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ORIGINAL RESEARCH

Dual Anti-HER2 Therapy Vs Trastuzumab Alone with Neoadjuvant Anthracycline and Taxane in HER2-Positive Early-Stage Breast Cancer: Real-World Insights

Baha Sharaf[1], Faris Tamimi[1], Haneen Al-Abdallat[2], Suhaib Khater[1], Osama Salama[1], Anas Zayed[1], Osama El Khatib[1], Assem Qaddoumi[1], Malek Horani[1], Yosra AL-Masri[1], Wafa Asha[1], Bayan Altalla'[1], Hira Bani Hani[1], Hikmat Abdel-Razeq[1,2]

[1]King Hussein Cancer Center, Amman, Jordan; [2]School of Medicine, The University of Jordan, Amman, Jordan

Correspondence: Hikmat Abdel-Razeq, Department of Internal Medicine, King Hussein Cancer Center, 202 Queen Rania Al Abdullah Street P.O. Box: 1269, Amman, 11941, Jordan, Tel +962-6 5300460, Ext: 1000, Email habdelrazeq@khcc.jo

Introduction: The integration of anti-HER2 targeted therapy with chemotherapy has demonstrated an increase in pathologic complete response rates (pCR) in patients with HER2-positive early-stage breast cancer (EBC). This study presents real-world data on the use of trastuzumab with or without pertuzumab, in combination with anthracycline and taxanes-based chemotherapy regimen.

Methods: We conducted a retrospective analysis of patients with HER2-positive EBC who underwent neoadjuvant chemotherapy (NACT), treated between January 2014 and September 2021. The regimen included four cycles of doxorubicin and cyclophosphamide (AC), followed by four cycles of docetaxel every three weeks, with anti-HER2 therapy administered alongside docetaxel. Outcomes assessed included pCR, 3-year disease-free survival (DFS), and surgical outcomes.

Results: During the study period, 484 consecutive patients with HER2-positive EBC, median age of 47 (range, 21–80) years, were enrolled. (64.7%) of patients received dual anti-HER2 therapy, while 35.3% received single-agent trastuzumab. The overall pCR rate was 44.2%, with a higher rate (55.6%) in hormone receptor (HR)-negative patients compared to HR-positive patients (39.8%), p=0.002. Although dual therapy resulted in a higher pCR rate (46.6%) compared to trastuzumab alone (39.8%), the difference was not statistically significant (p=0.15). The estimated 3-year DFS was 86.1% with dual therapy and 83.1% with trastuzumab alone (p=0.37). Further stratification revealed superior 3-year DFS in node-negative disease (96.4%) compared to node-positive disease (82.3%), p=0.0021. Patients who achieved pCR had a significantly better 3-year DFS (89.3%) compared to those with residual disease (82.2%), p=0.0177. Rate of breast conserving surgery (BCS) was lower (15.2%) among patients who received trastuzumab alone, compared to 26.5% among those who received dual anti-HER2 [Odds Ratio (OR)= 0.50, 95% Confidence Interval (CI), 0.30–0.80, p=0.005].

Conclusion: Dual anti-HER2 therapy did not significantly enhance DFS but was associated with higher BCS rates, highlighting its potential to improve surgical outcomes.

Keywords: dual anti-HER2 regimen, pertuzumab, trastuzumab, breast cancer, neoadjuvant

Introduction

Breast cancer continues to pose a significant global health burden, with 2.3 million new cases reported in 2020, constituting 11.7% of all newly diagnosed cancer cases. This malignancy resulted in approximately 685,000 deaths, emphasizing its profound impact.[1] Among these cases, 15–20% are characterized as human epidermal growth factor receptor (HER2)-positive.[2,3] HER2-positive breast cancer often carries a less favorable prognosis when compared to other subtypes.[4] However, it exhibits heightened sensitivity to cytotoxic chemotherapy, providing patients with an opportunity to achieve a pathologic complete response (pCR) through neoadjuvant chemotherapy (NACT).[5]

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Moreover, the combination of agents targeting HER2-activated signaling pathways has shown promise in improving chemosensitivity, leading to an increased rate of pCR.[6]

Improving pathological complete response (pCR) is a critical endpoint in HER2-positive early breast cancer (EBC) because it serves as a robust surrogate marker for long-term outcomes, including survival and recurrence rates. Achieving pCR is associated with significantly better disease-free survival (DFS) and overall survival (OS), particularly in aggressive subtypes such as HER2-positive and triple-negative breast cancer.[7] pCR reflects the effectiveness of neoadjuvant therapy in eradicating tumor burden, reducing the risk of residual disease and distant metastases, which are key factors influencing recurrence and mortality.

Various clinical trials have validated the effectiveness of HER2-targeted therapies, either alone or in combination, highlighting the enhanced responsiveness of HER2-positive breast cancer to tailored neoadjuvant therapy.[8,9]

Trastuzumab is a humanized monoclonal antibody directed against the extracellular domain of HER2.[10] The addition of trastuzumab to NACT resulted in a significant improvement in the pCR rate in HER2-positive breast cancer patients in addition to the improvement in disease-free survival (DFS) and overall survival (OS).[8,9] Hence, trastuzumab stands as a pivotal element in neoadjuvant therapy for HER2-positive early-stage breast cancer (EBC) patients.

Following trastuzumab, multiple HER2-targeting agents, such as pertuzumab, have gained approval, contributing to enhanced efficacy when combined with trastuzumab. Pertuzumab functions by binding to HER2 at a distinct site, thereby preventing HER2 dimerization with other members of the HER family. The approval of pertuzumab for use in conjunction with trastuzumab and docetaxel in neoadjuvant therapy primarily emanated from the Phase II NEOSPHERE trial, with pCR approaching 45.8% with improvements in DFS, too.[11]

After standard neoadjuvant therapy, the adjuvant treatment strategy can now be tailored based on the achievement of pCR. For patients attaining pCR, the adjuvant anti-HER2 therapy involves administering trastuzumab for the remainder of the one-year total anti-HER2 therapy. Despite achieving pCR, there remains a residual risk of recurrence, especially in individuals with a high tumor burden at the time of diagnosis, as evidenced by a pooled analysis conducted by the German Breast Group (GBG).[12]

Data extrapolated from the adjuvant APHINITY trial suggests that the ongoing use of pertuzumab in the adjuvant setting is particularly beneficial for patients with node-positive disease. After a median follow-up of 74 months, in the node-positive cohort, the 6-year invasive DFS (iDFS) rates were 88% for the pertuzumab arm compared to 83%, for the placebo arm, with an HR of 0.72 (95% CI, 0.59–0.87). No discernible benefit was noted in cases of node-negative (N0) disease. The pertuzumab-associated benefit was found to be independent of hormone receptor (HR) status.[13] However, when considering the results from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis and the APHINITY trial, which includes two follow-up durations,[13,14] it becomes evident that extended follow-up is crucial in HER2+ early breast cancer, particularly for comprehensively capturing the therapeutic benefits, especially in the HR-positive subgroup. The KATHERINE trial introduced a strategy for patients with residual disease, switching them to Trastuzumab emtansine (T-DM1), resulting in a remarkable 11% improvement in DFS. Notably, only 18.7% of patients received dual anti-HER2 therapy (trastuzumab/pertuzumab), while the majority (80.2%) received trastuzumab as a single agent.[15]

While clinical trials provide valuable insights, their applicability to broader patient populations may not fully encompass the diversity encountered in routine practice due to strict eligibility criteria and controlled environments. These factors often exclude patients with comorbidities or those with characteristics outside the trial's parameters, potentially limiting the generalizability of findings. Real-world data, derived from diverse clinical settings, are essential for validating the efficacy and safety of interventions, offering a more comprehensive understanding of their impact across heterogeneous patient populations.

In this study, we aim to compare pCR with single anti HER2 therapy (trastuzumab) versus dual anti HER2 therapy (trastuzumab and pertuzumab) and its relation to DFS and breast-conserving surgery (BCS) rate in patients receiving chemotherapy with anthracycline and taxanes, based on the National Surgical Adjuvant Breast and Bowel Project (NSABP)-B27 protocol, and to determine if these treatment outcomes differ according to baseline patients' characteristics in a real-world setting.

Materials and Methods

Study Population and Design

This is a retrospective study that included all consecutive adult female patients (18 years or older) diagnosed with HER2-positive breast cancer who received neoadjuvant therapy at our institution. We included patients with pathologically confirmed cases and comprehensive medical records, which encompassed treatment regimens and follow-up data. HER2 was defined positive as IHC+3 or IHC+2 with positive Fluorescence in Situ Hybridization (FISH), adhering to the guidelines set forth by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) for HER2 testing in breast cancer. Figure 1 illustrates patients' flow. Patients with missing or insufficient data on anti-HER2 therapy regimens, dosages, or treatment durations were excluded. Additionally, patients who switched between trastuzumab monotherapy and dual anti-HER2 therapy during the treatment period and those with concurrent malignancies were excluded, too.

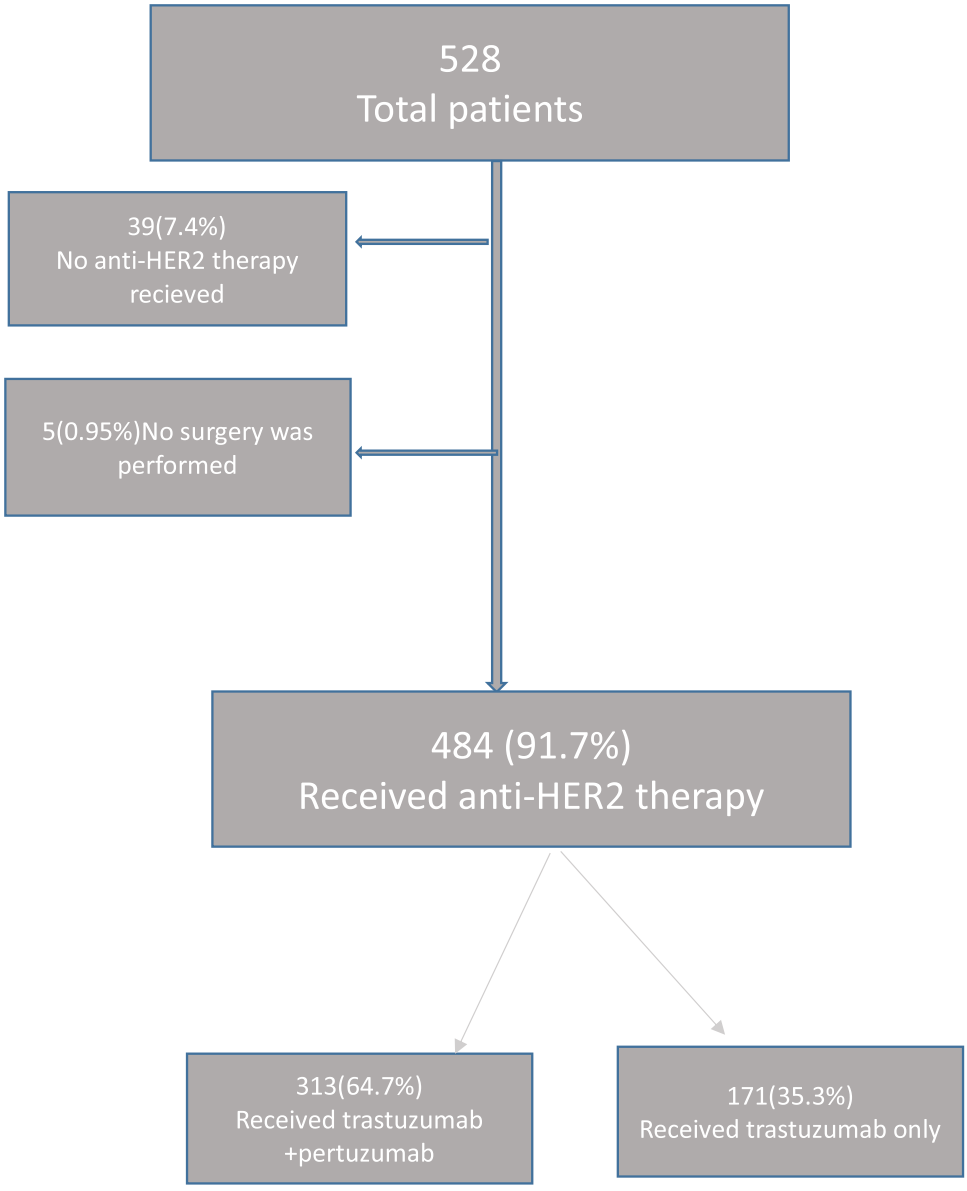

Figure 1 Flow diagram of patients included in the study.

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Overall survival (OS) was defined as the duration from the initial histological diagnosis of breast cancer to death from any cause or the last recorded medical encounter. Disease-free survival (DFS) was defined as the time from the date of surgery to either the occurrence of relapse or death, whichever came first.

Data Collection

We extracted data concerning patient demographics, clinical characteristics, and treatment regimens from medical records. This included details such as age at diagnosis, prior history of breast cancer, HR status (including estrogen and progesterone receptors), HER2 status by IHC, lymph node involvement at diagnosis, and the type of anti-HER2 therapies administered (either trastuzumab alone or in combination with pertuzumab). We compared the two treatment groups using chi-square tests for categorical variables and independent t-tests for continuous variables where applicable.

Disease-Free Survival Analysis

Disease-free survival (DFS) was defined as the time from surgery until recurrence of breast cancer or death from any cause. To identify factors affecting DFS, we conducted univariable and multivariable Cox proportional hazards regression analyses. The included variables are previous diagnosis of breast cancer, tumor grade, lymphovascular invasion, HR status, HER2 status by IHC, tumor size, lymph node involvement, treatment response, and the type of anti-HER2 treatment. Variables significant in the univariable analysis were included in the multivariable model to adjust for potential confounders and identify independent predictors of DFS.

DFS rates were estimated using the Kaplan–Meier method, with differences between groups assessed using the Log rank test.

Analysis of Surgical Outcomes

To identify predictors influencing the type of surgery, both univariable and multivariable logistic regression models were employed. Variables included age at diagnosis, previous breast cancer history, HR status, HER2 status assessed by IHC, tumor size and lymph node involvement at diagnosis, and anti-HER2 therapies received.

Analysis of Response to Neoadjuvant Treatment Analysis

The response to neoadjuvant treatment, categorized into pCR or residual disease (RD), was analyzed as the dependent variable. Factors considered in the analysis included tumor size, HR status, lymph node involvement, type of anti-HER2 therapy, and HER2 expression by IHC. Similar to the surgical decision analysis, we first conducted univariable logistic regression for each factor to evaluate its association with treatment response. Factors showing significance were then included in a multivariable logistic regression model to determine their independent effects on achieving a pCR versus RD.

For both analyses, odds ratios (OR) with 95% confidence intervals (CI) were calculated. Statistical significance was set at a p-value of <0.05. All statistical analyses were performed using jamovi (The jamovi project, 2022, Version 2.3) and R (R Core Team, 2021, Version 4.1), with R packages retrieved from the MRAN snapshot dated 2022–01-01.

Results

Patient Characteristics

Our study encompassed 484 patients with a median age of 47 (21–80) years and a median follow-up of 35.3 (range, 7.0–94.0) months, of whom a minor portion (n=17, 3.5%) had a previous diagnosis of breast cancer. The majority were HR-positive (n=349, 72.1%), and a significant proportion (n=372, 76.9%) had lymph nodes involvement prior to neoadjuvant therapy. Analysis of neoadjuvant regimens revealed that 171 (35.3%) patients received trastuzumab, while 313 (64.7%) others were given pertuzumab in combination with trastuzumab. Patient characteristics indicate a significant difference in age (48 years vs 46 years, p=0.023), and lymph node involvement (71.9% vs 86%, p=0.001) between the dual anti-HER2 therapy group and the trastuzumab alone group, Table 1.

Table 1 Patient Characteristics by Anti-HER2 Treatment Group

Variable	Total (484)	Trastuzumab + Pertuzumab (313)	Trastuzumab (171)	p-value
Median age (years) (IQR)	47.0 (38.0 to 54.0)	48.0 (39.0 to 55.0)	46.0 (35.5 to 53.5)	0.023
Previous history of breast cancer	17 (3.5%)	11 (3.5%)	6 (3.5%)	1.0
Histology				
IDC	474 (97.9%)	309 (98.7%)	165 (96.5%)	0.222
ILC	6 (1.2%)	2 (0.6%)	4 (2.3%)	
Other	4 (0.8%)	2 (0.6%)	2 (1.2%)	
Grade				
1	4 (0.8%)	4 (1.3%)	0 (0.0%)	0.521
2	185 (38.2%)	118 (37.7%)	67 (39.2%)	
3	292 (60.3%)	189 (60.4%)	103 (60.2%)	
NR	3 (0.6%)	2 (0.6%)	1 (0.6%)	
Lympho-vascular Invasion				
Not present	275 (56.8%)	187 (59.7%)	88 (51.5%)	0.093
Present	187 (38.6%)	110 (35.1%)	77 (45.0%)	
NR	22 (4.5%)	16 (5.1%)	6 (3.5%)	
Hormone Receptor (HR)				
Positive	349 (72.1%)	228 (72.8%)	121 (70.8%)	0.702
Negative	135 (27.9%)	85 (27.2%)	50 (29.2%)	
HER2 by IHC				
+2	34 (7.0%)	25 (8.0%)	9 (5.3%)	0.350
+3	450 (93.0%)	288 (92.0%)	162 (94.7%)	
Axillary Lymph Nodes				
Not involved	112 (23.1%)	88 (28.1%)	24 (14.0%)	0.001
Involved	372 (76.9%)	225 (71.9%)	147 (86.0%)	
Tumor Size				
<50 mm	293 (60.5%)	196 (62.6%)	97 (56.7%)	0.058
≥50 mm	185 (38.2%)	111 (35.5%)	74 (43.3%)	
NR	6 (1.2%)	6 (1.9%)	0 (0.0%)	

Abbreviations: SD (Standard Deviation); HER2 (Human Epidermal Growth Factor Receptor-2); IDC (Invasive Ductal Carcinoma); ILC (Invasive Lobular Carcinoma); NR (Not Reported); IHC (Immunohistochemistry).

Treatment Response and Predictors

To identify factors predictive of response to neoadjuvant therapy, our analysis included variables such as tumor size, HR status, lymph node involvement, type of anti-HER2 therapy and HER2 expression levels as determined by IHC scoring (+2 vs +3). Through univariable logistic regression analysis, only HR negativity [OR=0.53, 95% CI, 0.35–0.79, p=0.002] and high HER2 expression; HER2 by IHC score of +3 [OR=0.25, 95% CI, 0.09–0.57, p=0.003] emerged as significant predictors of a favorable

Table 2 Response to Neoadjuvant Treatment Based on Tumor Characteristics and Anti-HER2 Received

Variable	pCR	OR (95% CI) (Univariable)	p-value	OR (95% CI) (Multivariable)	p-value
Tumor Size*					
<50 mm	135 (46.1%)	1.23 (0.85–1.78)	0.284	1.27 (0.87–1.87)	0.224
≥50 mm	76 (41.1%)				
Hormone Receptor					
Positive	139 (39.8%)	0.53 (0.35–0.79)	0.002	0.54 (0.36–0.82)	0.004
Negative	75 (55.6%)				
Lymph Nodes					
Not involved	57 (50.9%)	1.42 (0.93–2.17)	0.105	1.33 (0.85–2.06)	0.209
Involved	157 (42.2%)				
Anti-HER2					
Pertuzumab + Trastuzumab	146 (46.6%)	1.32 (0.91–1.94)	0.146	1.32 (0.89–1.97)	0.163
Trastuzumab	68 (39.8%)				
HER2 by IHC					
+2	6 (17.6%)	0.25 (0.09–0.57)	0.003	0.26 (0.09–0.60)	0.003
+3	208 (46.2%)				

Note: * 6 patients had missing data regarding tumor size.
Abbreviations: pCR (Pathological Complete Response); RD (Residual Disease); OR (Odds Ratio); HER2 (Human Epidermal Growth Factor Receptor 2); and IHC (Immunohistochemistry).

response to treatment. Further analysis was performed using multivariable logistic regression to adjust for potential confounders upheld the significance of these factors. Hormone receptor-negative status maintained a strong association with treatment response [OR=0.54, 95% CI, 0.36–0.82, p=0.004], and same for HER2 by IHC score of +3 [OR=0.26, 95% CI, 0.09–0.60, p=0.003], Table 2.

Type of Surgery

Rates of breast conserving surgery (BCS) were significantly higher among patients with smaller tumors (<50 mm) compared to those with larger ones (≥50 mm); 29.0% compared to 13.0% [OR=0.36, 95% CI, 0.22–0.59, p<0.001], and among patients who received dual anti-HER2 compared to those who received trastuzumab alone; 26.5% compared to 15.2% [OR=0.50, 95% CI, 0.30–0.82, p=0.007]. This significance persisted following multivariable adjustment, confirming the influence of both tumor size and anti-HER2 treatment type on surgical decisions, Table 3.

Table 3 Rate of Breast-Conserving Surgery (BCS) by Patients' Characteristics and Anti-HER2 Received

Variable	Breast-Conserving Surgery (n=109)	Mastectomy (n=375)	OR (Univariable)	p-value	OR (Multivariable)	p-value
Mean age (SD)	47.7 (10.3)	46.3 (10.8)	46.3 (10.8)			
History of Breast Cancer						
No previous history	107 (22.9%)	360 (77.1%)	2.23 (0.62–14.29)	0.292	2.12 (0.56–13.84)	0.335
Previous history	2 (11.8%)	15 (88.2%)				
Hormone Receptor						
Positive	84 (24.1%)	265 (75.9%)	1.39 (0.86–2.33)	0.191	1.36 (0.82–2.32)	0.246
Negative	25 (18.5%)	110 (81.5%)				
HER2 by IHC						
2+	6 (17.6%)	28 (82.4%)	0.72 (0.26–1.68)	0.482	0.57 (0.21–1.38)	0.245
3+	103 (22.9%)	347 (77.1%)				

(*Continued*)

Table 3 (Continued).

Variable	Breast-Conserving Surgery (n=109)	Mastectomy (n=375)	OR (Univariable)	p-value	OR (Multivariable)	p-value
Tumor Size						
≥50 mm	24 (13.0%)	161 (87.0%)	2.74 (1.69–4.59)	<0.001	2.74 (1.68–4.63)	<0.001
<50 mm	85 (29.0%)	208 (71.0%)				
Lymph Nodes						
Involved	82 (22.0%)	290 (78.0%)	1.12 (0.67–1.83)	0.647	0.88 (0.52–1.48)	0.643
Not involved	27 (24.1%)	85 (75.9%)				
Anti-HER2						
Trastuzumab	26 (15.2%)	145 (84.8%)	2.01 (1.25–3.33)	0.005	2.00 (1.22–3.36)	0.008
Pertuzumab + trastuzumab	83 (26.5%)	230 (73.5%)				

Note: * 6 patients had missing data regarding tumor size.
Abbreviations: OR (Odds Ratio); SD (Standard Deviation); HER2 (Human Epidermal Growth Factor Receptor 2); IHC (Immunohistochemistry).

Factors Affecting DFS

In univariable analysis, lymphovascular invasion, tumor size, lymph node involvement, and treatment response to neoadjuvant therapy had a significant impact on DFS, Table-4. In multivariable analysis, however, only positive axillary lymph nodes [HR=3.00, 95% CI, 1.06–8.54, p=0.039], Table 4.

With a median follow-up of 35.3 (range, 7.0–94.0) months, Kaplan–Meier survival analysis revealed significant differences in 3-year DFS rates among our patient cohort based on pathological response post-neoadjuvant treatment and lymph node involvement at diagnosis. Patients who achieved a pCR exhibited a notably higher 3-year DFS rate of 89.3%,

Table 4 Univariable and Multivariable Analysis for Disease-Free Survival (DFS)

Variable	HR (Univariable)	p-value	HR (Multivariable)	p-value
History of Breast Cancer				
No previous history	1.60 (0.50–5.10)	0.431	1.62 (0.50–5.25)	0.417
Previous history				
Hormone Receptor				
Positive	1.62 (0.96–2.74)	0.071	1.54 (0.90–2.64)	0.113
Negative				
HER2 by IHC				
+2	1.77 (0.43–7.25)	0.428	1.66 (0.40–6.92)	0.486
+3				
Lymph Nodes				
Not involved	3.87 (1.40–10.68)	0.009	3.00 (1.06–8.54)	0.039
Involved				
Anti HER2				
Pertuzumab + trastuzumab	1.33 (0.77–2.29)	0.306	1.22 (0.70–2.11)	0.483
Trastuzumab				
Tumor Size				
<50 mm	1.71 (1.02–2.87)	0.040	1.64 (0.98–2.75)	0.059
≥50 mm				
Lymphovascular invasion				
Not present	2.07 (1.22–3.52)	0.007	1.73 (1.00–3.01)	0.051
Present				

Note: * 6 patients had missing data regarding tumor size.
Abbreviations: DFS (Disease-Free Survival); HR (Hazard Ratio); SD (Standard Deviation); HER2 (Human Epidermal Growth Factor Receptor 2); IHC (Immunohistochemistry); NR (Not Reported).

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in contrast to those with residual disease, who had a DFS rate of 81.8% (p=0.016). Additionally, patients without lymph node involvement at the time of diagnosis demonstrated a significantly higher 3-year DFS rate of 95.1% compared to those with lymph node involvement, whose DFS rate was 82.3% (p=0.009).

Discussion

The escalating global burden of breast cancer necessitates continual refinement of treatment strategies.[1] In our cohort involving 484 patients with HER2-positive EBC, we aimed to assess pCR and 3-year DFS with neoadjuvant dual anti-HER2 therapy using pertuzumab and trastuzumab in conjunction with anthracycline and taxane-based chemotherapy as used in the neoadjuvant NSABP-B27 protocol.[16] Additionally, we examined the impact of this treatment regimen on surgical outcomes.

The assessment of clinical endpoints is crucial for evaluating the effectiveness and safety of cancer-targeted therapies in clinical trials.[17,18] Overall survival (OS), defined as the time from randomization until death from any cause, has traditionally served as the "gold standard" endpoint in oncology trials, directly reflecting the impact of interventions on patients' survival.[17] In the specific context of HR+/HER2-breast cancers, clinical endpoints include DFS and pCR. Recognized by the Food and Drug Administration (FDA) as standard endpoints for trials seeking regulatory approval, these measures, including pCR, provide valuable insights.[19] pCR was defined as the absence of residual invasive cancer in the breast and axilla (ypT0/is, ypN0) at surgery after neoadjuvant treatment, and according to various studies this is linked to improved survival.[6,11,20] However, the use of pCR as a reliable surrogate in HR+ disease remains undetermined. A recent study on HER2-breast cancer patients reported an association between pCR and improved OS, yet statistical analysis of this correlation was not conducted.[7] These observations underscore the evolving landscape of surrogate markers like pCR in predicting long-term outcomes, necessitating further research and statistical scrutiny to establish their reliability in the context of specific breast cancer subtypes.

The median age of our cohort was 47 (21–80) years, with 72.1% exhibiting HR positivity and 76.9% presenting with LN involvement before neoadjuvant therapy. The comparatively younger age of our breast cancer patients, coupled with a higher proportion presenting with locally advanced or metastatic disease, highlights variations from global reports.[21,22] The observed higher 3-year DFS in LN-negative patients (96.39%) contrasts with 82.35% in LN-positive patients (p<0.0021), aligning with trends observed in other studies.[23–25]

In the realm of real-world clinical practice, our study investigated neoadjuvant therapy based on dual blockade with pertuzumab and trastuzumab for HER2-positive EBC, achieving a pCR rate of 46.6%. This aligns with results from clinical trials such as NeoSphere (45.8%),[11] Tryphaena (46.6–66.2%),[26,27] and real-world data reported by Hall et al (47%).[28] However, our pCR rates were lower than those reported in the BERENICE trial (60.7–61.8%); 43% of entire cohort were LN negative,[29,30] and Boér et al (54%),[31] Medina et al (62.1%),[32] and González-Santiago et al (66%).[33] It is important to note that the studies by Boér et al and Medina et al had smaller sample sizes of 82 and 87 patients, respectively (Table 5).

Furthermore, González Santiago et al's cohort had nearly 50% of patients with stage 1 and 2 diseases, and 40% were HR-negative. These differences in patients' characteristics and study designs may account for the variation in pCR rates.

Table 5 Summary of Published Studies with Dual Anti-HER2

Studies (Reference Number)	Number of Patients	Study Groups	Overall Number of Baseline Participants	Median Age (range)	Lymph Node (LN) Status	Hormone Receptor (HR) Status	pCR	DFS
Our Study	484	AC/T Pertuzumab + Trastuzumab	313	48 (21–80)	LN+: 225 (71.9%) LN-: 88 (28.1%)	HR+: 228 (72.8%) HR-: 85 (27.2%)	Overall: 46.2% Based on HR: HR+ve: 39.8% HR-ve: 55.6% Based on LN: LN+ve: 42.2% LN-ve: 50.9%	3-year DFS 86.1%

(*Continued*)

Table 5 (Continued).

Studies (Reference Number)	Number of Patients	Study Groups	Overall Number of Baseline Participants	Median Age (range)	Lymph Node (LN) Status	Hormone Receptor (HR) Status	pCR	DFS
NeoSphere Trial[11,34]	417	Arm B Pertuzumab, Trastuzumab, and Docetaxel.	107	Arm B 50 (28–77)	NA	HR+: 50 (46.7%) HR-: 57 (53.3%)	Overall:45.8% Based on HR: HR+ve: 26% HR-ve: 63.2% Based on LN: +ve:6.5 LN-ve :39.3%	At 329 w 84.1%
TRYPHAENA Trial[26,27]	225	Group A: 5-fluorouracil, epirubicin and cyclophosphamide (FEC) for 3 cycles followed by 3 cycles of docetaxel, with pertuzumab plus trastuzumab in all cycles	73	49.0 (27–77)	NA	(A) HR+: 39 (53.4%) (A) HR-: 34 (46.6%)	61.6%	3-year DFS 87%
		Group B: FEC for 3 cycles followed by 3 cycles of docetaxel, with pertuzumab and trastuzumab in cycles 4–6 only (ie with docetaxel).	75	49.0 (24–75)	NA	(B)HR+: 35 (46.7%) (B) HR-: 40 (53.3%)	57.3%	3-yearDFS 88%
		Group C: Docetaxel plus carboplatin for six cycles, with pertuzumab plus trastuzumab in all cycles	77	50.0 (30–81)	NA	(C) HR+: 40 (51.9%) (C) HR-: 37 (48.1%)	66.2%	3-year DFS 90%
BERENICE Trial[29,30]	400	Arm A: AC+ paclitaxel, pertuzumab, trastuzumab. (pertuzumab continued with trastuzumab for one year after surgery)	199	49 (42.0–59.0)	LN-ve: 80 (40.2%) LN+ve: 111 (55.7%) Nx: 8 (4.0%)	HR+: 128 (64.3%) HR-: 65 (32.7%) Unknown: 6 (3.0%)	Overall:61.8% Based on HR: HR+ve: 51.6% HR-ve: 81.5%	3-year DFS 93.58%
		Arm B: FEC+ docetaxel, pertuzumab, trastuzumab (pertuzumab continued with trastuzumab for one year after surgery)	201	49 (42.0–59.0)	LN -ve :74 (36.8%) LN +ve:118 (58.8%) Nx: 9 (4.5%)	HR+: 124 (61.7%) HR-: 75 (37.3%) Unknown: 2 (1.0%)	Overall:60.7% Based on HR: HR+ve:57.3% HR-ve:68%	3-year DFS 90.78%

(*Continued*)

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Table 5 (Continued).

Studies (Reference Number)	Number of Patients	Study Groups	Overall Number of Baseline Participants	Median Age (range)	Lymph Node (LN) Status	Hormone Receptor (HR) Status	pCR	DFS
KRISTINE[35]	444	Arm B: Docetaxel, carboplatin, and trastuzumab plus pertuzumab	221	Arm B 49 (41–57)	A: Palpable: 45 B: non-palpable: 67 C: N/A: 16	For arm B HR+: 62.0% HR-ve:38%	Overall: 55.7% Based on HR: HR+ve:43.8% HR-ve:73.2% Based on clinical staging: II–IIIA: 57.9% IIIB–IIIC: 44.7%	3-year iDFS 92%
Boér et al[31]	82	Pertuzumab + Trastuzumab-based NST	82	50.3 (27–77)	cN: statuscN 0: 13 (15.8%) cN 1–3: 69 (84.1%)	HR+: 43% HR-: 57%	Overall: 54% Based on chemotherapy: Anthracycline: 53% Anthracycline-free:75% C 0–1: 55% Cn 2–3: 47% Based on HR: HR+ve: 51% HR-ve: 55%	2-year DFS 97% 5-year DFS 82%
Medina et al[32]	87	AC (Dose -dense)-DPT (66.7%) DPT (33.3%)	87	54 (30–83)	LN+: 79.3% LN-: 20.7%	HR+: 50.6% HR-: 49.4%	Overall: 62.1% Based on chemotherapy Anthracycline: 65.5% Anthracycline-free: 55.2% Based on LN: LN+ve: 60.9% LN-ve: 66.7% Based on HR: HR+ve: 47.7% HR-ve: 76.7%	NA

Note: AC/DTP refers to specific chemotherapy regimens, with AC is Anthracycline and Cyclophosphamide, DTP indicating Docetaxel, Trastuzumab, and Pertuzumab.
Abbreviations: DFS (Disease-Free Survival); iDFS (Invasive Disease-Free Survival); LN+ (Lymph Node Positive) and LN- (Lymph Node Negative); HR+ (Hormone Receptor Positive) and HR- (Hormone Receptor Negative); NA (Not Available or Not Applicable); and NST (Neoadjuvant Systemic Therapy). cN: Clinical nodal status.

Nevertheless, to the best of our knowledge, this represents the largest cohort study providing real-world data on pCR with neoadjuvant treatment involving pertuzumab and trastuzumab in HER2-positive EBC patients.

The review article by Ischii and et.al emphasized that only the level of HER2 expression, rather than the HR status, predicted efficacy.[36] Our analysis, however, found that the variation in HER2 expression level (2+ vs 3+) had a significant impact on efficacy, with rates of 46.2% compared to 17.6% (HR 0.25 [0.09–0.57], p=0.003). Additionally, our study observed considerably higher pCR rates in HR-negative patients (55.6%) compared to HR-positive patients (39.8%, p=0.002), consistent with patterns seen in other studies.[8,15,31]

Additionally, our data indicated higher pCR rates with dual anti-HER2 therapy (46.6%) compared to trastuzumab alone (39.8%, p=0.15), with estimated 3-year DFS rates also favoring dual anti-HER2 therapy (86.1%) over trastuzumab alone (83.1%, p=0.37), though not reaching statistical significance.

Comparing our study with NeoSphere, which employed taxane-based neoadjuvant therapy and adjuvant FEC and trastuzumab, both studies exhibited similar outcomes, particularly in DFS. NeoSphere reported an overall DFS rate of 84%, closely mirroring our study's DFS rate of 86.1%.

Post-surgery, the majority (89.4%) of our patients received adjuvant trastuzumab, while none received pertuzumab or T-DM1. The landscape of anti-HER2 therapy has evolved significantly over the years, witnessing the development and testing of various agents, including pertuzumab, neratinib, and T-DM1. Trastuzumab has historically been the mainstay in adjuvant therapy; however, recent approvals for therapies such as the combination of trastuzumab and pertuzumab and neratinib following trastuzumab signify a paradigm shift in the adjuvant treatment approach for HER2-positive breast cancer.[37,38]

Neoadjuvant systemic therapy (NST) is widely utilized in EBC to shrink tumors, increase resection rates, and make patients eligible for b BCS. While the improved rate of conversion from mastectomy to BCS is a significant finding, its implications extend beyond surgical outcomes, directly influencing patient quality of life and overall treatment goals. Breast-conserving surgery is often associated with better aesthetic outcomes, higher patient satisfaction, and improved body image compared to mastectomy. Additionally, preserving breast tissue can have psychological benefits, including reduced emotional distress and improved self-esteem, which are critical for long-term survivorship.

From a clinical perspective, achieving BCS without compromising oncological safety aligns with the broader goals of personalized cancer care. It underscores the potential of dual anti-HER2 therapy not only to control disease but also to enhance surgical options, thereby integrating effective tumor management with patient-centered care priorities. These outcomes reinforce the importance of considering both oncological and quality-of-life measures when evaluating therapeutic strategies. While a prior trial by Boér et al[31] observed a higher rate of conversion from mastectomy to BCS with the addition of pertuzumab, several subsequent trials did not replicate these findings.[39,40] In our study, we found a significant improvement in the rate of BCS with the addition of pertuzumab, with an odds ratio of 0.50 (95% CI [0.30–0.80], p=0.005) However, factors such as multifocal/multicentric disease and large tumor size contributed to the necessity for mastectomy. This discordance highlights the disparity between high rates of pCR and low rates of BCS.

Limitations

This study has several limitations inherent in its retrospective design. First, the potential for selection bias exists due to the non-randomized treatment allocation, which may have influenced the outcomes. Other is the difference in follow-up durations between the two arms, which could introduce bias into the survival analysis. In our center, trastuzumab was the standard of care as of October 2017, after which we began using a combination of pertuzumab and trastuzumab. As a result, the median follow-up time for trastuzumab was 59.4 months, compared to 26.8 months for the pertuzumab and trastuzumab combination. Truncating the follow-up period at three years helps minimize this bias in calculating the DFS but also limits the assessment of long-term outcomes.

Conclusion

Although dual anti-HER2 therapy has shown significant improvement in pCR compared to trastuzumab alone, our results demonstrated that this benefit did not extend to long-term survival. This finding underscores the importance of switching from trastuzumab to T-DM1 or continuing pertuzumab in the adjuvant setting for patients with residual disease. However, the addition of pertuzumab did improve the rate of conversion from mastectomy to BCS.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Declarations

The study was approved by the Institutional Review Board (IRB) (Approval Number: 22 KHCC 184) at King Hussein Cancer Center, and all procedures were performed based on the regulations of Helsinki. Given the retrospective nature of the study and lack of patients' identifiers, consent to participate was waived by the IRB.

Consent for Publication

Data submitted are entirely unidentifiable, and there are no details on individuals reported within the manuscript.

Disclosure

The author(s) report no conflicts of interest in this work.

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