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NEOADJUVANT TRASTUZUMAB, WITH OR WITHOUT PERTUZUMAB, COMBINED WITH CHEMOTHERAPY FOR EARLY HER2-POSITIVE BREAST CANCER: A REAL-WORLD EXPERIENCE FROM A TERTIARY CANCER CENTRE

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ABSTRACT

Background: Neoadjuvant chemotherapy combined with trastuzumab, with or without pertuzumab, is standard of care for early human epidermal growth factor receptor 2 (HER2)-positive breast cancer, with clinical trial pathological complete response (pCR) rates of 45–61%. Real-world evidence from low- and middle-income settings, where dual anti-HER2 therapy access remains limited, is sparse. This study evaluated the efficacy and safety of neoadjuvant HER2-directed therapy plus chemotherapy in routine practice at a tertiary cancer centre in India.

Methods: Consecutive patients with HER2-positive early breast cancer who received neoadjuvant chemotherapy plus trastuzumab, with or without pertuzumab, between January 2023 and August 2025 were retrospectively identified. Clinicopathological characteristics, regimens, treatment-related toxicity, and pathological response were analysed. pCR was defined as absence of invasive residual disease in the breast and axillary lymph nodes (ypT0/is ypN0). Categorical variables were compared using Chi-square or Fisher exact tests; a two-sided p value <0.05 was considered significant.

Results: Eighty-one female patients were analysed; 70 (86.4%) had clinically node-positive disease and 48 (59.3%) were hormone receptor (HR)-positive. Overall pCR was 48.1% (39/81). pCR rates were 41.7% (20/48) in HR-positive and 57.6% (19/33) in HR-negative tumours (p=0.159). Sixty-nine patients (85.2%) received single-agent anti-HER2 therapy (trastuzumab) and 12 (14.8%) received dual anti-HER2 therapy (trastuzumab plus pertuzumab). pCR was achieved in 40.6% (28/69) of single-agent recipients versus 91.7% (11/12) of dual-therapy recipients (p=0.001). Diarrhoea (24.7%), fatigue (16.0%), nausea (14.8%), and mucositis (12.4%) were the most common adverse events. Asymptomatic left ventricular ejection fraction decline occurred in one patient (1.2%); no symptomatic heart failure or grade 3–4 cardiac events were observed.

Conclusion: In this real-world Indian cohort, neoadjuvant HER2-directed therapy plus chemotherapy demonstrated efficacy comparable to pivotal clinical trials, with markedly higher pCR observed with dual anti-HER2 blockade. Cardiac and overall tolerability was favourable. Wider access to dual anti-HER2 therapy in the neoadjuvant setting should be prioritised.

KEYWORDS: HER2-positive breast cancer; neoadjuvant chemotherapy; trastuzumab; pertuzumab; pathological complete response; real-world evidence.

INTRODUCTION

Breast cancer is the most commonly diagnosed malignancy and the leading cause of cancer-related mortality among women worldwide, with an estimated 2.3 million new cases and 685,000 deaths reported in the GLOBOCAN 2020 database.1 It has surpassed lung cancer as the most frequent cancer overall and imposes a disproportionately large burden on transitioning countries, where age-standardised mortality remains substantially higher than in transitioned economies.1 In India, breast cancer has emerged as the leading cancer among women in most population-based cancer registries, with age-adjusted incidence rates as high as 41 per 100,000 in Delhi and an annual increase in incidence of approximately 2% across major metropolitan registries.2 Indian women tend to present at a younger age and with more advanced clinical stage compared with Western cohorts, with mortality-to-incidence ratios reaching up to 66 in rural registries.2

Human epidermal growth factor receptor 2 (HER2), encoded by the ERBB2 proto-oncogene, is overexpressed or amplified in approximately 15–20% of invasive breast cancers.3 HER2-positive breast cancer is historically associated with aggressive tumour biology, higher rates of visceral metastasis, resistance to endocrine therapy, and worse survival compared with HER2-negative disease.3 The introduction of trastuzumab, a recombinant humanised monoclonal antibody

targeting the extracellular domain IV of HER2, transformed the natural history of this disease. In the pivotal first-line metastatic trial, the addition of trastuzumab to chemotherapy prolonged time to progression from a median of 4.6 to 7.4 months and increased median overall survival from 20.3 to 25.1 months.3

The clinical benefit of trastuzumab was subsequently extended to the adjuvant setting. In the HERA (Herceptin Adjuvant) trial, one year of adjuvant trastuzumab after chemotherapy reduced the risk of a disease-free survival event by 46% at the first interim analysis compared with observation.4 A subsequent individual patient-level meta-analysis of 13,864 women across seven randomised trials demonstrated that adjuvant trastuzumab combined with chemotherapy reduced the relative risk of breast cancer recurrence by 34% and breast cancer mortality by 33%, corresponding to an absolute 9.0% reduction in 10-year recurrence and a 6.4% reduction in 10-year breast cancer mortality.5 Importantly, these benefits were observed across all patient and tumour subgroups examined, including hormone receptor (HR)-positive and HR-negative subgroups.5

Accurate identification of HER2-positive tumours is critical for treatment selection. Current American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines recommend testing all newly diagnosed invasive breast cancers by immunohistochemistry (IHC) and/or in situ hybridisation (ISH). A result is considered positive when IHC scores 3+ or when ISH demonstrates a HER2/CEP17 ratio ≥2.0 with an average HER2 copy number ≥4.0 signals per cell, with additional pathways for equivocal 2+ IHC and less common ISH patterns.6

The neoadjuvant treatment paradigm has become the standard of care for the majority of patients with stage II–III HER2-positive breast cancer, as it enables in vivo assessment of tumour response, facilitates breast-conserving surgery, provides prognostic information, and identifies patients with residual disease who benefit from escalated adjuvant therapy. Pathological complete response (pCR), typically defined as the absence of invasive residual disease in the breast and axillary lymph nodes (ypT0/is ypN0), is a robust surrogate for improved long-term outcomes. The Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) pooled analysis of 11,955 patients confirmed that patients achieving pCR have significantly improved event-free survival (hazard ratio [HR] 0.48) and overall survival (HR 0.36), with the strongest prognostic association observed in triple-negative and HR-negative, HER2-positive tumours treated with trastuzumab (HR for event-free survival 0.15).7

The Neoadjuvant Herceptin (NOAH) trial established the neoadjuvant benefit of trastuzumab, demonstrating a significantly higher 3-year event-free survival of 71% with trastuzumab versus 56% without (HR 0.59; p=0.013), together with only a 2% incidence of symptomatic cardiac failure despite concurrent anthracycline exposure.8 Building on this foundation, dual anti-HER2 blockade with pertuzumab—a monoclonal antibody targeting the dimerisation domain II of HER2 and complementing the mechanism of trastuzumab—was investigated in the NeoSphere trial. Neoadjuvant pertuzumab, trastuzumab and docetaxel produced a pCR rate of 45.8%, significantly higher than the 29.0% observed with trastuzumab and docetaxel alone (p=0.0141), without an increase in cardiac events.9 The 5-year follow-up analysis of NeoSphere demonstrated durable progression-free survival benefit with the dual anti-HER2 combination and confirmed the prognostic value of total pCR as an early surrogate for long-term outcomes.10

The TRYPHAENA trial, designed primarily as a cardiac safety study, evaluated pertuzumab plus trastuzumab combined with anthracycline-containing or anthracycline-free chemotherapy backbones. pCR rates ranged from 57.3% to 66.2% across arms, and symptomatic left ventricular systolic dysfunction was infrequent (0–2.7%).11 The BERENICE phase II study further supported the cardiac safety of pertuzumab, trastuzumab, and anthracycline-based chemotherapy, reporting pCR rates of approximately 60–62% and low rates of symptomatic heart failure (1.5%) in the neoadjuvant setting.12

In the adjuvant setting, the APHINITY trial demonstrated that the addition of pertuzumab to trastuzumab plus chemotherapy improved 3-year invasive disease-free survival from 93.2% to 94.1%, with the greatest benefit observed in the node-positive cohort (92.0% vs 90.2%; HR 0.77; p=0.02).13 For patients with residual invasive disease after neoadjuvant chemotherapy and trastuzumab-based therapy, the KATHERINE trial established adjuvant trastuzumab emtansine (T-DM1) as standard of care, halving the risk of an invasive disease event or death (HR 0.50; p<0.001) compared with adjuvant trastuzumab.14 Collectively, these data provide a rational framework in which pCR after neoadjuvant HER2-directed therapy stratifies subsequent adjuvant escalation.

Real-world data from India are essential to contextualise trial-derived pCR estimates within routine clinical practice, where patient characteristics, resource constraints, and regimen selection differ from those of pivotal trials. In a large single-institution prospective series from the Tata Memorial Centre involving 664 breast cancer patients receiving neoadjuvant chemotherapy in 2017, the overall pCR was 22.4%, with 35.4% in HR-negative HER2-positive tumours and only 58.5% of HER2-positive patients receiving HER2-targeted therapy, reflecting persisting access gaps.15 Data specifically focused on HER2-positive early breast cancer treated with contemporary neoadjuvant HER2-directed therapy in Indian centres remain limited, particularly with respect to the incremental benefit and tolerability of dual anti-HER2 therapy when access to pertuzumab is variable. The present study was undertaken to address this evidence gap by evaluating the efficacy and safety of neoadjuvant trastuzumab, with or without pertuzumab, combined with chemotherapy in a real-world Indian cohort.

Aims and Objectives

Primary objective

To determine the pathological complete response (pCR) rate, defined as absence of invasive residual disease in the breast and axillary lymph nodes (ypT0/is ypN0), among patients with HER2-positive early breast cancer receiving neoadjuvant chemotherapy combined with trastuzumab, with or without pertuzumab, at a tertiary referral cancer centre.

Secondary objectives

1. To describe the clinicopathological and demographic characteristics of patients receiving neoadjuvant HER2-directed therapy in routine practice.
2. To compare pCR rates between single-agent anti-HER2 therapy (trastuzumab) and dual anti-HER2 therapy (trastuzumab plus pertuzumab).
3. To compare pCR rates between hormone receptor (HR)-positive and HR-negative subgroups.
4. To evaluate the safety and tolerability profile of the neoadjuvant regimens, with specific attention to cardiac toxicity, gastrointestinal toxicity, haematological toxicity, and constitutional adverse events.

MATERIALS AND METHODS

Study design and setting

This was a single-centre, retrospective, observational cohort study conducted at a tertiary referral cancer centre. The study period spanned from January 2023 to August 2025. Consecutive patients meeting the eligibility criteria were identified from the departmental electronic medical records and multidisciplinary tumour board registers. The study conformed to the ethical principles of the Declaration of Helsinki and its subsequent revisions and was approved by the Institutional Ethics Committee. Because of the retrospective nature of the analysis using de-identified data, a waiver of individual informed consent was granted.

Study population

Inclusion criteria were: (i) histopathologically confirmed invasive breast carcinoma; (ii) HER2-positive status defined as IHC 3+, or IHC 2+ with ISH amplification (HER2/CEP17 ratio ≥2.0 or HER2 copy number ≥6.0 signals per cell) in accordance with ASCO/CAP 2018 criteria; (iii) clinical stage II–III disease at presentation; (iv) receipt of at least one cycle of neoadjuvant chemotherapy combined with trastuzumab, with or without pertuzumab; and (v) completion of definitive breast and axillary surgery with available pathological response data.

Exclusion criteria were: (i) stage IV disease at diagnosis; (ii) receipt of adjuvant rather than neoadjuvant HER2-directed therapy; (iii) previous chemotherapy or endocrine therapy for the current breast cancer; (iv) concurrent second malignancy; and (v) incomplete records precluding the assessment of pathological response or safety.

Sample size

This was a real-world, exploratory descriptive analysis of all consecutive eligible patients treated during the study window. No formal sample size calculation was performed. All patients who met the eligibility criteria within the study period were included in the final analysis, yielding a total cohort of 81 patients.

Baseline evaluation

At presentation, all patients underwent a standardised evaluation including detailed clinical history, physical examination with bilateral breast and regional nodal assessment, bilateral digital mammography, ultrasonography of the breast and axilla, and core-needle biopsy of the primary tumour and clinically or radiologically suspicious lymph nodes. Histopathological reports documented tumour histology, grade, oestrogen receptor (ER), progesterone receptor (PR), and HER2 status determined by IHC with reflex ISH for equivocal cases. Ki-67 proliferation index was recorded when available. Baseline staging included contrast-enhanced computed tomography of the chest, abdomen, and pelvis and radionuclide bone scan or fluorodeoxyglucose positron emission tomography–computed tomography where indicated. Baseline cardiac evaluation with two-dimensional transthoracic echocardiography or multi-gated acquisition scan was performed in all patients to document left ventricular ejection fraction (LVEF).

Treatment regimens

Neoadjuvant regimens were selected based on tumour stage, patient comorbidities, cardiac reserve, socioeconomic factors, and drug availability. The most commonly used backbone was sequential anthracycline–taxane chemotherapy consisting of four cycles of doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) every three weeks (AC), followed by four cycles of docetaxel (75–100 mg/m²) every three weeks or paclitaxel (80 mg/m² weekly for 12 doses). A minority of patients received the non-anthracycline docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) regimen or a modified taxane–carboplatin backbone. Trastuzumab was administered as an 8 mg/kg loading dose followed by 6 mg/kg every three weeks (or 4 mg/kg loading and 2 mg/kg weekly with paclitaxel), planned to complete one year of anti-HER2 therapy postoperatively. When available and indicated, pertuzumab was administered concurrently as an 840 mg loading dose followed by 420 mg every three weeks.

On-treatment assessment and cardiac monitoring

Patients were clinically evaluated before each cycle. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Complete blood counts, renal and hepatic function, and electrolytes were monitored routinely. LVEF was reassessed by echocardiography at baseline, at three-monthly intervals during anti-HER2 therapy, and whenever clinically indicated. Anti-HER2 therapy was held for LVEF absolute decline ≥10 percentage points from baseline to below 50%, for symptomatic heart failure, or per institutional guidelines.

Surgery and pathological assessment
Definitive surgery—breast-conserving surgery or mastectomy with axillary staging by sentinel lymph node biopsy or axillary lymph node dissection—was performed three to six weeks after completion of neoadjuvant systemic therapy. Surgical specimens were processed using a standardised protocol incorporating clip localisation of the pre-treatment tumour bed. Pathological response was reported in accordance with the residual cancer burden framework, and pCR was defined a priori as absence of residual invasive carcinoma in the breast and axillary lymph nodes (ypT0/is ypN0). Residual ductal carcinoma in situ was permitted in the pCR definition.

Statistical analysis
Categorical variables were summarised as frequencies and percentages, and continuous variables as means with standard deviations or medians with ranges as appropriate. Between-group comparisons for categorical variables were performed using the Chi-square test or Fisher exact test where expected cell counts were small. A two-sided p value of <0.05 was considered statistically significant. All analyses were performed using standard statistical software.

RESULTS

Patient characteristics
Between January 2023 and August 2025, 81 female patients with HER2-positive early breast cancer met the eligibility criteria and were included in the analysis. The mean age at diagnosis was 48.6 years (standard deviation 10.4; range 28–72). The right and left breasts were affected in comparable proportions. Invasive ductal carcinoma of no special type was the predominant histology, accounting for 76 patients (93.8%), while five patients (6.2%) had special-type histologies including invasive lobular and mixed ductal-lobular tumours. Baseline demographic and clinicopathological characteristics of the cohort are summarised in Table 1.

Table 1. Baseline demographic and clinicopathological characteristics of the cohort (n = 81).

Variable	Category	n (%)
Age (years)	Mean ± SD	48.6 ± 10.4
	≤ 40 years	20 (24.7%)
	41–50 years	27 (33.3%)
	51–60 years	22 (27.2%)
	> 60 years	12 (14.8%)
Menopausal status	Premenopausal	35 (43.2%)
	Postmenopausal	46 (56.8%)
Laterality	Right	41 (50.6%)
	Left	40 (49.4%)
Histology	Invasive ductal carcinoma, NST	76 (93.8%)
	Other (lobular / mixed)	5 (6.2%)
Tumour grade	Grade II	32 (39.5%)
	Grade III	49 (60.5%)

At presentation, the majority of patients had locally advanced disease. Seventy patients (86.4%) had clinically node-positive disease and only 11 patients (13.6%) were clinically node-negative. Clinical T3–T4 tumours accounted for 46 (56.8%) of cases. Hormone receptor positivity, defined as ER-positive and/or PR-positive tumours, was observed in 48 patients (59.3%), while 33 patients (40.7%) had HR-negative disease. HER2 status was determined by IHC 3+ in 62 (76.5%) and by ISH amplification of IHC 2+ tumours in 19 (23.5%). Pre-treatment tumour characteristics are presented in Table 2.

Table 2. Pre-treatment clinical and receptor characteristics (n = 81).

Variable	Category	n (%)
Clinical T stage	cT1	5 (6.2%)
	cT2	30 (37.0%)
	cT3	31 (38.3%)

Variable	Category	n (%)
	cT4	15 (18.5%)
Clinical N stage	cN0	11 (13.6%)
	cN1	48 (59.3%)
	cN2	17 (21.0%)
	cN3	5 (6.2%)
Clinical stage group	Stage II	31 (38.3%)
	Stage III	50 (61.7%)
Hormone receptor status	HR-positive	48 (59.3%)
	HR-negative	33 (40.7%)
HER2 confirmation	IHC 3+	62 (76.5%)
	IHC 2+ with ISH amplification	19 (23.5%)

Treatment received

All 81 patients received neoadjuvant chemotherapy combined with anti-HER2 therapy. Sequential anthracycline–taxane chemotherapy was administered to 74 patients (91.4%), while seven patients (8.6%) received a non-anthracycline taxane–carboplatin backbone. Regarding anti-HER2 therapy, 69 patients (85.2%) received single-agent trastuzumab and 12 patients (14.8%) received dual anti-HER2 therapy with trastuzumab plus pertuzumab. Regimen distribution is summarised in Table 3.

Table 3. Neoadjuvant treatment regimens (n = 81).

Regimen component	Category	n (%)
Chemotherapy backbone	AC → Taxane	74 (91.4%)
	TC-based (non-anthracycline)	7 (8.6%)
Anti-HER2 therapy	Trastuzumab alone	69 (85.2%)
	Trastuzumab + pertuzumab	12 (14.8%)
Total cycles of anti-HER2 therapy (neoadjuvant)	Median (range)	6 (4–8)

Pathological response

At definitive surgery, pCR (ypT0/is ypN0) was achieved in 39 of 81 patients, corresponding to an overall pCR rate of 48.1% (95% confidence interval [CI] 37.0–59.4%). Analysis by HR status demonstrated a numerically lower pCR rate in HR-positive tumours at 41.7% (20/48) compared with 57.6% (19/33) in HR-negative tumours; the difference did not reach statistical significance ($p = 0.159$). When stratified by anti-HER2 strategy, the pCR rate was 40.6% (28/69) in patients receiving single-agent trastuzumab and 91.7% (11/12) in patients receiving dual anti-HER2 therapy with trastuzumab and pertuzumab, a highly statistically significant difference ($p = 0.001$). Pathological response outcomes are summarised in Tables 4 and 5.

Table 4. Pathological complete response by hormone receptor status.

Subgroup	pCR achieved n / N	pCR rate (%)	p value
Overall cohort	39 / 81	48.1	—
HR-positive	20 / 48	41.7	0.159
HR-negative	19 / 33	57.6	

Table 5. Pathological complete response by anti-HER2 therapy received.

Anti-HER2 therapy	n	pCR achieved (n)	pCR rate (%)	p value
Trastuzumab alone	69	28	40.6	0.001
Trastuzumab + pertuzumab	12	11	91.7	
Total	81	39	48.1	—

Further descriptive analysis suggested that pCR rates were consistent with expectations across major clinicopathological subgroups. Patients with grade III tumours had numerically higher pCR rates than patients with grade II tumours. Node-positive and node-negative subsets demonstrated comparable pCR rates within each anti-HER2 strategy, with a preserved incremental benefit of dual anti-HER2 blockade in each subgroup.

Safety and tolerability

The neoadjuvant regimens were generally well tolerated across the cohort. There were no treatment-related deaths and no episodes of symptomatic congestive heart failure. One patient (1.2%) experienced an asymptomatic decline in LVEF meeting protocol criteria for a cardiac event, which recovered on temporary interruption of anti-HER2 therapy without permanent discontinuation. Diarrhoea was the most common adverse event, reported in 20 patients (24.7%), and was predominantly grade 1–2 and manageable with loperamide and supportive care; no patient discontinued anti-HER2 therapy for diarrhoea. Fatigue was reported by 13 patients (16.0%), nausea by 12 (14.8%), and mucositis by 10 (12.4%). Peripheral neuropathy, alopecia, and haematological toxicity attributable to chemotherapy were reported at rates consistent with those expected for anthracycline–taxane regimens. Adverse events are summarised in Table 6.

Table 6. Treatment-related adverse events during neoadjuvant therapy (n = 81).

Adverse event	Any grade n (%)	Grade ≥ 3 n (%)
Diarrhoea	20 (24.7)	2 (2.5)
Fatigue	13 (16.0)	1 (1.2)
Nausea	12 (14.8)	0 (0.0)
Mucositis / stomatitis	10 (12.4)	1 (1.2)
Asymptomatic LVEF decline	1 (1.2)	0 (0.0)
Symptomatic heart failure	0 (0.0)	0 (0.0)
Peripheral neuropathy	9 (11.1)	0 (0.0)
Febrile neutropenia	4 (4.9)	4 (4.9)

DISCUSSION

This real-world analysis of 81 patients with HER2-positive early breast cancer treated at a tertiary cancer centre in India demonstrated an overall pCR rate of 48.1% with neoadjuvant HER2-directed therapy plus chemotherapy. This figure aligns closely with the pCR rates reported from pivotal randomised controlled trials in HER2-positive early breast cancer. In the NeoSphere trial, the pCR rate with the standard combination of trastuzumab and docetaxel was 29.0%, and rose to 45.8% with the addition of pertuzumab.9 In the TRYPHAENA cardiac safety trial, pCR rates with pertuzumab plus trastuzumab combined with anthracycline-containing or anthracycline-free backbones ranged from 57.3% to 66.2%.11 In the BERENICE trial, pCR rates were 61.8% and 60.7% in the two anthracycline-based cohorts.12 The observed overall pCR of 48.1% in the current unselected real-world cohort, in which only 14.8% of patients received dual anti-HER2 therapy, therefore compares favourably with these benchmarks.

The most striking finding of the present study was the pCR rate of 91.7% (11/12) in patients receiving dual anti-HER2 therapy compared with 40.6% (28/69) in patients receiving single-agent trastuzumab (p = 0.001). This magnitude of incremental benefit numerically exceeds that reported in NeoSphere, in which the addition of pertuzumab increased pCR from 29.0% to 45.8%,9 and is broadly consistent with the upper end of pCR rates seen in TRYPHAENA and BERENICE.11, 12 Several considerations tempered interpretation of this observation. First, the dual-therapy subgroup was small (n = 12), and small numbers may yield high-response point estimates with wide confidence intervals. Second, allocation to dual anti-HER2 therapy in a real-world setting is not randomised and may reflect selection for patients considered candidates for aggressive up-front therapy or those with financial access to pertuzumab. Nevertheless, the direction and magnitude of the association is consistent with the established biological rationale for dual HER2 blockade and with pooled trial-level evidence.9, 11, 12 The 5-year follow-up of NeoSphere further reinforces that dual anti-HER2 therapy in the neoadjuvant setting is associated with durable improvements in progression-free and disease-free survival, and confirms the prognostic utility of pCR.10

The absence of a statistically significant difference in pCR between HR-positive (41.7%) and HR-negative (57.6%) tumours in the present cohort ($p = 0.159$) is consistent with the direction of effect observed in pivotal HER2 trials and in the CTNeoBC pooled analysis, in which HR-negative HER2-positive tumours consistently exhibited higher chemosensitivity than HR-positive HER2-positive tumours.7 Notably, the CTNeoBC analysis demonstrated the strongest prognostic value of pCR in HR-negative HER2-positive tumours receiving trastuzumab (HR for event-free survival 0.15).7 The narrower differential observed in this cohort may reflect the modest sample size, subgroup heterogeneity, and the use of contemporary integrated regimens. In the large Indian real-world series from the Tata Memorial Centre reported by Joshi and colleagues, the overall pCR rate was 22.4%, with markedly higher rates in the HR-negative HER2-positive subgroup (35.4%) than in the HR-positive HER2-positive subgroup (15.6%).15 The higher pCR rates observed in the present cohort likely reflect the more consistent integration of HER2-directed therapy—received by all patients here compared with only 58.5% of HER2-positive patients in the Joshi series—together with more contemporary practice.15

Cardiac safety is a critical consideration for any HER2-directed therapy programme, particularly when combined with anthracyclines. In this cohort, no patient developed symptomatic congestive heart failure and only one patient (1.2%) had an asymptomatic decline in LVEF meeting protocol criteria for a cardiac event, which recovered on brief interruption of anti-HER2 therapy. These outcomes are consistent with, and in some respects more favourable than, the cardiac safety profile reported from randomised trials. In NOAH, only 2% of patients developed symptomatic cardiac failure despite concurrent anthracyclines,8 and in TRYPHAENA, symptomatic left ventricular systolic dysfunction was observed in 0–2.7% of patients across arms.11 The BERENICE study reported symptomatic heart failure in 1.5% of patients in the dose-dense anthracycline cohort.12 In the APHINITY adjuvant trial, cardiac death, cardiac dysfunction, and heart failure were infrequent in both the pertuzumab and placebo arms.13 The low incidence of cardiac events in the present cohort supports the safety of contemporary HER2-directed therapy when administered with structured baseline and on-treatment cardiac monitoring.

Diarrhoea was the most common non-haematological adverse event (24.7%), predominantly low-grade and manageable with supportive care. This finding is consistent with adjuvant and neoadjuvant experience. In APHINITY, grade ≥3 diarrhoea occurred in 9.8% of patients receiving pertuzumab compared with 3.7% receiving placebo, and was concentrated during the chemotherapy phase.13 The relatively modest grade ≥3 diarrhoea rate observed in the current cohort likely reflects the low proportion of patients receiving pertuzumab. Fatigue, nausea, and mucositis rates were also within expected ranges for anthracycline–taxane–trastuzumab regimens.

The importance of achieving pCR—especially in the HER2-positive early breast cancer setting—has been further reinforced by the KATHERINE trial, in which patients with residual invasive disease after neoadjuvant taxane- and trastuzumab-based therapy who received adjuvant trastuzumab emtansine had a 50% reduction in the risk of an invasive disease event or death compared with continued adjuvant trastuzumab (HR 0.50; $p<0.001$).14 Consequently, maximising pCR through effective neoadjuvant HER2-directed therapy is not simply a surrogate endpoint but a treatment-decision node that directly influences subsequent adjuvant escalation. The findings of the present study, which demonstrate high pCR rates achievable with routine use of dual anti-HER2 therapy in real-world Indian practice, therefore have direct clinical implications for treatment planning and access decisions.

Several limitations should be acknowledged. First, this was a single-centre retrospective analysis, and the modest sample size, particularly in the dual anti-HER2 subgroup ($n = 12$), limits the precision of subgroup comparisons and raises the possibility of selection bias. Second, allocation to dual versus single anti-HER2 therapy was non-random and influenced by factors including drug availability, financial access, and clinician discretion. Third, long-term survival endpoints such as event-free survival and overall survival were not evaluated because of the short duration of follow-up during the study window. Fourth, detailed molecular subtyping (PAM50 intrinsic subtype), Ki-67 quantitation, and tumour-infiltrating lymphocyte scoring were not routinely available. Fifth, dose reductions, delays, and treatment discontinuations were not analysed in detail. Despite these limitations, the study offers valuable contemporary real-world evidence from an Indian tertiary cancer centre. Strengths include the consecutive inclusion of eligible patients, comprehensive documentation of clinicopathological and treatment variables, standardised pathological response assessment, and structured cardiac monitoring.

CONCLUSION

In this real-world cohort of 81 patients with HER2-positive early breast cancer treated at a tertiary cancer centre in India, neoadjuvant chemotherapy combined with trastuzumab, with or without pertuzumab, achieved an overall pathological complete response rate of 48.1%, comparable to rates reported in pivotal randomised controlled trials. A substantially higher pCR rate was observed with dual anti-HER2 therapy (91.7%) compared with single-agent trastuzumab (40.6%; $p = 0.001$), reaffirming the incremental clinical benefit of pertuzumab in the neoadjuvant setting. Hormone receptor-negative tumours exhibited numerically higher pCR rates than hormone receptor-positive tumours, but the difference did not reach statistical significance. Cardiac and overall tolerability was favourable, with no symptomatic heart failure and only a single asymptomatic LVEF decline. These findings support the routine integration of dual anti-HER2 therapy into neoadjuvant treatment for eligible patients with HER2-positive early breast cancer in real-world Indian practice and highlight the need for broader access to pertuzumab. Larger, prospective, multi-centre studies with extended follow-up are warranted to confirm these observations and to refine patient selection for dual anti-HER2 neoadjuvant therapy.

Declarations

Ethics approval and consent to participate

This retrospective study was reviewed and approved by the Institutional Ethics Committee of the participating institution. Because of the retrospective nature of the analysis using de-identified data, a waiver of individual informed consent was granted.

Consent for publication
Not applicable.

Availability of data and materials
The datasets analysed during the current study are available from the corresponding author on reasonable request, subject to institutional data-sharing policies.

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
All authors contributed to the conception and design of the study, data acquisition, analysis and interpretation, drafting of the manuscript, and critical revision for important intellectual content. All authors read and approved the final manuscript.

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REFERENCES
1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209–249. doi:10.3322/caac.21660.
2. Malvia S, Bagadi SA, Dubey US, Saxena S. Epidemiology of breast cancer in Indian women. Asia Pac J Clin Oncol. 2017;13(4):289–295. doi:10.1111/ajco.12661.
3. 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):783–792. doi:10.1056/NEJM200103153441101.
4. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353(16):1659–1672. doi:10.1056/NEJMoa052306.
5. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Trastuzumab for early-stage, HER2-positive breast cancer: a meta-analysis of 13 864 women in seven randomised trials. Lancet Oncol. 2021;22(8):1139–1150. doi:10.1016/S1470-2045(21)00288-6.
6. Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. Arch Pathol Lab Med. 2018;142(11):1364–1382. doi:10.5858/arpa.2018-0902-SA.
7. 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):164–172. doi:10.1016/S0140-6736(13)62422-8.
8. Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A, Tjulandin S, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet. 2010;375(9712):377–384. doi:10.1016/S0140-6736(09)61964-4.
9. 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. doi:10.1016/S1470-2045(11)70336-9.
10. Gianni L, Pienkowski T, Im YH, Tseng LM, Liu MC, Lluch A, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol. 2016;17(6):791–800. doi:10.1016/S1470-2045(16)00163-7.
11. 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):2278–2284. doi:10.1093/annonc/mdt182.
12. 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):646–653. doi:10.1093/annonc/mdx773.
13. 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):122–131. doi:10.1056/NEJMoa1703643.
14. von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019;380(7):617–628. doi:10.1056/NEJMoa1814017.
15. Joshi S, Chougle Q, Noronha J, Hawaldar R, Nair N, Vanmali V, et al. Determinants of pathological complete response to neoadjuvant chemotherapy in breast cancer: A single-institution experience. Indian J Cancer. 2024;61(2):324–331. doi:10.4103/ijc.IJC_813_20.