. De-escalation strategies in human epidermal growth factor receptor 2 (her2)-positive early breast cancer (bc): Final analysis of the west german study group adjuvant dynamic marker-adjusted personalized therapy trial optimizing risk assessment and therapy response prediction in early bc her2- and hormone receptor-positive phase ii randomized trial-efficacy, safety, and predictive markers for 12 weeks of neoadjuvant trastuzumab emtansine with or without endocrine therapy (et) versus trastuzumab plus et. J Clin Oncol. 2017;35(26):3046-54. https://doi.org/10.1200/jco.2016.71.9815.
50. Wolff AC, Hammond MEH, Allison KH, Harvey BE, McShane LM, Dowsett M. Her2 testing in breast cancer: American society of clinical oncology/college of american pathologists clinical practice guideline focused update summary. J Oncol Pract. 2018;14(7):437-41. https://doi.org/10.1200/jop.18.00206.
51. Stjepanovic N, Kumar S, Jerzak KJ, Trudeau M, Warner E, Cao X, et al. Analysis of factors associated with pathological complete response in patients with her2-positive breast cancer receiving neoadjuvant chemotherapy. Clin Breast Cancer. 2024;24(8):e723-e30. https://doi.org/10.1016/j.clbc.2024.08.010.
52. Chen W, Li FX, Lu DL, Jiang J, Li J. Differences between the efficacy of her2(2+)/fish-positive and her2(3+) in breast cancer during dual-target neoadjuvant therapy. Breast. 2023;71:69-73. https://doi.org/10.1016/j.breast.2023.07.008.
53. Guo X, Zhang J, Gong X, Wang J, Dai H, Jiao D, et al. Axillary lymph node dissection in triple-negative or her2-positive breast cancer patients with clinical n2 achieving pathological complete response after neoadjuvant therapy: Is it necessary? Breast. 2024;73:103671. https://doi.org/10.1016/j.breast.2024.103671.
54. Heil J, Kuerer HM, Pfob A, Rauch G, Sinn HP, Golatta M, et al. Eliminating the breast cancer surgery paradigm after neoadjuvant systemic therapy: Current evidence and future challenges. Ann Oncol. 2020;31(1):61-71. https://doi.org/10.1016/j.annonc.2019.10.012.
55. Luo Y, Jiang H, Liu C, Zhang C. Axillary downstaging and the impact of clinical axillary status on efficacy of neoadjuvant therapy for her2-positive breast cancer: A network meta-analysis. Technol Cancer Res Treat. 2023;22:15330338221150325. https://doi.org/10.1177/15330338221150325.