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De-escalation of Treatment of HER2 Positive Breast Cancer after Pathological Complete Response to Neoadjuvant Chemotherapy; a Retrospective Analysis

Ethraa Khaled
Cairo University
Sara Shams
Cairo University
Ahmed A.M.Abdelhafeez
hbaboda@kasralainy.edu.eg

Cairo University
Shaimaa Lashin
Cairo University

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Abstract

Background

The teatement of choice for the neo-adjuvant treatment of HER2-positive early breast cancer includes trastuzumab–pertuzumab (TP) with chemotherapy. For those achieving pathological complete response (pCR), the optimal adjuvant strategy remains less clearly defined.

Method

We retrospectively included patients with HER2-positive early or locally advanced breast cancer who achieved pCR after neo-adjuvant TP-based chemotherapy between January 2021 and December 2023. Disease-free survival (DFS), overall survival (OS), and cardiac dysfunction were assessed.

Results

A total of 356 patients were included: 86 (24.2%) received adjuvant trastuzumab and 270 (75.8%) received adjuvant trastuzumab–pertuzumab. After a median follow-up of 24.8 months, the estimated 3-year DFS for the overall cohort was 89.8%. DFS did not significantly differ between the trastuzumab arm (87.7%) and the dual blockade arm (90.5%) (log-rank p = 0.2213).In subgroup analyses, clinical N3 disease and younger patients less than 40 years derived a significant benefit from dual blockad.No other significant differences in DFS were detected across subgroups defined by clinical T stage, hormone receptor status, HER2 IHC score, tumor grade, or Ki-67 index.Cardiac safety was consistent with previous reports, with no significant difference in dysfunction between trastuzumab (23.8%) and trastuzumab–pertuzumab (18.1%) (p = 0.922).

Conclusions

Among patients who achieved pCR following neo-adjuvant TP-based chemotherapy, de-escalation to adjuvant trastuzumab monotherapy appears to be a safe strategy that does not compromise DFS in most cases.

Introduction

HER2-enriched breast cancer represents 15–20% of BC and is considered one of the most aggressive subtypes (1).

Current guidelines recommend a neo-adjuvant chemotherapy backbone combined with anti-HER2 therapy (trastuzumab-based) as standard for HER2-positive early breast cancer. (2)

Achieving a pathologic complete response (pCR) is associated with enhanced event-free survival (EFS) and overall survival (OS) in patients with HER2-positive breast cancer (3). Furthermore, the incorporation of pertuzumab has demonstrated an additional increase in pCR rates (4).

Continuation of anti-HER2 therapy in the adjuvant setting for one year is considered standard, based on evidence from four pivotal phase III trials (HERA, NSABP B-31, NCCTG N9831, and BCIRG-006), which demonstrated nearly 40% relative risk reduction in recurrence and progression, with durable benefit confirmed on long-term follow-up (5–7)

Adjuvant pertuzumab showed improved DFS when added to trastuzumab especially in node positive patients (8), but this trial only included patients treated with upfront surgery, without prior neo-adjuvant therapy or pCR assessment. Data regarding the value of adjuvant pertuzumab in patients achieved PCR who have better outcome is limited and the optimal treatment for this group is not clear.(9)

The aim of this research is to be a pilot exploratoty study to assess the effectiveness and safety of de-escalation strategies for adjuvant anti-HER2 therapy in individuals with HER2-positive breast cancer who have attained a pathological complete response (pCR) after undergoing neo-adjuvant chemotherapy and anti-HER2 treatment.

Methods

This research represents a retrospective analysis conducted at the Clinical Oncology and Nuclear Medicine Department of Al Kasr Al-Ainy Hospital, as well as the Dar Al-Salam Center of Oncology from january 2021 to December 2023

Inclusion criteria included: female patients, age ≥ 18 years, histologically confirmed invasive breast cancer (AJCC, stage I-III), HER2 positive (score 3 by IHC or 2 + amplified by ISH), and patients who underwent chemotherapy in the neo-adjuvant setting (4–8 cycles) alongside dual anti-HER2 blockade and achieved PCR.

Exclusion criteria comprised: pregnancy-associated breast cancer, patients with multiple primary malignancies, patients who underwent fewer than 2 cycles of neo-adjuvant dual anti-HER2 regimens, and incomplete medical records.

Data extracted from records included: Demographic data (age, menopausal status, family history, comorbidities), Clinico-pathological data (pathological type, Grade, hormone receptor status as assessed by standard immunohistochemistry (IHC), HER2neu status, stage (TNM) and KI67, Treatment-related data (type of chemotherapy, duration, number of cycles, date of starting chemotherapy, type & date of surgery, adjuvant hormonal treatment, adjuvant anti-HER2 treatment -type, duration and adverse events

Primary outcomes:Disease-free survival–defined as the time from primary treatment (surgery) to loco-regional recurrence, distant recurrence, or death

Secondary outcome parameters include: Cardiac dysfunction, defined as decrease by ≥ 10 points from the baseline or a decrease to < 50% during the anti-HER2 treatment period

Descriptive statistics included the baseline characteristics of the study population. Continuous variables are represented as means ± standard deviation (SD). The comparison of categorical variables is performed using the Chi-square test or Fisher's exact test, as appropriate. Survival outcomes are assessed through the Kaplan–Meier method,differences among groups are analyzed using the log-rank test. The median follow-up duration was calculated using the reverse Kaplan-Meier method based on disease-free survival (DFS) data.A two-sided p-value of < 0.05 is considered statistically significant.

Ethical declaration :The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its subsequent amendments. Ethical approval was obtained from Faculty of medicine,Cairo university, number: MS-577-2024.Given the retrospective nature of the study, the requirement for informed consent to participate was waived by the Ethics Committee/Institutional Review Board. **Clinical trial number**: not applicable as this is a retrospective and observational study.

Results

After screening medical records, 356 patients with HER2-positive breast cancer who received neo-adjuvant chemotherapy at the Clinical Oncology and Nuclear Medicine Department, Al Kasr Al-Ainy Hospital, and Dar Al-Salam Oncology Center between January 2021 and December 2023 were deemed eligible for final analysis.

Patient age ranged from 25 to 83 years (median 46; mean 47.9 ± 11.1). Premenopausal status was observed in 239 cases (67.1%) and postmenopausal status in 117 (32.9%). A family history of cancer was reported in 81 cases (30.3%), including 27 (7.5%) with breast cancer. Comorbidities such as hypertension, diabetes mellitus, ischemic heart disease, or liver cirrhosis were documented in 132 cases (37.1%) as shown in Table 1

Table 1
Demographic data and risk factors of the studied patients who achieved pCR after neoadjuvant trastuzumab pertuzumab based treatment.

N = 356		
Age	Mean ± SD	47. 9 ± 9.78
	Range	25–83
Menopausal Status	Pre-menopausal	237 (67.1%)
	Post-menopausal	117 (32.9%)
Family History of Breast Cancer	No	240(67.4%)
	Yes	27 (7.58%)
	NA	89 (25%)
Comorbidities	No	224 (62.9%)
	Yes	132 (37.1%)
Diabetic	No	297 (83.4%)
	Yes	59 (16.6%)
Hypertensive	No	253 (71.1%)
	Yes	103 (28.9%)
Cardiac	No	325 (91.3%)
	Yes	31 (8.7%)
Hepatic	No	347 (97.5%)
	Yes	9 (2.5%)

Regarding clinical data breast cancer was right-sided in 178 cases (50.0%), left-sided in 174 (48.9%), and bilateral in 4 (1.1%) patients. Advanced tumors (T3–T4) were observed in 213 cases (60.0%), while 141 (39.8%) were T1–T2. Node-positive disease was present in 287 cases (80.8%), compared with 68 (19.2%) node-negative cases as demonstrated in Table 2

Table 2
:Baseline clinical data of the studied patients who achieved pCR after neoadjuvant trastuzumab pertuzumab based treatment.

		n = 356
Breast Side	**Right**	**178 (50%)**
	Left	**174 (48.9%)**
	Bilateral	**4 (1.1%)**
Site Within Breast	**UOQ**	193 (55.8%)
	UIQ	39 (11.3%)
	Central	48 (13.9%)
	LOQ	30 (8.7%)
	LIQ	36 (10.4%)
Clinical T Stage	**T0**	3 (0.8%)
	T1	6 (1.7%)
	T2	132 (37.2%)
	T3	78 (22%)
	T4	135 (38%)
	Tx	1 (0.3%)
Clinical N stage	**N0**	68 (19.2%)
	N1	164 (46.2%)
	N2	74 (20.8%)
	N3	49 (13.8%)
Supraclavicular L.N. Clinical/Imaging	**Yes**	46 (13%)
	No	309 (87%)

All patients were histologically confirmed by biopsy: 349 (98%) with tru-cut biopsy, 7 with excisional biopsy ,Pathological data and ER ,PR ,her2neu and KI67 is shown in Table 3

Table 3
Baseline Pathological Characteristics of the Patients who achieved pCR after neoadjuvant trastuzumab pertuzumab based treatment.

Table 5 Baseline Pathological Characteristics of the Patients		**n = 356**
Histopathological Type	**IDC**	181 (87.4%)
	ILC	18 (8.7%)
	IMC	7 (3.4%)
Biopsy Grade	**II**	247 (69.38%)
	III	102 (28.7%)
	I	1 (0.29%)
	NA	6 (1.68%)
HER2 Score	**+ 2**	31 (8.7%)
	+ 3	325 (91.3%)
HR status	**Negative**	95 (26.7%)
	Positive	261 (73.3%)
KI67	**Low (less than 20%)**	36 (10.1%)
	High (more than 20%)	173 (48.6%)
	Not available	147 (41.3%)

In this cohort, the most frequently administered regimen was taxane–platinum–based therapy, given to 262 patients (73.59%), with paclitaxel-based combinations (46.3%) being more common than docetaxel-based combinations (27.2%). Anthracycline–taxane combinations were used in 75 patients (21.06%). Less commonly employed regimens included taxanes alone in 3.4% (n = 12), anthracyclines alone in a single patient (0 .3%), and the combination of anthracyclines, taxanes, and platinum agents in 1.7% (n = 6) of the patients.

All The number of administered cycles ranged from 2 to 10, with a mean of 5.28 cycles (SD = 1.30) and a median of 5 cycles (IQR = 4–6). The most common regimens were 6 cycles, administered to 113 patients (31.7%), and 5 cycles, administered to 107 patients (30%).

Following completion of neoadjuvant chemotherapy, all patients proceeded to definitive surgical management. Modified radical mastectomy (MRM) was performed in 63.8% of cases (n = 227), whereas breast-conserving surgery (BCS) was undertaken in 36.2% (n = 129).

Pathological complete response (pCR) was achieved in all patients. The majority demonstrated ypT0N0 status, while 44 patients (12.36%) had residual carcinoma in situ present in the surgical specimen

All patients received adjuvant anti-HER2 therapy to complete a total duration of one year from the initiation of treatment. Of the 356 patients, 270 (75.8%) continued dual blockade, while 86 (24.2%) received trastuzumab alone.

After a median follow-up period of 24.77 months, disease recurrence was documented in 23 patients (6.4%). Of these, 4 patients (17.4%) experienced loco-regional recurrence, whereas 19 patients (82.6%) developed distant metastases.

Comparison of patients characteristics showed that dual blockade group included more statistically significant more advanced T and N stage as compared to trastuzumab only group while all other confounding factors were balanced.Table 4

Table 4
comparison of patient characteristics of patients received adjuvant trastuzumab only vs dual blockade groups

Age in years	**Dual blocake (n = 270)**	**Trastuzumab only(n = 86)**	**P vaue**
(Mean ± SD)	**47.9(± 10.8)**	**47.8(± 12)**	**0.9**
Premenopausal N(%)	177(65.5)	60(69.7)	0.6
Co morbidities N(%)	105(39%)	27(31.5%)	0.13
Clinical T stage N(%)			
T0	2(0.7)	1(1.3)	0.001
T1	6(2.2)	0	
T2	85(31.5)	47(54.7)	
T3	57(21.5)	21(24.4)	
T4	118(43.7)	17(19.8)	
Clinical N stage N(%)			
N0	34(12.6)	34(39.5)	0.001
N1	125(46.5)	39(45.3)	
N2	66(24.5)	8(9.3)	
N3	44(16.4)	5(5.8)	
Grade N(%)			
1	1(0.4)	0	0.23
2	192(72.7)	55(64)	
3	71(26.9)	31(36)	
HR positive N(%)	196(72.5)	65(75.5)	0.43
KI67 more than 20% N(%)	130(48)	43(50)	0.45

By treatment arm, mean DFS was 36.1 months with trastuzumab alone and 42.9 months with trastuzumab–pertuzumab, with no statistically significant difference (p = 0.2213). Three-year DFS was 87.7% in the trustuzumab arm vs. 90.5% in the dual blockade arm. This difference, however, did not reach statistical significance (log-rank p = 0.2213). Figure 1

Subgroup analysis of DFS was conducted to investigate whether certain subgroups might derive greater benefit from one regimen over the other,Age and N3 stage showed better DFS in favor of combination trastuzumab and pertuzumab.Table 5

Table 5
Subgroup Analysis of the Efficacy of combination adjuvant trastuzuamb +pertuzumab as compared to trastuzumab alone : Disease-Free Survival Outcomes

Subgroup		**Mean Survival – Single Blockade (months)**	**Mean Survival – Dual Blockade (months)**	**Difference (months)**	**P-value**
Age group	(20–39)	31.735	38.562	6.827	0.0274
	(40–59)	36.268	42.275	6.007	0.9179
	(> 60)	37.526	39.255	1.729	0.5900
HER2 Score	IHC 2+	39.290	31.447	7.843	0.4853
	IHC 3+	35.118	43.002	8.884	0.1383
HR-Status	positive	36.269	42.923	6.654	0.3256
	negative	35.278	35.409	0.131	0.4489
T Stage	T0-2	36.535	44.550	8.015	0.0949
	T3-4	34.672	37.781	3.109	0.4433
N Stage	N0	33.663	32.659	1.004	0.9786
	N1	38.428	34.950	5.522	0.7451
	N2	30.392	33.409	3.017	0.1927
	N3	11.938	38.048	26.11	0.0010
Ki67	< 20%	39.290	34.007	5.283	0.4561
	> 20%	34.384	38.665	4.281	0.3401
Tumor grade	Grade II	36.177	42.538	6.361	0.4709
	Grade III	35.373	38.829	3.456	0.2378

Cardiac dysfunction was observed in 63 patients (18%) of the study population. All events were asymptomatic. Anti-HER2 therapy was temporarily interrupted in affected patients, with subsequent

recovery of LVEF in 58 cases (92.1%). Permanent discontinuation of anti-HER2 therapy due to persistent LVEF decline was required in 5 patients (7.9%). No cardiac-related deaths occurred. The mean nadir LVEF was 58.9%.

Upon analysis of the adjuvant anti-HER2 treatment regimens, cardiac dysfunction was noted in 15 patients (23.8%) who were treated with trastuzumab alone, compared to 48 patients (18.1%) who received trastuzumab–pertuzumab. This indicates an absolute difference of 5.7% and a relative risk of 1.314 (95% CI: 0.80–2.27), which was not statistically significant (p = 0.922).

Discussion

The median age of the cohort was 46 years, markedly younger than the median age reported in international datasets. In the SEER registry, the median age at breast cancer diagnosis is 63 years, with HER2-positive patients being slightly younger but still older than our population.(10, 11)

Egyptian series, such as the meta-analysis by Azim et al. have reported a median age of 51 years, consistent with our findings of a younger demographic profile.(12)

The cohort also exhibited a higher disease burden than that reported in large neo-adjuvant HER2-positive trials such as NeoSphere and TRYPHAENA. Specifically, 60.2% of patients presented with T3–T4 tumors, and 80.8% were clinically node-positive, including 46.2% with N1 and 13.8% with N3 disease. This stage distribution is in line with Egyptian cancer registries and meta-analyses, which consistently report more advanced presentation compared with Western populations (4, 12, 13).

The mean DFS was 42.6 months, with an estimated 3-year DFS of 89.9%. These outcomes are broadly comparable to those reported in clinical trials and real-world series, although the slightly lower 3-year DFS in this cohort likely reflects the higher baseline risk profile.

In clinical trials, TRYPHAENA reported a 3-year DFS of 87–90% in patients achieving pCR, while TRAIN-2 demonstrated 3-year DFS rates of 92–94% with dual blockade (14, 15). A pooled analysis of pertuzumab-containing regimens showed 4-year EFS rates of 86–95% (16). Another real-world data are consistent: a pooled cohort of 641 patients reported a 3-year DFS of 92.2% (17).

By treatment arm, mean DFS was 36.1 months with trastuzumab alone and 42.9 months with trastuzumab–pertuzumab, with no statistically significant difference (p = 0.2213). The corresponding 3-year DFS rates were 87.7% versus 90.5%. While the absolute benefit was modest, longer follow-up may clarify whether clinically meaningful differences emerge, particularly in high-risk subgroups

In the present cohort, when stratified by nodal status, node-positive patients receiving trastuzumab–pertuzumab achieved a 6.9-month longer mean DFS compared to those receiving trastuzumab alone; however, this difference did not reach statistical significance (p = 0.2602). On further stratification, a strong signal emerged in patients with clinical N3 disease: those who continued adjuvant dual blockade achieved substantially longer mean DFS than those treated with trastuzumab alone (38.0 vs. 11.9

months; p = 0.001). These findings suggest that patients with the highest nodal burden may derive the greatest benefit from continued pertuzumab in the adjuvant setting.

This observation is consistent with the APHINITY adjuvant trial, where node-positive—but not node-negative—patients experienced an absolute invasive DFS benefit from pertuzumab 6-year iDFS: 88% vs. 83%. Notably, APHINITY did not report outcomes stratified by pCR status, leaving this subgroup question unresolved (8)

Other studies have reported comparable findings. Kook et al. evaluated 386 patients with early HER2-positive breast cancer (median follow-up 49 months). The 3-year RFS was 96.1% for the overall cohort, with no significant difference between adjuvant trastuzumab–pertuzumab and trastuzumab alone (94.2% vs. 95.6%; HR 1.80, 95% CI 0.62–5.19, p = 0.280. Several differences in baseline risk may partly explain the divergence from the present study's results. In the Kook et al. cohort, a lower proportion of patients were node-positive (73.8%) or had N3 disease (8.3%) compared with 80.8% and 13.8%, respectively, in the current cohort. In addition, only 17.9% of patients received dual blockade, and nodal burden was not stratified beyond positive versus negative status.(18)

Another subgroup with apparent benefit was patients younger than 40 years, who had significantly longer survival with dual blockade (38.6 vs. 31.7 months; p = 0.0274). This may reflect the more aggressive baseline disease biology typical of younger patients, making them more sensitive to treatment intensification.

Taken together, these findings suggest that adjuvant de-escalation to trastuzumab monotherapy may be appropriate for most patients achieving pCR. However, patients with very high nodal burden (N3) and possibly younger age at diagnosis appear to derive meaningful benefit from continuing dual blockade. Exploratory signals in patients with HER2 IHC 3 + and other high risk features warrant further study, although statistical power in this cohort was insufficient for definitive conclusions.

Cardiac dysfunction was documented in 63 patients (18%), with a mean nadir LVEF of 58.9%. Permanent discontinuation of anti-HER2 therapy was required in only five cases. There was no significant difference in cardiotoxicity between patients receiving adjuvant trastuzumab alone and those receiving trastuzumab–pertuzumab (p = 0.922).These findings indicate that dual HER2 blockade does not confer additional cardiotoxicity compared with trastuzumab monotherapy, provided that routine cardiac monitoring and risk assessment are implemented.

These results are consistent with previously published clinical trial data. In TRYPHAENA, all patients received neo-adjuvant trastuzumab–pertuzumab plus chemotherapy, with LVEF decline reported in 10.7% of patients and symptomatic dysfunction in only 12.5% of those affected.(14)

Similarly, NeoSphere demonstrated very low rates of left ventricular systolic dysfunction (0–1%) and modest LVEF declines (1–3%)(19). In the BERENICE cardiac safety study, LVEF decline occurred in 13.6% and 12.1% of patients across two cohorts, with NYHA class III/IV heart failure in ≤ 1.5%.(20)

Finally, the adjuvant APHINITY trial reported primary cardiac events in 1.0% and secondary events in 2.8% after 45 months, with stable rates after extended follow-up to 74 months. Collectively, these data confirm that the addition of pertuzumab does not significantly increase the incidence of cardiotoxicity compared with trastuzumab alone, provided that structured cardiac monitoring is maintained. (21)

In the current era of precision oncology, treatment strategies in HER2-positive early breast cancer are increasingly response-adapted, with escalation for patients who do not achieve pCR—as demonstrated in the KATHERINE trial—and de-escalation for patients with low-risk disease and excellent treatment responses, including pCR. (22)

In this analysis, adjuvant de-escalation to trastuzumab alone following pCR appeared safe in most patients. However, patients with high nodal burden (N3) disease derived a significant DFS benefit from continuing trastuzumab–pertuzumab, suggesting that this high-risk subgroup may require treatment intensification despite achieving pCR. These findings underscore the need for prospective validation in larger, stratified cohorts but remain clinically relevant given the persistently elevated relapse risk associated with extensive nodal disease.

However, several limitations should be mentioned. First, the fact that this is a retrospective studys.Second the relative small number of patients included but the aim of this study is to be a pilot study to determine which subgroups pertuzumab should be given or omitted.So,we need prospective trial included advanced stage to assess the role of adjuvant pertuzumab in patients achieved pCR.

Third, the dual blockade arm included more advanced stage .Also, Certain subgroups—most notably patients with N3 disease—were small, limiting the statistical power and generalizability of subgroup-specific inferences. Finally, the median follow-up duration was relatively short, yielding sufficient power for disease-free survival analysis but leaving overall survival outcomes immature.

Conclusion

According to our study, no difference between adjuvant trastuzumab vs dual blockade trastuzumab and pertuzumab in patients achieved PCR .In spite of being retrospective study with relatively small number of patients and short follow up, this study serve as basis and Pilot study for well-constructed studies for selection of patients who can safely pertuzumab be omitted.

Declarations

Ethical declaration:The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its subsequent amendments. Ethical approval was obtained from Faculty of medicine,Cairo university, number: MS-577-2024.Given the retrospective nature of the study, the requirement for informed consent to participate was waived by the Ethics Committee/Institutional Review Board.

Conflict of interest and funding : The authors declare no competing interests.No specific funding was received for this study

Clinical trial number: not applicable as this is a retrospective and observational study.

Data availability The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request

Author Contribution

Dr Shaimaa Lasheen contributed to the study conception , study design ,review of data and drafting the manuscript. DR Ethraa and Sara Shams contributed to patient recruitment, data collection, and clinical assessment,drafting the manuscipt. Dr Ahmed Abdelhafeez performed the statistical analysis, interpreted the result,supervised the study, critically reviewed the manuscript, and provided final approval for publication. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Figures

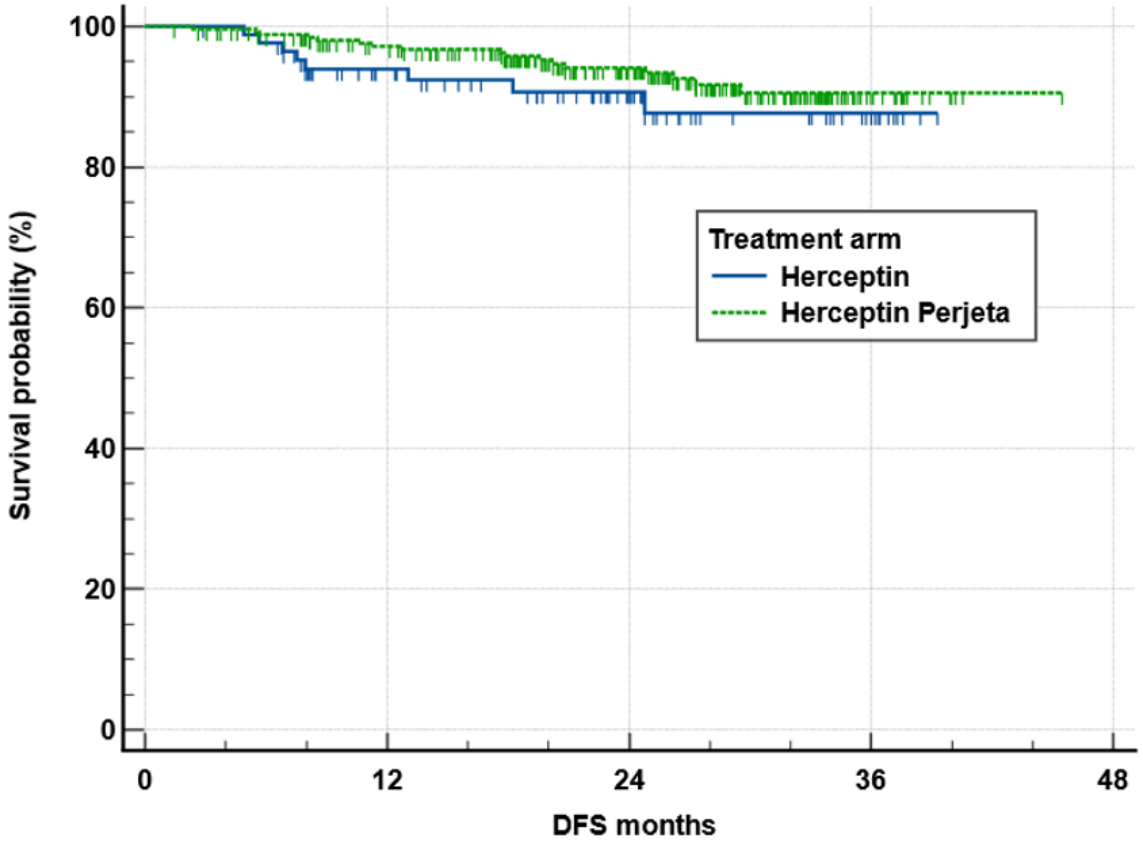


Figure 1

Kaplan Meier curve for DFS based on the type of adjuvant anti-HER2.