ORIGINAL ARTICLE

Pathological Response Rate with Neoadjuvant Treatment with or without Pertuzumab in Patients with Stage II and III HER2-Positive Breast Cancer: A Single-Center Study

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ABSTRACT

Background: HER2-positive breast cancer accounts for 15-20% of all breast cancer cases. Neoadjuvant therapy has significantly improved treatment outcomes, particularly with HER2-targeted agents such as trastuzumab and pertuzumab.

Objective: To compare pathological complete response rates in stage II and III HER2-positive breast cancer patients receiving neoadjuvant therapy with or without pertuzumab.

Methods: This retrospective observational study was conducted at a tertiary care hospital in Karachi. Medical records of patients aged ≥ 18 years with stage II or III HER2-positive breast cancer who received neoadjuvant chemotherapy between January 2022 and December 2023 were reviewed. Patients were grouped based on HER2 blockade strategy: single-agent trastuzumab versus dual-agent trastuzumab plus pertuzumab. The primary endpoint was pathological complete response (pCR).

Results: A total of 79 patients were included, with 66 (83.5%) receiving dual HER2 blockade and 13 (16.5%) receiving trastuzumab alone. The pCR rate was 60.6% in the dual blockade group and 53.8% in the trastuzumab-alone group (p=0.650). However, when assessed using a three-tier classification (no response, partial response, complete response), a significant difference was observed (p=0.040), with no absolute non-responders in the dual blockade group. On multivariate analysis, ER-negative status (OR = 7.17, p=0.026), taxane use (OR = 15.13, p=0.003), and high-grade tumors (OR = 0.185, p=0.028) were significant predictors of pCR. Dual HER2 blockade was not an independent predictor (p=0.163).

Conclusion: Dual HER2 blockade did not significantly increase overall pCR rates but was associated with eliminating non-response, suggesting a potential role in reducing treatment failure. ER status, tumor grade, and taxane-based regimens were key determinants of response. These findings underscore the need for individualized treatment strategies and cost-benefit considerations in low-resource settings.

Keywords: *HER2-positive breast cancer, neoadjuvant chemotherapy, pathological complete response, trastuzumab, pertuzumab, estrogen receptor status, real-world data, Pakistan.*

INTRODUCTION

HER2-positive breast cancer, defined by the overexpression of the human epidermal growth factor receptor 2 (HER2), accounts for approximately 15-20% of all invasive breast cancer cases and is associated with aggressive clinical behavior and poorer outcomes if left untreated [1]. The advent of HER2-targeted therapies—most notably trastuzumab and pertuzumab—has significantly improved patient survival, transforming the disease into a more manageable and treatable subtype [2, 3]. Pathological complete response (pCR), defined as the absence of invasive cancer in both the breast and axillary lymph nodes (ypT0/is ypN0), has emerged as a robust surrogate marker for long-term survival in HER2-positive and other high-risk breast cancer subtypes [4, 5].

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Trastuzumab, a monoclonal antibody directed against the extracellular portion of the HER2 receptor, continues to serve as a cornerstone of neoadjuvant treatment. Combining it with pertuzumab, which targets a different site on the HER2 receptor, enhances the inhibition of HER2 signaling pathways. In the NEOSPHERE trial, patients receiving trastuzumab, pertuzumab, and docetaxel showed significantly higher pCR rates compared to those treated with trastuzumab and docetaxel alone [6]. Similarly, dual HER2 blockade has consistently demonstrated superior efficacy across multiple meta-analyses of randomized controlled trials [7, 8]. The APHINITY trial further established the benefit of pertuzumab by showing improved invasive disease-free survival in patients with HER2-positive operable breast cancer when added to trastuzumab and chemotherapy in the adjuvant setting [9]. Real-world data reinforce these findings, confirming that neoadjuvant dual HER2-targeted therapy significantly improves pCR rates, particularly in patients with clinically node-positive disease [10, 11]. The safety profile of this treatment

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regimen has also been well characterized, with trials such as TRYPHAENA demonstrating its tolerability when combined with various chemotherapy backbones [12]. However, despite the global acceptance of dual HER2 blockade, real-world evidence from low- and middle-income countries (LMICs) remains limited. A local observational study from Pakistan reported that the addition of trastuzumab to neoadjuvant chemotherapy nearly doubled pCR rates, underscoring the need to offer targeted therapies to all eligible patients with HER2-overexpressing breast cancer [13]. Cost-effectiveness remains a major barrier to the widespread adoption of dual HER2 blockade in LMICs. While economic analyses from high-income countries such as Canada have demonstrated favorable cost-effectiveness for pertuzumab in the neoadjuvant setting [14], findings from countries like the Philippines highlight the financial challenges, where even single-agent trastuzumab is not considered cost-effective unless its price is reduced substantially [15].

This single-center retrospective study evaluates the pathological complete response (pCR) rates in stage II-III HER2-positive breast cancer patients treated with neoadjuvant chemotherapy combined with either single-agent (trastuzumab) or dual-agent (trastuzumab + pertuzumab) HER2 blockade. Secondary objectives include a comparison of treatment-related toxicities. By contributing real-world data from a resource-limited setting, this study aims to support context-specific, cost-effective strategies for the management of HER2-positive breast cancer in LMICs.

METHODS

This was a retrospective observational study carried out at the Department of Oncology, Aga Khan University Hospital. Following approval from the Institutional Ethical Review Committee (ERC # 2023-9201-27354), medical records of patients with stage II or III HER2-positive breast cancer were reviewed to assess pathological complete response (pCR) rates after neoadjuvant chemotherapy. Written informed consent was not required since the data was retrospectively reviewed from patients' medical records files.

The study included patients treated between January 2022 and December 2023. Data collection was carried out following ethical clearance. All procedures were performed in accordance with the principles outlined in the Declaration of Helsinki. Patient confidentiality was maintained by anonymizing identifiable information, and data access was restricted to study investigators.

Inclusion criteria were as follows: patients aged 18 years or older with histologically confirmed stage II or III HER2-positive breast cancer; HER2 positivity defined as immunohistochemistry (IHC) 3+ or IHC 2+ with confirmatory HER2 gene amplification by fluorescence in situ hybridization (FISH); receipt of neoadjuvant chemotherapy with or without dual HER2 blockade; and either hormone receptor-positive or -negative disease. Both male and female patients were eligible. Exclusion criteria included HER2-equivocal tumors without confirmed amplification (IHC 2+ and FISH-negative), poor functional status (ECOG performance score ≥ 3), and significant cardiac dysfunction such as New York Heart Association (NYHA) class III or IV congestive heart failure, left ventricular ejection fraction (LVEF) <50%, or a history of myocardial infarction within six months before treatment. Patients were also excluded if they had received prior systemic therapy or surgery for breast cancer before the neoadjuvant regimen, or if treatment or follow-up data were incomplete, preventing pCR assessment.

Clinical, pathological, and treatment-related information was extracted from electronic medical records. This included demographic data (age, gender), tumor features (stage, histological type, grade, ER/PR status, HER2 score), treatment details (chemotherapy regimen, use of trastuzumab and/or pertuzumab), treatment response (pCR status), and adverse events documented during neoadjuvant therapy.

All data were analyzed using IBM SPSS Statistics version 27. Descriptive statistics were reported as mean ± standard deviation (SD) for continuous variables and frequency (percentage) for categorical variables. Chi-square or Fisher's exact test was used to compare categorical variables, and independent sample *t*-tests for continuous variables. Pathological complete response (pCR) was the primary outcome, assessed as a binary variable (achieved *vs*. not achieved). A multinomial classification (no response, partial response, complete response) was also applied to evaluate patterns of tumor regression. Logistic regression was used to identify independent predictors of pCR. A p-value < 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 79 patients with stage II or III HER2-positive breast cancer were included, with 66 patients (83.5%) receiving dual HER2 blockade (trastuzumab plus pertuzumab) and 13 patients (16.5%) receiving trastuzumab alone. Baseline characteristics were well-balanced between groups (**Table 1**), with no significant differences in age (49.5 ± 13.0 *vs*. 47.3 ± 14.5 years, p=0.585), ECOG performance status, tumor stage, histologic subtype, or receptor status. Chemotherapy regimens showed non-significant trends, with anthracyclines used more frequently in the trastuzumab-alone group (76.9% *vs*. 51.5%, p=0.092) and carboplatin more common in the combination group (43.9% *vs*. 15.4%, p=0.054). Safety profiles were comparable.

Table 1: Baseline clinical, pathological, and treatment characteristics of HER2-positive breast cancer patients receiving dual HER2 blockade (trastuzumab + pertuzumab) versus trastuzumab alone.

Variable	Category	Total (n=79)	Combination (n=66)	Trastuzumab (n=13)	p-Value
Age (Mean±SD)		49.2 ± 13.2	49.5 ± 13.0	47.3 ± 14.5	0.585
ECOG Performance Status	ECOG 0	36 (45.6%)	31 (47.0%)	5 (38.5%)	0.799
	ECOG 1	39 (49.4%)	32 (48.5%)	7 (53.8%)	
	ECOG 2	4 (5.1%)	3 (4.5%)	1 (7.7%)	
T Stage (cT)	cT1	1 (1.3%)	1 (1.5%)	0 (0.0%)	0.518
	cT2	38 (48.1%)	29 (43.9%)	9 (69.2%)	
	cT3	23 (29.1%)	20 (30.3%)	3 (23.1%)	
	cT4	16 (20.3%)	15 (22.7%)	1 (7.7%)	
	cTx	1 (1.3%)	1 (1.5%)	0 (0.0%)	
N Stage (cN)	cN0	15 (19.0%)	10 (15.2%)	5 (38.5%)	0.185
	cN1	44 (55.7%)	39 (59.1%)	5 (38.5%)	
	cN2	17 (21.5%)	15 (22.7%)	2 (15.4%)	
	cN3	3 (3.8%)	2 (3.0%)	1 (7.7%)	
Overall Stage	IIA	13 (16.5%)	8 (12.1%)	5 (38.5%)	0.183
	IIB	25 (31.6%)	22 (33.3%)	3 (23.1%)	
	IIIA	23 (29.1%)	20 (30.3%)	3 (23.1%)	
	IIIB	14 (17.7%)	13 (19.7%)	1 (7.7%)	
	IIIC	4 (5.1%)	3 (4.5%)	1 (7.7%)	
Histology	IDC	65 (82.3%)	54 (81.8%)	11 (84.6%)	0.809
	IC + IC-NST	14 (17.7%)	12 (18.2%)	2 (15.4%)	
Histologic Grade	1	1 (1.3%)	0 (0.0%)	1 (7.7%)	0.057
	2	31 (39.2%)	25 (37.9%)	6 (46.2%)	
	3	47 (59.5%)	41 (62.1%)	6 (46.2%)	
Chemotherapy Regimen	Anthracycline Use	44 (55.7%)	34 (51.5%)	10 (76.9%)	0.092
	Carboplatin Use	31 (39.2%)	29 (43.9%)	2 (15.4%)	0.054
Taxanes Group	Paclitaxel Use	34 (43.0%)	27 (40.9%)	7 (53.8%)	0.389
	Docetaxel Use	29 (36.7%)	24 (36.4%)	5 (38.5%)	0.886
Receptor Status	ER Positive	41 (51.9%)	32 (48.5%)	9 (69.2%)	0.171
	PR Positive	34 (43.0%)	28 (42.4%)	6 (46.2%)	0.804
	HER2 3+ byIHC	60 (75.9%)	50 (75.8%)	10 (76.9%)	0.928
	HER2 2+ (FISH+)	19 (24.1%)	16 (24.2%)	3 (23.1%)	
Side Effects Profile	Cardiomyopathy	3 (3.8%)	3 (4.5%)	0 (0.0%)	0.433
	Oral Mucositis	5 (6.3%)	5 (7.6%)	0 (0.0%)	0.305
	Nausea	4 (5.1%)	4 (6.1%)	0 (0.0%)	0.362
	Vomiting	3 (3.8%)	3 (4.5%)	0 (0.0%)	0.433
	Neuropathy	6 (7.6%)	5 (7.6%)	1 (7.7%)	0.988
	Febrile. Neutropenia	2 (2.5%)	2 (3.0%)	0 (0.0%)	0.525
	Skin Rash	3 (3.8%)	2 (3.0%)	1 (7.7%)	0.421
	Diarrhea	21 (26.6%)	20 (30.3%)	1 (7.7%)	0.092

Values are presented as a number (percentage) unless otherwise specified. ECOG = Eastern Cooperative Oncology Group; cT = clinical tumor stage; cN = clinical nodal stage; IDC = invasive ductal carcinoma; IC = invasive carcinoma; IC-NST = invasive carcinoma of no special type; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; IHC = Immunohistochemistry; FISH = fluorescence in situ hybridization; SD = standard deviation.

Pathological Response by HER2 Blockade

Pathological complete response (pCR) rates did not differ significantly between groups when analyzed as a binary outcome (60.6% for dual blockade *vs*. 53.8% for trastuzumab alone, p=0.650). However, when assessed using a three-tier classification (no response/partial response/complete response), the distribution differed significantly (p=0.040), with no patients in the dual blockade group showing absolute non-response compared to 15.4% in the trastuzumab-alone group. Due to the presence of low expected cell counts (3 cells <5), the Fisher-Freeman-Halton exact test was used, confirming a statistically significant association (p = 0.040) (**Table 2**).

Table 2: Comparison of pathological response between patients receiving dual HER2 blockade (trastuzumab + pertuzumab) and those receiving trastuzumab alone.

Variable	Category	Total (n=79)	Combination (n=66)	Trastuzumab (n=13)	p-Value
Pathological Response (2-tier)	pCR	47 (59.5%)	40 (60.6%)	7 (53.8%)	0.650
	No pCR	32 (40.5%)	26 (39.4%)	6 (46.2%)	
Pathological Response (3-tier)	No Response	2 (2.5%)	0 (0.0%)	2 (15.4%)	0.040
	Partial Response	30 (38.0%)	26 (39.4%)	4 (30.8%)	
	Complete Response	47 (59.5%)	40 (60.6%)	7 (53.8%)	

Values are presented as a number (percentage). pCR = pathological complete response.

Binary logistic regression analysis identified three significant independent predictors of pCR. Estrogen receptor-negative status was associated with 7.2-fold higher odds of pCR (OR 7.170, 95% CI 1.269-40.494, p=0.026). Taxane administration showed the strongest association with pCR (OR 15.133, 95% CI 2.587-88.522, p=0.003), though the wide confidence interval suggests this estimate should be interpreted cautiously. Grade 3 tumors had significantly higher pCR rates compared to grade 1-2 tumors (OR 0.185, 95% CI 0.041-0.831, p=0.028). The HER2 blockade strategy (combination *vs*.

Table 3: Multivariable logistic regression analysis for predictors of pathological complete response (pCR) in HER2-positive breast cancer patients

Variable	Coefficient (B)	OR (Exp(B)	95% CI for OR	p-Value
Age	0.013	1.013	0.956-1.074	0.662
Her2 Blockade (Combination *vs.*Trastuzumab)	-1.344	0.261	0.040-1.723	0.163
Anthracycline (Yes *vs.* No)	0.500	1.650	0.062-43.658	0.765
Carboplatin (Yes *vs.* No)	1.272	3.569	0.191-66.798	0.395
ER Status (Positive *vs.* Negative)	1.970	7.170	1.269-40.494	0.026
PR Status (Positive *vs.* Negative)	1.050	2.857	0.613-13.310	0.181
HER2 Status (3+ *vs.* FISH+)	-0.473	0.623	0.140-2.769	0.534
Stage Final (Stage II *vs.* Stage III)	-1.175	0.309	0.081-1.178	0.085
Histology Classified (IDC *vs.* IC-NST)	1.080	2.943	0.406-21.315	0.285
Taxane Given (Yes *vs.* No)	2.717	15.133	2.587-88.522	0.003
Grade Classified (Grade 1/2 *vs.* Grade 3)	-1.687	0.185	0.041-0.831	0.028
Constant	-2.324	0.098	-	0.435

OR = odds ratio; CI = confidence interval; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; FISH = fluorescence in situ hybridization; IDC = invasive ductal carcinoma; IC-NST = invasive carcinoma of no special type.

trastuzumab alone) did not significantly predict pCR (OR 0.261, 95% CI 0.040-1.723, p=0.163). Other variables, including age, anthracycline use, carboplatin use, PR status, HER2 status, tumor stage, and histology, showed no significant association with pCR (all p>0.05). The overall model demonstrated excellent fit (χ^2=37.721,p<0.001; Nagelkerke R^2=0.513) and classification accuracy of 77.2%. The detailed regression coefficients,odds ratios, and confidence intervals are provided in Table **3**.

DISCUSSION

Our findings add to the growing evidence on neoadjuvant treatment strategies for HER2-positive breast cancer. While the pathological complete response (pCR) rates were not significantly different between the dual blockade and trastuzumab-only groups when analyzed as a binary outcome (60.6% *vs*. 53.8%, *p*=0.650), a more detailed three-tier classification (no response/partial response/complete response) revealed a significant difference (*p*=0.040). Importantly, there were no absolute non-responders in the dual blockade group, compared to 15.4% in the trastuzumab-alone group, suggesting a potential role for dual blockade in minimizing treatment failure. The similarity in binary pCR rates between dual HER2 blockade and trastuzumab alone aligns with findings from real-world studies in which pertuzumab did not significantly impact pCR outcomes [16]. This contrasts with the results from the NeoSphere trial, where dual HER2 blockade was associated with improved pCR and survival outcomes, establishing total pCR as a surrogate for long-term benefit [6]. Similarly, real-world data from a UK tertiary referral cancer center reported a higher pCR rate with dual therapy: 46.3% (37/78; 95% CI: 35.3-57.2) [10]. The complete absence of non-responders in our dual blockade group is consistent with the TRYPHAENA cardiac safety study, where pertuzumab-containing regimens yielded more consistent response profiles [12]. These observations suggest that the added benefit of dual blockade may lie more in preventing absolute treatment failure rather than enhancing overall pCR, a hypothesis that warrants further investigation in larger, prospective datasets.

The strong association between estrogen receptor (ER)-negative status and pCR (OR 7.17) supports established biological principles. ER-negative/HER2-positive tumors have been shown to respond more favorably to chemotherapy and HER2-targeted therapies [5, 6, 17]. This is further substantiated by real-world evidence showing low pCR rates in ER- and PgR-positive tumors [10]. The underlying mechanism may involve the reciprocal inhibition between ER and HER2 pathways, whereby ER negativity permits unopposed HER2 signaling, rendering tumors more susceptible to HER2 blockade [18]. These findings are consistent with meta-analyses across neoadjuvant trials that report consistently higher pCR rates in hormone receptor-negative subgroups [19].

Our analysis also revealed a strong association between taxane use and pCR (OR 15.13), which exceeds the effect sizes typically observed in randomized clinical trials. A prior study with a median follow-up of 38 months showed significantly higher pCR (34% *vs*. 18%) in patients treated with docetaxel compared to those receiving four cycles of CVAP [20]. The high odds ratio in our analysis may reflect underlying selection bias or population differences, particularly as patients not receiving taxanes may represent a subset with contraindications or less aggressive disease. Nevertheless, the robust benefit of taxanes in breast cancer is well documented in the literature [20, 21].

The inverse correlation between low-grade tumors and pCR (OR 0.185) is consistent with previous reports. One study demonstrated that Scarff-Bloom-Richardson (SBR) grade III tumors were significantly more responsive to neoadjuvant therapy than grade I tumors ($p < 10^{-6}$), with tumor responsiveness also associated with dynamic changes in grade ($p = 0.007$) concluding SBR grade as a strong predictive factor of chemosensitivity in invasive ductal breast cancer, regardless of the chemotherapy regimen used [22]. The safety profile observed in our study is in line with both the CLEOPATRA and TRYPHAENA trials, which demonstrated acceptable tolerability with pertuzumab-containing regimens [12, 23].

Study limitations include its small sample size, retrospective design, potential for confounding due to unmeasured variables, and the unequal distribution between treatment groups with a smaller trastuzumab-only cohort. Reported adverse events were presented as all-grade toxicities, a decision made due to the limited sample size, which restricted meaningful stratification by severity. Although treatment interruptions and delays due to toxicity were infrequent, they were not separately accounted for and therefore represent an additional limitation. The wide confidence intervals for several predictors, particularly taxanes, highlight these limitations. Nonetheless, the consistency of our findings with larger clinical trials and their underlying biological plausibility lends credibility to our observations.

Clinical implications of this study are particularly noteworthy as it represents the first real-world evidence from a lower-middle-income country (LMIC) like Pakistan, where such data are critically lacking. This adds valuable insight to global literature by reflecting treatment outcomes in a resource-constrained healthcare setting. Our findings reinforce the predictive value of ER status, with ER-negative tumors responding more favorably to neoadjuvant therapy. The marked association between taxane use and pCR supports their continued

prioritization in treatment protocols, especially where optimizing efficacy with limited resources is essential. Importantly, the absence of absolute non-responders in the dual HER2 blockade group suggests a potential role for pertuzumab in preventing treatment failure rather than simply increasing overall response rates. Tumor grade also emerged as a meaningful predictor and should be factored into treatment planning. Together, these observations offer a practical framework for tailoring neoadjuvant strategies in LMICs and highlight the need for context-specific guidelines.

Future directions include validating these findings in larger cohorts, especially the strong association with taxane use. Given the absence of non-responders in the dual blockade group, further molecular studies could explore mechanisms of complete resistance in trastuzumab-only cases. Cost-effectiveness analyses of pertuzumab in LMICs and simplified predictive models tailored to such settings are also needed.

CONCLUSION

This single-center retrospective study provides valuable real-world evidence on the pathological response outcomes of neoadjuvant HER2-targeted therapy in patients with stage II and III HER2-positive breast cancer. While the overall pathological complete response (pCR) rates were comparable between patients receiving single *versus* dual HER2 blockade, the absence of absolute non-responders in the dual blockade group suggests a potential benefit in minimizing treatment failure. Estrogen receptor negativity and taxane-based chemotherapy emerged as strong independent predictors of pCR, underscoring the importance of tumor biology and chemotherapy selection in treatment planning.

Given the financial and infrastructural limitations often faced in low- and middle-income countries, these findings highlight the need for context-specific therapeutic strategies that balance efficacy, accessibility, and cost. Future prospective studies with larger sample sizes and molecular profiling are warranted to refine patient selection for dual HER2 blockade and to further personalize treatment approaches in resource-constrained settings.

ETHICS APPROVAL

This study received an exemption from the Institutional Review Board with 2023-9201-27354. All procedures performed in studies involving human participants followed the ethical standards of the institutional and/ or national research committee and the Helsinki Declaration.

CONSENT FOR PUBLICATION

Not applicablle as the data was retrospectively reviewed from patients' medical records files.

AVAILABILITY OF DATA

The data is available with the corresponding author upon reasonable request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

MAH: Study concept and design, data collection, and manuscript drafting. YAR: Study concept, manuscript editing, and final approval. IMA: Study concept, revision of initial draft, data interpretation, and manuscript drafting. MSM:critical revision, ZN: manuscript drafting & statistical analysis, MYS: Study concept and revision of initial draft, MRS: data collection and manuscript drafting.

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