

# Pathologic Complete Response in HER2-Positive Breast Cancer Patients Receiving Trastuzumab in Neoadjuvant Setting

Fareeha Sheikh<sup>1</sup>, Adil Nazir<sup>1</sup>, Samia Yasmeen<sup>1</sup>, Farhana Badar<sup>2</sup>, Usman Ahmad<sup>1</sup> and Neelam Siddiqui<sup>1</sup>

## ABSTRACT

**Objective:** To compare the pathological complete response in human epidermal growth factor receptor type 2 (HER-2) positive breast cancer patients getting neoadjuvant chemotherapy with or without trastuzumab.

**Study Design:** Retrospective randomised double-arm observational study.

**Place and Duration of Study:** Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, from 2008 to 2016.

**Methodology:** HER2-positive, lymph node positive, breast cancer patients receiving neoadjuvant chemotherapy (NACT) were retrospectively observed. Patients getting neoadjuvant trastuzumab, fulfilling the inclusion criteria were studied. The comparison group included randomly selected equal number of HER2-positive breast cancer patients having similar tumor characteristics, getting NACT only. Pathological complete response (pCR) was defined as no residual invasive or *in situ* residual tumor in breast tissue, or in the lymph nodes. One hundred and fifty-six patients were studied. Eighty-nine patients with HER2-positive disease received trastuzumab preoperatively. Sixty-four (n=64) patients received the complete standard dose of neoadjuvant trastuzumab along with chemotherapy. Almost equal number of patients (n=67) with HER2-positive disease were selected by random assortment for the reference group who did not receive trastuzumab before surgery.

**Results:** The pathological complete response of study group was (n=32) 50%, which was 26.1% higher than the reference group (n=16) 23.9%; and this difference was statistically significant with a p-value of 0.002 (<0.05). The overall pCR was 36.6% (n=48).

**Conclusion:** Addition of trastuzumab to neoadjuvant chemotherapy doubled the pCR in HER2-positive breast cancer. Targeted therapy should be offered to all eligible patients with HER2-overexpressing breast cancer.

**Key Words:** HER-2, Trastuzumab, Pathological complete response, Neoadjuvant chemotherapy.

## INTRODUCTION

The human epidermal growth factor receptor 2 (HER2), previously called HER2/Neu or ERBB-2, belongs to the epidermal growth factor receptor (EGFR) family. These receptors are crucial for the activation of sub-cellular signal transduction pathways controlling epithelial cell growth and differentiation and possibly angiogenesis.<sup>1</sup> About 15-30% of all invasive breast cancers are HER2-positive (overexpressing).<sup>2,3</sup> Several studies have suggested that HER2-positive tumors are associated with aggressive disease, poor prognosis and have a higher risk of relapse than HER2-negative cancers.<sup>4-7</sup>

Addition of trastuzumab to adjuvant chemotherapy results in durable survival benefits for patients with

HER2-positive breast cancer. This was shown in the combined analysis of the North Central Cancer Treatment Group (NCCTG) N9831 trial and the National Adjuvant Breast and Bowel Project (NSABP) B-31 clinical trials.<sup>8</sup> With a median on-study time of 8.4 years, the addition of trastuzumab resulted in a 37% improvement in the overall survival (OS) and a 40% improvement in disease-free survival. The first data for neoadjuvant trastuzumab came from a single centre, randomised study, which showed almost double pCR.<sup>9</sup>

The patients who achieved pCR after neoadjuvant treatment have a better long-term outcome.<sup>10,12</sup> In a meta-analysis of 36 trials enrolling nearly 5800 patients with HER2-positive disease receiving neoadjuvant therapy, those who achieved a pCR (including breast and axilla) had superior event-free survival (EFS) and OS compared with those who did not.<sup>11</sup> Consequently, increasing the rate of pCR became the endpoint of neoadjuvant trials with the expectation of translation into improved survival. Based on these results, FDA has given accelerated approval to drugs in neoadjuvant setting.<sup>11,13</sup>

Limited data is available regarding response of trastuzumab in Pakistani population, as majority of the patient population cannot get it due to cost issues.

<sup>1</sup> Department of Medical Oncology, Shaukat Khanum Memorial Cancer Hospital, Lahore, Pakistan

<sup>2</sup> Department of Biostatistics and Epidemiology, Shaukat Khanum Memorial Cancer Hospital, Lahore, Pakistan

Correspondence: Dr. Fareeha Sheikh, Department of Medical Oncology, Shaukat Khanum Memorial Cancer Hospital, 7A Block R-3 M.A., Johar Town, Lahore, Pakistan  
E-mail: fareeha8808@gmail.com

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The purpose of this study was to determine the effectiveness of trastuzumab in the local population having HER-2 overexpression, so that it can be used as a reference for future studies.

### METHODOLOGY

The study was a retrospective, observational double-arm study. All patients receiving trastuzumab in neoadjuvant setting at Shaukat Khanum Memorial Cancer Hospital from 2008 to August 2016, fulfilling the inclusion criteria, were observed. The study protocols were reviewed by the Institutional Review Board and exemption was taken for informed consent as no direct interaction with patients was involved. Medical records were reviewed from the computer based hospital information system. The pre-aimed primary endpoint was to compare the pCR in HER-2 overexpressing breast cancer patients getting NACT with or without trastuzumab. The secondary endpoints were to study the frequency of breast conservation in patients getting trastuzumab preoperatively along with chemotherapy irrespective of the PCR; and added toxicities and influence of other baseline characteristics. Locally advanced HER2-positive breast cancer patients with cytologically proven axillary nodes receiving standard NACT with or without trastuzumab were studied.

All patients had been tested for HER2-overexpression according to algorithms, developed by a joint consensus panel convened by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP). Patients were eligible for neoadjuvant trastuzumab, if they had HER2-positive breast cancer defined as immunohistochemical (IHC) stain of 3+ or FISH positive. The comparison group (n=67) included randomly selected equal number of HER2-positive breast cancer patients having similar tumor characteristics, getting neoadjuvant chemotherapy without trastuzumab.

A normal cardiac function had been documented at baseline by echocardiography; and cardiology opinion was taken for borderline cases before administration of trastuzumab, as it has a documented side effect of cardiotoxicity. Patients received four cycles of trastuzumab 6mg/kg intravenously every 3 weeks, starting from a loading dose of 8mg/kg in the first cycle or 12 doses of 2mg/kg weekly with a loading dose of 4mg/kg in the first cycle concomitantly with taxane-based therapy. Pathological complete response (pCR) was defined as no residual invasive or *in situ* residual tumor in breast tissue, or in the lymph nodes.<sup>14</sup> Toxicities were assessed according to National Cancer Institute Common Terminology Criteria version 4.0. Lumpectomy or quadrantectomy and segmentectomy were stated as breast conservation procedures.

Data was collected through the computer-based Hospital Information System (HIS). Statistical analysis

was performed by using SPSS version 20. For categorical variables, percentages (proportions) were reported as shown in Table I and II. Bivariate analysis was done using Chi-square or Fisher exact test, wherever appropriate, to establish the association between two categorical variables with  $p < 0.05$  considered as statistically significant. Univariable analysis was done to establish the relationship of one explanatory variable at a time with the outcome variable. The odds ratio, confidence interval, and p-value were calculated for each variable and reported in Table III column 4. In the multivariable analysis, statistical analysis was done by using step-wise regression method. All the factors with  $p < 0.05$  were considered statistically significant independent risk factors affecting pathological complete response. The odds ratio, confidence interval, and p-value were calculated for each variable and reported in Table III column 5.

### RESULTS

During the study period, 89 patients with HER2-positive disease received trastuzumab preoperatively. Twenty patients (22.5%) could not get the complete planned cycles of trastuzumab preoperatively due to financial

**Table I:** Baseline characteristics of patients with HER2-positive tumors treated with trastuzumab and a reference group of patients with HER2-positive tumors treated without trastuzumab.

Characteristics	Chemotherapy without trastuzumab (n=67, 51.2%)	Chemotherapy with trastuzumab (n=64, 48.8%)
Age, years		
≤40	25 (37.3%)	19 (30.2%)
41-50	24 (35.8%)	19 (30.2%)
51-60	15 (22.4%)	20 (31.7%)
Above 60	3 (4.5%)	5 (7.9%)
Clinical tumor stage		
cT1	1 (1.49%)	0 (0.00%)
cT2	33 (49.25%)	41 (64.06%)
cT3	10 (14.93%)	7 (10.94%)
cT4	22 (32.84%)	15 (23.44%)
cTx	1 (1.49%)	1 (1.56%)
Stage		
II A + B	39 (58.2%)	45 (72.6%)
III A	13 (19.4%)	8 (12.9%)
III B	12 (17.9%)	9 (14.5%)
III C	3 (4.5%)	0 (0%)
Tumor grade		
2	23 (34.3%)	29 (45.3%)
3	44 (65.7%)	35 (54.7%)
Tumor histology		
Ductal invasive	59 (88.06)	57 (89.06%)
Lobular invasive	1 (1.49%)	1 (1.56%)
Others	7 (10.45%)	6 (9.38%)
ER/PgR status		
ER negative/PgR negative	41 (61.2%)	24 (37.5%)
ER positive/PgR positive	16 (23.9%)	27 (42.2%)
ER positive/PgR negative	10 (14.9%)	11 (17.2%)
ER negative/PgR positive	0.00 (0.00)	2 (3.1%)

**Table II:** National Cancer Institute common toxicity criteria (version 4.0). Grading of adverse events of patients receiving neoadjuvant chemotherapy with or without trastuzumab.

Symptom	Grading	Chemotherapy without trastuzumab (n=67, 51.2%)	Chemotherapy with trastuzumab (n=64, 48.8%)
Mucositis	No mucositis	40 (59.7%)	29 (45.3%)
	Grade 1	12 (17.9%)	13 (20.3%)
	Grade 2	13 (19.4%)	20 (31.2%)
	Grade 3	2 (3%)	2 (3.2%)
	Grade 4	0 (0.0%)	0 (0.0%)
Diarrhea	No diarrhea	54 (80.6%)	50 (78.1%)
	Grade 1	2 (3%)	5 (7.8%)
	Grade 2	11 (16.4%)	7 (10.9%)
	Grade 3	0 (0.0%)	2 (3.2%)
	Grade 4	0 (0.0%)	0 (0.0%)
Vomiting	No vomiting	44 (65.7%)	50 (78.1%)
	Grade 1	17 (25.3%)	4 (6.3%)
	Grade 2	6 (9.0%)	10 (15.6%)
	Grade 3	0 (0.0%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)
Rash	No rash	59 (88.1%)	60 (93.7%)
	Grade 1	6 (8.9%)	1 (1.6%)
	Grade 2	1 (1.5%)	2 (3.1%)
	Grade 3	1 (1.5%)	1 (1.6%)
	Grade 4	0 (0.0%)	0 (0.0%)
Neuropathy	No neuropathy	53 (79.1%)	43 (67.2%)
	Grade 1	12 (17.9%)	12 (18.7%)
	Grade 2	2 (3.0%)	5 (7.8%)
	Grade 3	0 (0.0%)	4 (6.3%)
	Grade 4	0 (0.0%)	0 (0.0%)
Drop in EF*	No Drop in EF*	60 (89.5%)	62 (96.9%)
	Grade 1	4 (6.0%)	0 (0.0%)
	Grade 2	2 (3.0%)	2 (3.1%)
	Grade 3	1 (1.5%)	0 (0.0%)
	Grade 4	0 (0.0%)	0 (0.0%)
Febrile neutropenia	No Febrile Neutropenia	54 (80.6%)	55 (85.9%)
	Grade 1	0 (0.0%)	0 (0.0%)
	Grade 2	0 (0.0%)	0 (0.0%)
	Grade 3	13 (19.4%)	9 (14.1%)
	Grade 4	0 (0.0%)	0 (0.0%)

reasons or delayed approval while surgery could not be done in one (1.12%) patient due to disease progression while on therapy. Four (4.5%) patients had to undergo surgery earlier due to poor tolerance of chemotherapy. The study group, therefore, comprised 64 (n=64) patients who received full dose of neoadjuvant trastuzumab.

The overall pCR in entire population was (n=48) 36.6%. The pCR of the patients who received trastuzumab in the neoadjuvant setting was (n=32) 50%, which was 26.1% higher than the reference group (n=16) 23.9%. This difference was statistically significant with a p-value of 0.002 (<0.05). Breast conservation was possible in 57 (43.51%) patients in total and 51.56% in patients getting trastuzumab preoperatively as compared to 35.82% in patients who received chemotherapy alone. P-value was calculated as 0.69 which although was not statistically

significant, but still a considerable number of patients had a less extensive surgery.

Toxicities were documented according to National Cancer Institute Common Toxicity Criteria (version 4.0) grading of adverse events by reviewing the records in the computer-based Hospital Information System. By adding trastuzumab, there were no major differences in the toxicity profiles of both groups as shown in Table II. The drop in ejection fraction, which is a major concern with the addition of trastuzumab, was also almost equal in both groups with no major differences. No patient developed symptomatic heart failure and none had to stop trastuzumab before completing the planned therapy.

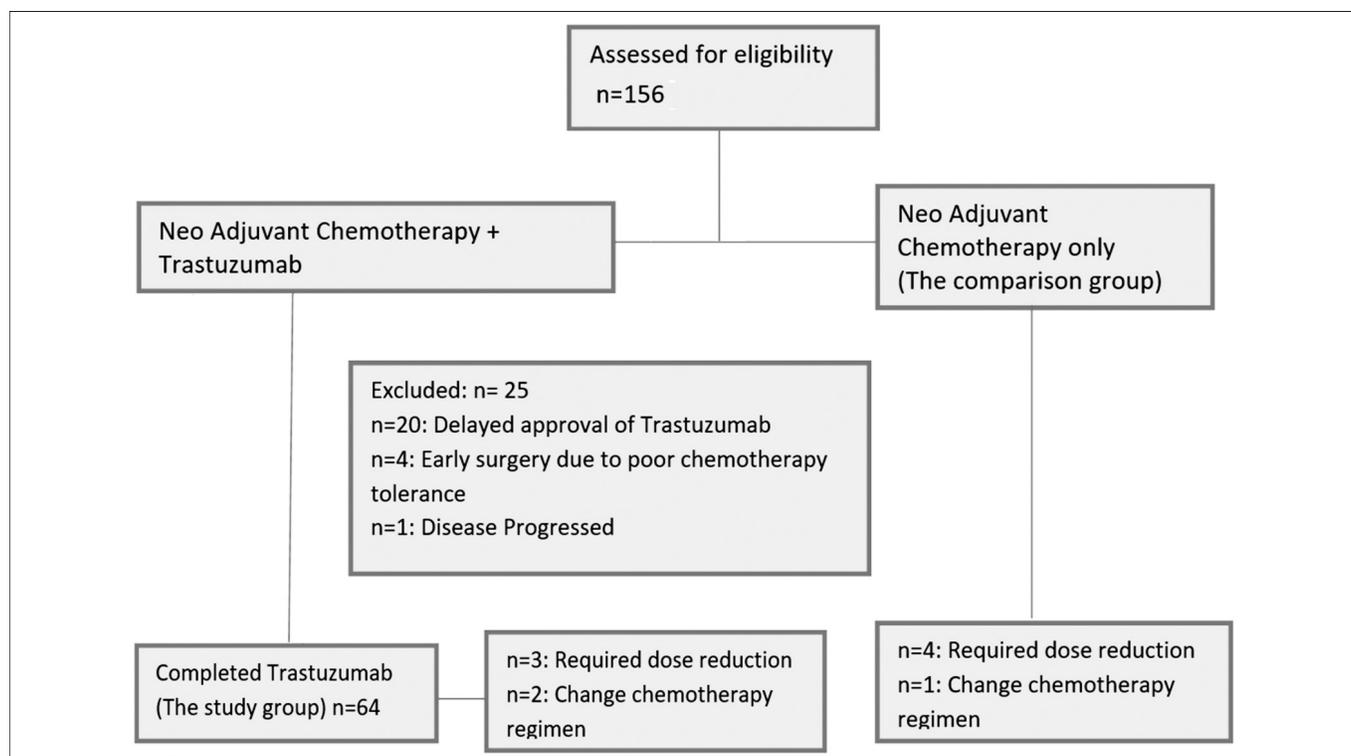
## DISCUSSION

This study demonstrated that HER2-positive (over-expressing) breast cancer patients, who received preoperative trastuzumab in combination with standard chemotherapeutic regimens, achieved significantly higher rates of pCR as compared to those who got chemotherapy alone. According to protocol pre-defined definition the pCR in entire patient population was 36.6%. Patients who received trastuzumab in the neoadjuvant setting had pCR of 50%, which was 26.1% higher than the reference group (23.9%), which is almost double in comparison. This response is significantly higher than the previously conducted international studies like GparQuattro study having a complete response rate of 31.7% in patients getting preoperative trastuzumab.<sup>15</sup> Similarly, trastuzumab in neoadjuvant setting in newly diagnosed locally advanced HER2-positive breast cancer patients has been studied in TECHNO trial which was a phase II single-arm study which showed a complete response rate of 39%.<sup>16</sup> The NOAH trial demonstrated a pCR rate of 43% in neoadjuvant trastuzumab combination group as compared to 22% in the chemotherapy alone group.<sup>17</sup> A recent study in the local population demonstrated the similar response rates of 54.8% comparable to this study population.<sup>18</sup>

Compared to all the above mentioned studies, this study has demonstrated a notably high pCR in these patients and can be future perspective for further studies. One possible reason for the better response can be the factor that all node-positive patients were included, depicting a better response in this high risk population. Although a single study at an individual centre with a small number of patients cannot be a true representative of the entire population, it definitely provides an insight for more studies so that possible causes of increased response in the local population can be studied. Different mechanisms of resistance to trastuzumab therapy have been studied including loss of PTEN and are thought to promote tumorigenesis by activating PI3K signalling

**Table III:** Factors associated with pCR in patients with HER2-positive tumors.

Factors	Category	Response		Univariable analysis odds ratio (95% CI), p-value	Multivariable variable analysis odds ratio (95% CI), p-value
		Yes	No		
		48 (36.6%)	83 (63.4%)		
Age in years	≤40	16 (33.3%)	28 (34.1%)	Ref	Ref
	41-50	12 (25.0)	31 (37.8%)	1.47 (0.59 3.64), 0.40	1.88 (0.65 5.41), 0.24
	51-60	16 (33.3)	19 (23.2%)	0.68 (0.27 1.68), 0.40	0.97 (0.34 2.76), 0.95
	Above 60	4 (8.3%)	4 (4.9%)	0.57 (0.12 2.60), 0.47	0.84 (0.13 5.25), 0.85
Histologic type	Lobular invasive	1 (2.1%)	1 (1.2%)	Ref	Ref
	Ductal invasive	42 (87.5%)	74 (89.2%)	1.76 (0.10 28.90), 0.69	1.24 (0.02 92.83), 0.92
	Others	5 (10.4%)	8 (9.6%)	1.60 (0.08 31.77), 0.76	0.79 (0.01 75.39), 0.92
Grading	Grade 2	20 (41.7%)	32 (38.6%)	Ref	Ref
	Grade 3	28 (58.3%)	51 (61.4%)	1.14 (0.55 2.35), 0.73	0.88 (0.37 2.09), 0.77
Stage	II A + B	26 (56.5%)	58 (69.9%)	Ref	Ref
	III A	6 (13.0%)	15 (18.1%)	1.12 (0.39 3.21), 0.83	1.18 (0.36 3.87), 0.78
	III B	14 (30.4%)	7 (8.4%)	0.22 (0.08 0.62), 0.004	0.16 (0.05 0.51), 0.002
	III C	0 (0.0%)	3 (3.6%)	NA	NA
ER/PgR status	ER negative/PgR negative	21 (43.8%)	44 (53.0%)	Ref	Ref
	ER positive/PgR positive	16 (33.3%)	27 (32.5%)	0.80 (0.36 1.81), 0.60	0.90 (0.35 2.33), 0.84
	ER positive/PgR negative	10 (20.8%)	11 (13.3%)	0.52 (0.19 1.43), 0.21	0.59 (0.19 1.82), 0.36
	ER negative/PgR positive	1 (2.1%)	1 (1.2%)	0.48 (0.03 8.01), 0.61	2.16 (0.09 54.66), 0.64
Neoadjuvant trastuzumab	No	16 (33.3%)	51 (61.4%)	Ref	Ref
	Yes	32 (66.7%)	32 (38.6%)	0.31 (0.15 0.66), 0.002	0.28 (0.11 0.67), 0.004



**Figure 1:** Consort diagram of patients.

pathway.<sup>19</sup> Since this study population has demonstrated a quite high response, studies are needed to look for genetic factors in our people which render our patients more susceptible to response to trastuzumab-based therapy like PTEN expression.<sup>20</sup> Although the study demonstrated a significantly higher pathological response in the neoadjuvant trastuzumab group, breast

conservation rate was not significantly different in both the patient groups, but less extensive surgery was possible in notable number of patients. Regarding toxicity profile, the addition of trastuzumab to standard chemotherapeutic regimens did not significantly increase the toxicity profile as compared to chemotherapy alone.

This study has several weaknesses. Firstly, it is a retrospective study, so all patients did not receive similar chemotherapeutic regimens. However, this was uniform for both study arms. It included a small number of patients; had it included a greater number of patients, results would have been more powerful. However, since all patients fulfilling the inclusion criteria were included, so there was no selection bias. Hence, results are likely depictive of response in our population.

## CONCLUSION

Combining trastuzumab with standard chemotherapy regimens in HER2-positive achieves significantly higher rate of pathological complete response without clinically significant increased toxicity. Further studies with larger number of patients are required to demonstrate mechanisms leading to better responses in this population and whether this increased response can be translated into increased survival rates.

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