The Breast 81 (2025) 103885

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

Is switching to T-DM1 still justified in HER2-negative residual breast cancer after neoadjuvant systemic therapy?

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ARTICLE INFO

Keywords:
Breast cancer
HER 2
Trastuzumab
Pertuzumab
Trastuzumab emtansine
Partial response
Guideline

ABSTRACT

The standard of care for HER2-positive and hormone receptor-positive breast cancer patients who receive neoadjuvant chemotherapy (NACT) combined with trastuzumab, with or without pertuzumab, is to continue with adjuvant T-DM1 in cases of an incomplete response according to KATHERINE trial results. However, the optimal management for patients with residual disease with loss of HER2 expression is not widely studied. Loss of HER2 expression after NACT with anti HER2 is a rarer event with questionable value both as a predictive prognostic marker.

1. Introduction

Recently, we encountered a clinical challenge during the multidisciplinary oncology meetings on two separate occasions in a short period, regarding the loss of HER2 expression following neoadjuvant chemotherapy (NACT) in HER2-positive, hormone-receptor positive, and node-positive breast cancer. Both patients received NACT combined with trastuzumab-pertuzumab and exhibited a selective partial response. By selective partial response we refer to a complete response in the HER2-positive component of the tumour, while residual hormonal-sensitive tumour remained. This raises the clinical question: "Should we continue trastuzumab-pertuzumab or switch to trastuzumab emtansine (T-DM1)?".

1.1. Standard of care after neoadjuvant therapy in HER 2 positive patients

It is well known that HER2-positive breast cancer patients with residual disease post-neoadjuvant therapy have a poorer prognosis. The KATHERINE trial addressed this issue by randomizing patients with residual disease following NACT and trastuzumab into adjuvant treatment with either T-DM1 or trastuzumab. The trial demonstrated that adjuvant T-DM1 reduced the risk of recurrence of invasive disease or death by 50 % compared to trastuzumab (HR 0.50; 95 % CI 0.39–0.64; p < 0.001) [1]. After 3 years, the invasive disease-free survival (iDFS) was better in the T-DM1 group (88.3 %) compared to the trastuzumab group (77.0 %) [1]. As a result, adjuvant T-DM1 has become the standard of care for patients with residual disease after NACT with trastuzumab (and pertuzumab in case of node-positive disease).

1.2. Survival and recurrence risk in patients with residual HER2 negative disease after NACT

Interestingly, a small subset of patients with loss of HER2 expression after NACT was included in this trial. Indeed, 70 patients (8.3 % of the KATHERINE study population) had residual HER2-negative breast cancer after surgery [2]. Table 1 presents the recurrence rates for this subgroup, stratified by the adjuvant treatment arm.

A chi-square analysis revealed a significant difference in the recurrence rate between T-DM1 and trastuzumab ($\chi 2 = 5.58$ and a p-value of 0.018). Based on this subgroup analysis, the authors concluded that retesting HER2 and hormone receptor status on residual disease should not be performed, as it does not alter the choice of adjuvant systemic treatment. However, given the small size of this subgroup, these conclusions should be interpreted with caution. Furthermore, a recent retrospective analysis of 60 patients with residual disease after NACT found that 13 % had lost HER2 overexpression/amplification [3]. In this small subgroup, the 5-year DFS and 5-year overall survival (OS) were 70

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https://doi.org/10.1016/j.breast.2025.103885
Received 25 December 2024; Received in revised form 10 January 2025; Accepted 17 January 2025
Available online 21 January 2025

Table 1
Recurrence rated in the subgroup of patients with residual HER2-negative diseases after NACT with trastuzumab.

Adjuvant therapy	No Recurrence	Recurrence	Total number of patients
T-DM1	28	0	28
Trastuzumab	31	11	42
Total number of patients	59	11	70

% and 84 %, respectively, for patients whose residual tumours remained HER2-positive, compared to 21 % and 50 % for those whose tumours became HER2-negative (P = 0.02 and < 0.001). These results suggest a potential negative prognostic impact of NACT-induced HER2 loss in residual tumours, leading to worse DFS and OS.

An earlier trial involving 107 patients with non-metastatic HER2-positive breast cancer treated with NACT demonstrated a 40 % incidence of HER2 loss in patients with residual disease after chemotherapy alone, compared to 14.7 % in those treated with chemotherapy and anti-HER2 agents ($P = 0.019$) [4]. In this trial, patients with HER2 loss tended to have a higher risk of relapse compared to those with maintained HER2 positivity (HR 2.41, $P = 0.063$). While these results do not provide guidance on the optimal adjuvant treatment, the detrimental survival association with HER2 loss in both trials may theoretically support the need for treatment escalation [3,4].

Recently, the Dana-Farber Institute published results from a meta-analysis involving 1080 breast cancer patients with residual disease after NACT [5]. Up to 29.5 % of patients experienced a change in HER2 expression (HER2 0, HER2-low, or HER2-positive) from the pre-treatment sample to residual disease, with a nearly equal distribution between decreased (50.5 %) and increased (49.5 %) HER2 expression. Changes in HER2 expression post-NACT were prognostic for patients with HER2-positive tumours at diagnosis (3-year recurrence-free survival for change versus no change: 71.6 % vs. 89.6 %, p = 0.006) but not for those with HER2-negative tumours at diagnosis (3-year recurrence-free survival for change versus no change: 79.3 % vs. 81.1 %, p = 0.31). These findings further support the detrimental impact of HER2 loss after NACT. However, several other studies have reported contradictory results, failing to link HER2 loss with an unfavourable prognosis [6]. Importantly, it should be noted that all these data are mostly retrospective or coming from small volume trials, making definitive conclusions difficult.

1.3. What is the optimal treatment in patients with residual HER2 negative disease after NACT?

The question of the optimal adjuvant treatment plan for cases with residual HER2-negative disease after NACT and trastuzumab-pertuzumab remains unsolved. Should we still switch to T-DM1, or is continuing with trastuzumab-pertuzumab sufficient?

From a theoretical standpoint, continuing dual HER2 blockade may be appropriate if there is a complete response in the HER2-positive component of the tumour after neo-adjuvant treatment. However, treatment escalation could be warranted if this population is at higher risk, as suggested by some of the aforementioned trials positioning HER2 loss as a detrimental prognostic marker.

In clinical practice, a complete response in the HER2-positive disease and a partial response in the hormone receptor-positive component of the tumour is generally considered an incomplete response. Therefore, the NCCN and ESMO guidelines recommend adjuvant T-DM1 in these cases [7,8]. ESMO rates the level of evidence as I, A with an ESMO-MCBS v1.1 score of A and an ESCAT score of I-A [2].

1.4. Practical considerations in patients with residual HER2 negative disease after NACT

In our opinion, there is currently limited evidence to definitively support switching to T-DM1 in patients with residual disease and HER2 loss following dual HER2 blockade. HER2 loss remains a contradictory prognostic and predictive marker, given the limited and inconclusive data. A subgroup analysis of the NeoSphere trial data will provide a better perspective, but ideally a randomised controlled trial is needed to provide evidence base guidance on what to do in the event of a selective response. This information is essential not only for understanding efficacy but also for assessing side effects, tolerability and cost-effectiveness. In the meantime, we believe that each case should be carefully considered by a multidisciplinary team, considering all individual risk factors.

CRediT authorship contribution statement

Wiebren Tjalma: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Laure-Anne Teuwen:** Writing – review & editing, Formal analysis, Conceptualization. **Sevilay Altintas:** Writing – review & editing, Formal analysis, Conceptualization. **Konstantinos Papadimitriou:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization.

Funding

None

References

[1] von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med Feb 14 2019;380(7):617–28. https://doi.org/10.1056/NEJMoa1814017.
[2] Loibl S, Huang C-S, Mano MS, et al. Adjuvant trastuzumab emtansine (T-DM1) vs trastuzumab (T) in patients with residual invasive disease after neoadjuvant therapy for HER2-positive breast cancer: subgroup analysis from KATHERINE. Ann Oncol 2020;(31). Abstract 960.
[3] Branco FP, Machado D, Silva FF, et al. Loss of HER2 and disease prognosis after neoadjuvant treatment of HER2+ breast cancer. Am J Transl Res. 2019;11(9):6110–6.
[4] Guarneri V, Dieci MV, Barbieri E, et al. Loss of HER2 positivity and prognosis after neoadjuvant therapy in HER2-positive breast cancer patients. Ann Oncol Dec 2013;24(12):2990–4. https://doi.org/10.1093/annonc/mdt364.
[5] Tarantino P, Ajari O, Graham N, et al. Evolution of HER2 expression between pre-treatment biopsy and residual disease after neoadjuvant therapy for breast cancer. Eur J Cancer Apr 2024;201:113920. https://doi.org/10.1016/j.ejca.2024.113920.
[6] Mogica JP, Tang H, Liang Y, et al. Prognostic impact of reduced HER2 protein expression in post-neoadjuvant therapy resection specimens: a single institution experience and review of the literature. Breast Dec 2023;72:103586. https://doi.org/10.1016/j.breast.2023.103586.
[7] NCCN. Clinical practice guidelines in oncology. Breast Cancer 2024. Version 4.2024, https://www.nccn.org (Assessed December 7, 2024).
[8] Loibl S, André F, Bachelot T, et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol Feb 2024;35(2):159–82. https://doi.org/10.1016/j.annonc.2023.11.016.