Cancer Treatment and Research Communications 37 (2023) 100772

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.sciencedirect.com/journal/cancer-treatment-and-research-communications

Real world data on the demographic and clinicopathological profile and management of patients with early-stage HER2-positive breast cancer and residual disease treated with adjuvant trastuzumab emtansine (KARMA study)

Silvia Antolín Novoa [a,*], Santiago Escrivá-de-Romaní [b], Pablo Tolosa Ortega [c], Lucía Oliva Fernández [d,e], Rafael López López [f,g], Ana López González [h], Pilar de la Morena Barrio [i], Isabel Echavarria Díaz-Guardamino [j], José Enrique Alés Martinez [k], Zita Garate [l], Lucia González-Cortijo [m]

[a] Breast Cancer Department, Hospital Universitario de A Coruña, As Xubias, 84, 15006 La Coruña, Spain
[b] Vall d'Hebrón Institute of Oncology (VHIO), Hospital Universitario Vall d'Hebron, Calle de Natzaret, 115-117, 08035 Barcelona, Spain
[c] Medical Oncology Department, Hospital Universitario 12 de Octubre, Avenida de Córdoba, s/n, 28041 Madrid, Spain
[d] Intercentre Clinical Management Unit of Integral Oncology of Málaga, Hospital Regional Universitario de Málaga, Avenida de Carlos Haya, 84, 29010 Málaga, Spain
[e] Biomedical Research Institute of Malaga (IBIMA), Hospital Universitario Virgen de la Victoria, Campus de Teatinos, s/n, 29010 Málaga, Spain
[f] Medical Oncology Dept. University Clinical Hospital and Health Research Institute of Santiago de Compostela (IDIS), Travesía da Choupana, s/n, 15706 Santiago de Compostela, Spain
[g] Centre for Biomedical Research in Networks on Cancer (CIBERONC), Avenida Monforte de Lemos, 3-5, Pabellón 11. Planta 0, 28029 Madrid, Spain
[h] Department of Medical Oncology, Complejo asistencial Universitario de León. Calle Altos de Nava, s/n, 24071 León, Spain
[i] Department of Hematology and Medical Oncology, Hospital General Universitario Morales Meseguer, Avenida Marqués de Los Vélez, s/n, 30008 Murcia, Spain
[j] Department of Medical Oncology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañon (IiSGM), CIBERONC, Calle del Doctor Esquerdo, 46, 28007 Madrid, Spain
[k] Oncology Unit, Hospital Nuestra Señora de Sonsoles, Av. Juan Carlos I, s/n, 05004 Ávila, Spain
[l] Roche Pharma Spain, Calle de la Ribera del Loira, 50, 28042 Madrid, Spain
[m] Department of Medical Oncology, Hospital Universitario Quirónsalud Madrid, Calle Diego de Velázquez, 1, 28223 Pozuelo de Alarcón, Madrid, Spain

ARTICLE INFO

Keywords:
Early breast cancer
Human epidermal growth factor receptor-2 (HER2)
Adjuvant treatment
Trastuzumab emtansine (T-DM1)

ABSTRACT

Introduction: Trastuzumab emtansine (T-DM1) significantly improves invasive disease-free survival and reduces the risk of recurrence in patients with HER2-positive early breast cancer (EBC) with residual disease (RD). The KARMA study aimed to describe the characteristics and management of these patients in clinical practice in Spain.

Material and methods: We conducted a multicentre retrospective study in patients with HER2-positive EBC with RD following neoadjuvant treatment (NeoT) and who had received ≥1 dose of T-DM1 as adjuvant treatment. The primary endpoint was the evaluation of sociodemographic and clinicopathological characteristics of these patients.

Results: A total of 114 patients were included (March–July 2020). At diagnosis, most tumours were infiltrating ductal carcinoma (IDC) (93.9 %), grade 2 (56.1 %), and hormone receptor (HR)-positive (79.8 %). Over 75 % of patients had disease in operable clinical stages (T1–3 N0–1). In the neoadjuvant setting, 86.8 % of patients received trastuzumab plus pertuzumab, and 23.6 % achieved radiological complete response. Breast-conserving surgery was performed in 55.8 % of patients. Surgical specimens showed that 89.5 % of patients had IDC, 49.1 % grade 2, 84.1 % HR-positive, and 8.3 % HER2-negative disease. Most patients had RD classified as RCB-II and Miller/Payne grade 3/4. Grade 3 treatment-related adverse events (trAEs) occurred in 5.3 % of patients. No grade 4/5 AEs occurred. Over 95 % of patients were free of invasive-disease during T-DM1 adjuvant treatment.

* Corresponding author at: Hospital Universitario de A Coruña, As Xubias, 84, 15006 La Coruña, Spain.
E-mail address: silvia.antolin.novoa@sergas.es (S. Antolín Novoa).

https://doi.org/10.1016/j.ctarc.2023.100772

Available online 1 November 2023

Conclusion: The KARMA study describes the characteristics of patients with HER2-positive EBC with RD after NeoT and the real-life management of a T-DM1 adjuvant regimen, which showed a manageable safety profile in line with the KATHERINE trial data.

Introduction

Female breast cancer is the most frequently diagnosed cancer worldwide, with an estimated incidence of 2.3 million new cases in 2020 and the leading cause of cancer mortality in women [1]. Overexpression of human epidermal growth factor receptor type 2 (HER2) is found in 15-20 % of breast cancers and is associated with poor prognosis, shorter survival, and higher rates of recurrence [2].

Neoadjuvant therapy has traditionally been used as the preferred treatment option in early breast cancer (EBC) for tumour downstaging to increase resectability and breast-conserving surgery rates [3,4]. Pathological complete response (pCR), defined as the absence of invasive disease in the breast and axillary lymph nodes at surgery following neoadjuvant therapy, is associated with longer disease-free survival (DFS) and overall survival in patients with early-stage HER2-positive breast cancer [5–9]. For these patients, the current standard of care is a neoadjuvant anthracycline/taxane-based regimen combined with anti-HER2 blockade with trastuzumab ± pertuzumab, followed by breast surgery [10,11]. Unfortunately, not all patients respond to neoadjuvant therapy, since 40 %–70 % of patients with HER2-positive EBC treated with neoadjuvant dual HER2-targeting with trastuzumab and pertuzumab achieve pCR, though rates of around 80 % have been reported in the HER2-enriched patient subgroup [12–16]. Improvement of clinical outcome in patients with residual disease after neoadjuvant treatment is therefore a key issue in this subset of high-risk patients.

Adjuvant trastuzumab emtansine (T-DM1) is emerging as standard treatment for patients with residual invasive disease following neoadjuvant chemotherapy plus anti-HER2 treatment as recommended according to ESMO guideline [10,11]. This antibody-drug conjugate contains the humanized anti-HER2 immunoglobulin G subclass 1 (IgG1) trastuzumab and the cytotoxic agent emtansine (DM1), a microtubule inhibitory maytansinoid [17]. T-DM1 maintains trastuzumab HER2 suppression activity while providing intracellular delivery of DM1 to HER2-overexpressing cells and limiting systemic exposure to chemotherapy [17,18]. The benefit of adjuvant T-DM1 for patients with residual HER2-positive EBC was demonstrated in the phase III open-label KATHERINE trial (NCT01772472), in which patients who had received taxane- and trastuzumab-containing neoadjuvant therapy were randomly assigned to receive 14 cycles of adjuvant T-DM1 or trastuzumab. After a median follow-up of 41.4 months, the interim analysis showed that T-DM1 significantly improved 3-year invasive DFS and halved the risk of recurrence of invasive disease or death compared to continuation of trastuzumab in the adjuvant setting [19]. Based on this pivotal study, the European Medicines Agency (EMA) approved the use of T-DM1 as adjuvant therapy of adult patients with HER2-positive EBC with invasive residual disease after neoadjuvant therapy on December 2019 [20].

A better characterization of patients with residual disease after neoadjuvant treatment and treated with adjuvant T-DM1 might contribute to find prognostic factors to identify patients who are likely to benefit from a T-DM1 adjuvant treatment [21].

In this scenario inmediately after the EMA approved T-DM1 as adjuvant therapy for patients with HER2-positive EBC with residual disease after neoadjuvant treatment, this study aimed to describe the characteristics and management of these patients treated with T-DM1 in routine clinical practice in Spain.

Materials and methods

Study design and patients

The KARMA study was a multicentre, retrospective, observational study conducted at 33 Spanish hospitals in accordance with the World Medical Association Declaration of Helsinki, all its amendments, and national regulations. The study was approved by the Independent Ethic Committee of Galicia (Spain) and all patients who were alive at the time of study start gave their written informed consent for retrospective chart review and study data collection.

Eligible patients were women aged 18 years or older, with histologically confirmed HER2-positive EBC (i.e., 3+ result by immunohistochemistry [IHC], or 2+ result by IHC and positive in situ hybridization [ISH] assessed as per local standard clinical practice) and pathological evidence of residual disease at surgery following neoadjuvant treatment, who had received both neoadjuvant therapy and at least one dose of adjuvant T-DM1 under routine clinical practice conditions, and who had available data on pathological response assessment in medical records. Patients were excluded if they had stage IV disease and/or had received adjuvant treatment with T-DM1 in a clinical trial setting, and/or had participated in any clinical trial during the administration of adjuvant therapy with T-DM1 for residual HER2-positive EBC.

To minimize selection bias, the enrolment of patients in the study began with the last patient who met screening criteria and had started adjuvant treatment with T-DM1 before the date of study start and continued to enrol patients following a reverse chronological order according to the date of T-DM1 initiation.

Study endpoints

The primary endpoint was the characterization of sociodemographic, clinical and pathological characteristics of patients treated with adjuvant T-DM1 for residual HER2-positive EBC following neoadjuvant treatment. For this purpose, a retrospective chart review was performed on the characteristics of patients and disease at diagnosis (age and race; family history of breast cancer; comorbidities; Eastern Cooperative Oncology Group [ECOG] performance status; menopausal status; tumour location, size, histology, and grade; HER2 and hormone receptors [HR] status; nodal status; Ki-67 rates; *BRCA* gene mutational status; and clinical stage [TNM]), at time of surgery (tumour histology and grade; HER2 and HR status; lymphovascular invasion [LVI]; residual tumour size; nodal status; Ki-67 rates; and pathological stage [TNM]), and at adjuvant treatment initiation (comorbidities, ECOG performance status, and left ventricular ejection fraction [LVEF]). Secondary endpoints included the patterns of neoadjuvant treatment used in patients with HER2-positive residual disease and the radiological response to neoadjuvant treatment based on RECIST criteria (version 1.1) [22] in the overall population and according to the imaging techniques applied as per local practice, such as magnetic resonance imaging (MRI) or mammography, and post-neoadjuvant therapy surgery (types of surgical procedure and rates of both breast conserving/non-conserving surgery and sentinel or axillary lymph node procedure). Furthermore, we assessed the pathological response evaluation systems used in routine clinical practice (Miller and Payne grading system [23], Residual Cancer Burden [RCB] [24], etc.) and characterized residual disease according to the pathological response assessment methods applied (i.e., Miller and Payne grading system [23]; grade by percentage of tumoral cellularity reduction in breast and lymph nodes, and RCB [24]; size of residual tumour bed, overall cancer cellularity,

percentage of *in situ* disease in the breast, number of positive lymph nodes and size of the largest nodal metastasis, plus RCB index [I: minimal residual disease; II: moderate residual disease; III: extensive residual disease]). Other secondary endpoints included the potential relationship between radiological response to neoadjuvant treatment and residual disease burden at time of surgery (measured by either the Miller and Payne grading system [23] or the RCB index [24]), the characterization of T-DM1 in the adjuvant setting (i.e., initial dose and treatment modifications and their reasons) and its safety profile (treatment-related adverse events [AEs] experienced by patients since treatment start graded according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 4.0), and the proportion of patients who remained free of invasive disease (defined as recurrence of ipsilateral invasive breast tumour, recurrence of ipsilateral locoregional invasive breast cancer, and distant disease recurrence) or who experienced invasive disease as distant recurrence after T-DM1 treatment initiation.

Post-hoc analyses included the description of breast cancer data at diagnosis of the patients who achieved clinical stage T1 N0 (considering T1mi, T1a, T1b y T1c) after neoadjuvant treatment, the characterization of peripheral neuropathy prior to and following T-DM1 initiation, and the description of thrombocytopenia during T-DM1 treatment based on the use of platinum in the neoadjuvant therapy combination.

Statistical considerations

A descriptive statistical analysis of the study variables was performed, including the calculation of measures of central tendency and dispersion (mean ± standard deviation [SD], median and interquartile range [IQR]) to describe quantitative variables, and counts and percentages to report qualitative variables. Mann–Witney U test (for unpaired data) or Wilcoxon signed-rank test (for paired data) were used for comparison of continuous variables that did not follow a normal distribution. For the comparison of proportions and/or frequency distributions, the Chi-squared test or Fisher's exact test were applied. A significance level of 0.05 was used for statistical testing. The statistical analyses were performed with the IBM Statistical Package for the Social Sciences (SPSS) version 22.0 (Armonk, NY: IBM Corp.).

Results

Patients

A total of 119 patients were enrolled in the study from March 2020 to July 2020. Five patients were excluded because they did not fulfil the screening criteria; therefore, 114 were evaluable for study analyses.

Patient and disease characteristics at diagnosis are shown in Table 1. Briefly, the median age of patients was 50 years, the majority of patients had an ECOG performance status score of 0 or 1 (81.6 %), and about half the patients (50.9 %) were premenopausal. Infiltrating ductal carcinoma (IDC) was present in most patients (93.9 %). Histological grades 2 and 3 tumours were found in 64 (56.1 %) and 36 (31.6 %) patients, respectively. Most patients (79.8 %) had HR-positive tumours. Mutated *BRCA1* and *BRCA2* were found in tumours of 4 (12.9) and 3 (9.7 %) patients, respectively. Positive nodal status was present in 59 (51.8 %) patients. The patients' most frequent clinical stages were stage IIA (55.3 %), followed by stage IIIA (14.9 %). Most patients (75.4 %) had disease in operable clinical stages (T1–3 N0–1).

Neoadjuvant treatment

Overall, 99 (86.8 %) patients had received trastuzumab plus pertuzumab in the neoadjuvant setting. Taxanes had been administered to 109 (95.6 %) patients and were combined with anthracyclines in 71 (62.3 %). Trastuzumab with or without pertuzumab was combined with taxane- and platinum-based chemotherapy in 22 (19.3 %) patients and

Table 1
Sociodemographic and clinical characteristics at diagnosis ($N = 114$).

Characteristic	Value
Age (years), median (IQR)	50.0 (42.0–60.0)
Race, n (%)	
Caucasian	107 (93.9)
Other [(1)]	6 (5.3)
NA	1 (0.9)
Menopausal status, n (%)	
Premenopausal	58 (50.9)
Postmenopausal	50 (43.9)
NA	6 (5.3)
Family history of breast cancer	58 (50.9)
ECOG performance status, n (%)	
0	84 (73.7)
1	9 (7.9)
2	1 (0.9)
NA	20 (17.5)
Tumour location, n (%)	
Left	55 (48.2)
Right	59 (51.8)
Tumour size (mm), median (IQR), ($n = 102$)	30.0 (20.8–44.0)
Tumour histology, n (%)	
Infiltrating ductal carcinoma	107 (93.9)
Infiltrating lobular carcinoma	4 (3.5)
Papillary carcinoma	1 (0.9)
NA	2 (1.8)
Tumour grade, n (%)	
Gx	1 (0.9)
G1	3 (2.6)
G2	64 (56.1)
G3	36 (31.6)
NA	10 (8.8)
Hormone receptor status, n (%)	
HR-positive (ER+ and/or PR+)	91 (79.8)
HR-negative (ER- and PR-)	23 (20.2)
HER2 status	
Immunohistochemistry, n (%)	
1^{+} [(2)]	1 (0.9)
2^{+} [(2)]	31 (27.2)
3^{+}	67 (58.8)
NA [(3)]	15 (13.2)
ISH, n (%)	
Positive	55 (48.2)
NA	59 (51.8)
BRCA mutational status, n (%) ($n = 31$)	
wild-type BRCA	20 (64.5)
mutated BRCA 1	4 (12.9)
mutated BRCA 2	3 (9.7)
Uncertain	2 (6.5)
NA	2 (6.5)
Ki-67 level (%), median (IQR) ($n = 109$)	30.0 (20.0–50.0)
≤30 % Ki-67, n (%)	55 (50.5)
>30 % Ki-67, n (%)	54 (49.5)
NA	5 (4.4)
Clinical stage, n (%)	
I	6 (5.3)
IIA	63 (55.3)
IIB	3 (2.6)
IIIA	17 (14.9)
IIIB	5 (4.4)
IIIC	3 (2.6)
Unclassified	5 (4.4)
NA	12 (10.5)
Nodal status, n (%)	
Positive	59 (51.8)
Negative	41 (36.0)
NA	14 (12.3)
Operable stage (T1-3 N0-1), n (%) [(4)]	86 (75.4)

ECOG: Eastern Cooperative Oncology Group; ER: estrogen receptor; G: grade; GERD: gastroesophageal reflux disease; HER2: human epidermal growth factor receptor type 2; HR: hormone receptor; IQR: interquartile range; ISH: in situ hybridization; NA: not available; PR: progesterone receptor.

(1) Other (Asian, Arab, Latin, Latin American, Armenian).

(2) Patients' data indicated ISH positive.

(3) Patients' data indicated ISH positive, except one patient's data that indicated unknown and ISH was not collected.

[4] Missing data: $n = 28$ (24.6 %).

with a single-agent taxane in 4 (3.5 %) patients. Neoadjuvant treatment patterns are shown in Table 2. A total of 62 (54.4 %) patients had received at least one hormonal therapy: aromatase inhibitors in 41 (66.1 %), antiestrogens in 22 (35.5 %), and luteinizing hormone-releasing hormone (LHRH) analogues in 7 (11.3 %).

Radiological response assessment to neoadjuvant treatment

Data on radiologic tumour response to neoadjuvant treatment were available for 89 (78.1 %) patients. Of these, 21 (23.6 %) achieved complete response (CR), and 63 (70.8 %) attained partial response (PR). Disease progression occurred in 2 (2.2 %) patients.

Overall, the most frequently used imaging techniques for the assessment of tumour response to neoadjuvant treatment were MRI (70.2 %), mammography (23.7 %), and ultrasound (18.4 %). The radiological response obtained according to the most frequently used imaging methods is shown in Table 3.

Clinicopathological characteristics and assessment at time of surgery

All patients had undergone surgery after neoadjuvant treatment ($n = 114$). Breast-conserving surgery was performed in 63 (55.8 %) patients. Sentinel lymph node biopsy was done in 52 (46.4 %) patients and axillary lymph node dissection was performed in 59 (52.7 %) ($n = 112$).

Surgical specimens showed that most patients (89.5 %) had IDC. Histological grade 2 and 3 tumours were found in 56 (49.1 %) and 33 (28.9 %) patients, respectively. Most patients (84.1 %) had HR+ tumours ($n = 63$). HER2 status was 3+ in the tumours of 31 (48.4 %) patients, 2+ in 13 (20.3 %), 1+ in 5 (7.8 %), and negative in 4 (6.3 %). Overall, 52 (76.5 %) patients had tumours with Ki-67 levels ≤30 % and 16 (23.5 %) patients >30 %. Patients who had the disease in T1 N0 stage (T1mi, T1a, T1b, and T1c) accounted for 32 (28.1 %) of the cases (**Supplementary Table 1S**). Clinicopathological characteristics at time of surgery are shown in Table 4.

Pathological response to neoadjuvant treatment

The pathological response to neoadjuvant treatment was evaluated by the RCB in 93 (81.6 %) patients and by the Miller and Payne system in 58 (50.9 %). Most patients (44.1 %) had moderate residual disease (RCB-II) when the RCB was used ($n = 93$). When the Miller and Payne system was applied for residual disease assessment, the majority of patients had grade 4 (34.5%) and grade 3 (31 %) response in the breast, and grade 5 (27.6 %) and grade 3 (24.1 %) response in lymph nodes. The characterization of residual disease according to the pathological response assessment method is shown in Table 4.

Table 2
Neoadjuvant treatment patterns ($N = 114$).

Treatment pattern, n (%)	Value
Trastuzumab +/- pertuzumab + anthracycline + taxane-based chemotherapy (no platinum) [1]	79 (69.3)
Trastuzumab +/- pertuzumab + platinum + taxane-based chemotherapy	22 (19.3)
Trastuzumab +/- pertuzumab + taxane only	4 (3.5)
Trastuzumab +/- pertuzumab + anthracycline + 5FU + CP	3 (2.6)
Trastuzumab +/- pertuzumab + anthracycline + taxane + platinum + 5FU + CP	2 (1.8)
Trastuzumab +/- pertuzumab + anthracycline + CP	1 (0.9)
Nor Trastuzumab nor pertuzumab	3 (2.6)

Anthracyclines (doxorubicin, epirubicin, adriamycin); CP: cyclophosphamide; FU: fluorouracil; Taxanes (paclitaxel, docetaxel, nab-paclitaxel); Platinum: carboplatin.

[1] One patient received pertuzumab + anthracycline + taxane + cyclophosphamide.

Table 3
Radiological response to neoadjuvant treatment according to the imaging technique used for tumour assessment ($N = 89$).

Imaging technique	Confirmed response (RECIST)			
	Complete response ($n = 21$; 23.6 %)	Partial response ($n = 63$; 70.8 %)	Stable disease ($n = 3$; 3.4 %)	Progressive disease ($n = 2$; 2.2 %)
MRI ($n = 80$)	20 (95.2)	51 (81.0)	1 (33.3)	2 (100.0)
Mammography ($n = 27$)	8 (38.1)	14 (22.2)	1 (33.3)	0 (0.0)
Ultrasound ($n = 21$)	3 (14.3)	11 (17.5)	2 (66.7)	0 (0.0)
Other ($n = 3$) [1]	0 (0.0)	3 (4.8)	0 (0.0)	0 (0.0)

MRI: magnetic resonance imaging; RECIST: Response Evaluation Criteria in Solid Tumours; Percentages may add more than 100 % as more than one imaging technique might have been used per patient; Percentages calculated over the total of patients with each response.

[1] Response was evaluated by computerized tomography (CT), contrast CT and Positron Emission Tomography-CT (PET-CT) in 1 patient each.

The analysis of the relationship between tumour size at diagnosis and residual disease burden measured by the RCB index did not reach statistical significance ($p = 0.110$) (**Supplementary Table 2S**).

Association between radiological response and residual disease burden

A statistically significant association was found between radiological complete response (rCR) to neoadjuvant treatment and residual breast cancer assessed by the RCB ($p = 0.007$) and by the Miller and Payne system ($p = 0.024$), with a higher proportion of patients with rCR attaining lower RCB indexes (**Supplementary Table 3S**) and lesser residual breast tumour (**Supplementary Table 4S**), respectively. No significant association was found between radiological response to neoadjuvant treatment and residual disease burden in lymph nodes assessed using the Miller and Payne grading system ($p = 0.285$).

Trastuzumab emtansine adjuvant treatment

At the time of T-DM1 treatment initiation, most patients (83.4 %) had an ECOG performance status of 0 or 1. The median LVEF value was 64 (IQR 59–66), and a total of 6 (5.3 %) patients had experienced new comorbid conditions, including skin infection, osteoarthritis, depression, anal fissure, asthenia, and urologic conditions, since their breast cancer diagnosis. Patients' clinicopathological characteristics at T-DM1 treatment initiation are shown in Table 5.

The administration of fewer than 14 cycles of T-DM1 was planned in 18 (17.5 %) patients due to previous neoadjuvant treatment consisting of >4 cycles (38.9 %), toxicity (27.8 %), and physician choice (5.6 %). At the time of study start, 70.2 % of patients were still under adjuvant treatment and had received a median of 6 cycles (IQR 3-10) of adjuvant T-DM1. Eleven (9.6 %) patients required a single dose reduction, mainly due to treatment-related AEs in 7 (77.8 %) patients. A total of 8 dose delays were performed in 7 (6.1 %) patients. Two (33.3 %) dose delays were caused by treatment-related AEs. Thrombocytopenia was the most common AE leading to dose reduction (44.4 %) and delay (50 %). Overall, 34 (29.8 %) patients had discontinued T-DM1 treatment at the time of analysis, of which 21 (61.8 %) had completed the planned number of cycles or the intended duration of treatment, whereas 13 (38.2 %) withdrew prematurely, mainly due to AEs ($n = 8$; 61.5 %). The most common AE leading to premature withdrawal was thrombocytopenia in half of the patients. Characterization of T-DM1 treatment is shown in Table 6.

Table 4
Clinicopathological characteristics at surgery ($N = 114$).

Parameter	Value
Residual tumour size (mm), median (IQR), ($n = 89$)	10.0 (1.0–20.0)
Tumour histology, n (%)	
Infiltrating ductal carcinoma	102 (89.5)
Infiltrating lobular carcinoma	4 (3.5)
Papillary carcinoma	1 (0.9)
NA	7 (6.1)
Tumour grade, n (%)	
Gx	1 (0.9)
G1	4 (3.5)
G2	56 (49.1)
G3	33 (28.9)
NA	20 (17.5)
Hormone receptor status, n (%) ($n = 63$)	
HR-positive (ER+ and/or PR+)	53 (84.1)
HR-negative (ER- and PR-)	10 (15.9)
HER2 status	
Immunohistochemistry, n (%) ($n = 64$)	
Negative [(1)]	4 (6.3)
1^+	5 (7.8)
2^+	13 (20.3)
3^+	31 (48.4)
NA	11 (17.2)
ISH, n (%) ($n = 24$)	
Positive	22 (91.7)
Negative	2 (8.3)
Ki-67 level, median (IQR) (%), ($n = 68$)	20.0 (5.0–30.0)
≤30 % Ki-67, n (%)	52 (76.5)
>30 % Ki-67, n (%)	16 (23.5)
Pathological stage, n (%)	
I	28 (24.6)
IIA	34 (29.8)
IIB	8 (7.0)
IIIA	10 (8.8)
IIIC	1 (0.9)
Unclassified	5 (4.4)
NA	28 (24.6)
Pathological response	
RCB index, n (%) ($n = 93$)	
RCB-I (Minimal residual disease)	29 (31.2)
RCB-II (Moderate residual disease)	41 (44.1)
RCB-III (Extensive residual disease)	16 (17.2)
NA	7 (7.5)
Miller and Payne criteria, n (%) ($n = 58$)	
Breast tumour	
Grade 1	6 (10.3)
Grade 2	10 (17.2)
Grade 3	18 (31.0)
Grade 4	20 (34.5)
Grade 5	4 (6.9)
Lymph nodes	
Grade 1	6 (10.3)
Grade 2	5 (8.6)
Grade 3	14 (24.1)
Grade 4	7 (12.1)
Grade 5	16 (27.6)
NA	10 (17.2)
Nodal status, n (%)	
Positive	62 (54.4)
Negative	44 (38.6)
NA	8 (7)
Lymphovascular invasion, n (%) [(2)]	26 (22.8)

ER: estrogen receptor; HER2: human epidermal growth factor receptor type 2; HR: hormone receptor; IQR: interquartile range; ISH: fluorescence in situ hybridization; G: grade; NA: not available; PR: progesterone receptor; RCB: Residual Cancer Burden.
[(1)] ISH positive ($n = 1$), Missing data: $n = 3$.
[(2)] Missing data: $n = 17$ (14.9 %). .

Table 5
Clinicopathological characteristics at adjuvant treatment initiation ($N = 114$).

Characteristic	Value
New comorbid conditions since breast cancer diagnosis, n (%)	6 (5.3)
Neurologic/psychiatric disorder	
Depression	2 (1.8)
Infectious disease	
Skin infection	1 (0.9)
Musculoskeletal disorder	
Osteoarthritis	1 (0.9)
Neoplasm	1 (0.9)
Other	
Anal fissure	1 (0.9)
Asthenia	1 (0.9)
Urologic disease	1 (0.9)
ECOG performance status, n (%)	
0	59 (51.8)
1	36 (31.6)
2	1 (0.9)
NA	18 (15.8)
LVEF, median (IQR) [(1)] ($n = 107$)	64 (59.0–66.0)

ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range; LVEF: left ventricular ejection fraction.
[(1)] CRF indicated 0 in 2 patients.

Safety

Overall, 49 (43 %) patients experienced at least one AE related to T-DM1. Treatment-related grade 3 AE were reported in 6 (5.3 %) patients: neutropenia ($n = 2$), thrombocytopenia ($n = 1$), peripheral neuropathy ($n = 1$), neurotoxicity ($n = 1$), and platelet count decrease ($n = 1$). No grade 4 or grade 5 AEs related to T-DM1 were reported. The most frequent AEs (>5 % of patients) related to adjuvant T-DM1 according to severity (NCI-CTCAE) are summarized in Table 7.

Overall, 20 (17.5 %) patients had peripheral neuropathy before the first cycle of T-DM1. At study start, these patients had received a median of 7 cycles (IQR 3.3–11.8) of adjuvant T-DM1. During treatment, the grade of peripheral neuropathy changed in severity in 4 (20 %) patients and resolved in 6 (30 %) patients. Nine (45 %) patients discontinued adjuvant T-DM1, mainly due to completion of planned cycles or conclusion of intended duration of treatment (66.7 %), whereas 33.3 % prematurely withdrew due to thrombocytopaenia ($n = 1$), peripheral neuropathy ($n = 1$), and patient's decision ($n = 1$).

During T-DM1 therapy, 41 (36 %) patients experienced peripheral neuropathy, of whom 16 (39 %) were already affected before starting treatment. At study start, these patients had received a median of 7 cycles (IQR 4–10.5) of T-DM1. Peripheral neuropathy resolved in 7 (17.1 %) patients. Data on peripheral neuropathy is detailed in **Supplementary Table 5S**.

A total of 8 (7 %) patients experienced thrombocytopenia during T-DM1 treatment, of whom 3 (37.5 %) had received platinum-based neoadjuvant therapy. Among patients who did not receive platinum (62.5 %), thrombocytopenia resolved in 80 % of patients, whereas it was only resolved in 33.3 % of those who had received platinum-based chemotherapy. Details on thrombocytopenia during T-DM1 are shown in **Supplementary Table 6S.**

Invasive disease after T-DM1 adjuvant treatment initiation

A total of 111 patients were evaluable for clinical assessment of invasive disease after starting adjuvant treatment with T-DM1, of whom 110 (99.1 %) were free of invasive disease, and one (0.9 %) experienced a distant recurrence in the lung.

Discussion

The KARMA study has, for the first time, characterized a cohort of patients with HER2-positive EBC with residual disease after neoadjuvant therapy who were treated with T-DM1 in the adjuvant setting under routine clinical practice conditions in Spain. This study offers an accurate and valuable overview of the real clinical practice in tertiary referral hospitals with sufficient resources to use dual HER2 blockade in combination with chemotherapy as neoadjuvant treatment for

Table 6
Trastuzumab emtansine treatment ($N = 114$).

Parameter	Value
Number of cycles, median (IQR) [1]	6.0 (3.0–10.0)
Initial dose (mg/weight), median (IQR) [2]	3.6 (3.6–3.6)
Dose reductions	
Patients with at least one dose reduction, n (%)	11 (9.6)
Total number of dose reductions	11
Reasons for dose reductions, n (%) ($n = 11$)	
AE	9 (81.8)
Physician's decision	1 (9.1)
Other	
Liver toxicity/emesis GII and asthenia	1 (9.1)
AEs leading to dose reduction, n (%) ($n = 9$)	
Thrombocytopenia	4 (44.4)
Neuropathy	2 (22.2)
Oesophageal spasms	1 (11.1)
Transaminitis	1 (11.1)
Weight loss	1 (11.1)
Treatment-related AEs leading to dose reduction, n (%) ($n = 9$) [3]	7 (77.8)
New dose, (mg), median (IQR) ($n = 10$) [4]	222.5 (200.0–241.3)
Dose delays	
Patients with at least one dose delay, n (%)	7 (6.1)
Total number of dose delays	8
Reasons for dose delays, n (%) ($n = 8$)	
AE	6 (75.0)
Patient's decision	1 (12.5)
Other	
Liver toxicity/emesis GII and asthenia	1 (12.5)
AEs leading to dose delay, n (%) ($n = 6$)	
Thrombocytopenia	3 (50.0)
Respiratory infection	1 (16.6)
Epithelitis	1 (16.6)
Pneumonitis	1 (16.6)
Treatment-related AEs leading to dose delay, n (%) ($n = 6$) [5]	2 (33.3)
End of treatment	
Treatment finalization at time of analyses, n (%)	34 (29.8)
Reasons for treatment finalization, n (%) ($n = 34$)	
Planned cycles/duration	21 (61.8)
Premature withdrawal	13 (38.2)
Reasons for premature withdrawal, n (%) ($n = 13$)	
AE	8 (61.5)
Physician's decision	3 (23.1)
Patient's decision	2 (15.4)
AEs leading to premature withdrawal, n (%) ($n = 8$)	
Thrombocytopenia	4 (50.0)
Neuropathy	2 (25.0)
Neurotoxicity	1 (12.5)
Neutropenia	1 (12.5)
Treatment-related AEs leading to premature withdrawal, n (%) ($n = 8$)	7 (87.5)

AE: adverse event; G: grade.
[1] Missing data: $n = 1$ (0.9 %).
[2] Two patients' data was not included as 3.6 mg were indicated in CRF, missing data: $n = 13$.
[3] Missing data: $n = 1$ (11.1 %).
[4] One patient's data was not included as 2.9 mg were indicated in CRF.
[5] Missing data: $n = 1$ (16.7 %).

Table 7
Most frequent adverse events related to adjuvant T-DM1 ($N = 114$).

Treatment-related AEs [1]	**Grade (NCI-CTCAE)**				
	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)	Grade 5 N (%)
Peripheral neuropathy	5 (4.4)	3 (2.6)	1 (0.9)	0 (0.0)	0 (0.0)
Asthenia	7 (6.1)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	1 (0.9)	4 (3.5)	1 (0.9)	0 (0.0)	0 (0.0)
Fatigue	6 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	5 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased appetite	3 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertransaminasaemia	2 (1.8)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal upper pain	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Aspartate aminotransferase increase	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myalgia	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AEs: adverse events. NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events. T-DM1: trastuzumab emtansine.
[1] Most frequent treatment-related AEs, experienced by more than one patient each.

managing these patients.

The choice of neoadjuvant treatments reported in the KARMA study is consistent with previous reports. Trastuzumab ± pertuzumab in combination with anthracycline- and taxane-based chemotherapy was the most frequent neoadjuvant therapy in our study, which had been previously defined as the routine treatment in HER2-positive patients [25]. In the KATHERINE study, the proportion of patients who received dual HER2 blockade was lower (about 18 %) than in the current study (86.8 %), while a similar proportion of patients received anthracycline-containing chemotherapy (about 75 %) [19]. Other neoadjuvant regimens omitting anthracyclines and including trastuzumab, pertuzumab, and/or platinum- and taxane-based chemotherapy have previously shown better safety profile regarding cardiotoxicity and at least equal pCR than anthracycline-based therapies in HER2-positive patients [26–28]. These regimens were also used in our study, though to a lesser extent.

Our results showed that breast-conserving surgery after neoadjuvant therapy was performed in approximately 55 % of patients, consistent with results from previous studies. In the TRAIN-2 trial, where patients received neoadjuvant dual HER2 blockade in combination with chemotherapy with or without anthracyclines, breast-conserving surgery occurred in 56 % and 43 % of women, respectively [28]. Additionally, a meta-analysis comprising ten randomised trials showed 65 % of breast-conserving therapies among patients receiving neoadjuvant therapy [29].

Previous clinical trials have shown higher pCR rates in HER2-positive patients compared with HER2-negative, as well as in HR-negative patients compared with HR-positive [12,14,27,30]. This has been shown in patients receiving neoadjuvant therapies consisting of pertuzumab, trastuzumab, and standard anthracycline- and taxane-containing chemotherapy [12,14], but also when the patient received dual HER2 blockade combined with anthracycline-free chemotherapy [27,28]. In our study, which included a cohort of patients with residual disease, most of the patients were HR-positive after the neoadjuvant treatment, which is in line with previous literature indicating that this type of patients is less likely to attained pCR.

In the present study, neoadjuvant treatment did not affect tumour subtypes. We had a steady frequency of IDC (about 90 %) and HR-positive tumours (80–85 %). After neoadjuvant treatment, the frequency of HER2-positive tumours slightly decreased but stayed above 90 %. HER2-positive to HER2-negative status changes in residual breast cancer have been observed following neoadjuvant systemic therapy [31–35]. Although the exact mechanisms causing a change in HER2 expression following neoadjuvant systemic therapy remain unknown, it has been proposed that intratumoral heterogeneity might be relevant and that HER2-directed neoadjuvant therapy induced clonal selection of HER2-negative cells. The change from HER2-positive to HER2-negative status might have clinical consequences. Recent research has revealed that HER2-negative residual disease following neoadjuvant systemic therapy is associated with a poor prognosis [32–34]. In addition, a previous study showed that invasive-disease-free survival (IDFS) events occurred in around one-quarter of the patients with HER2-negative residual disease after neoadjuvant systemic therapy treated with trastuzumab as adjuvant therapy. In contrast, no IDFS events occurred in the patients with HER2-negative residual disease treated with T-DM1 in the

KATHERINE trial [31], suggesting that the HER2-negative status of the residual disease doesn't exclude that patients might benefit from anti-HER2 treatment. Patients with tumours with >30 % of Ki-67 declined from 49.5 % at diagnosis to 23.5 % at surgery, probably as a consequence of the neoadjuvant therapy.

We found that the radiological response to neoadjuvant treatment would be associated with the extent of residual disease after surgery. Patients with radiological complete response showed minimal or moderate residual disease (RCB I and II index, respectively) and higher pathological response (Miller and Payne grade 4/5). Despite the low pCR in the breast tumour, a higher rate of patients attained complete response in the lymph nodes, which could have impacted the surgical strategy at this level.

Male breast cancer is uncommon, accounting for only 1 % of occurrences, around 10 % HER-2 positive [36–38]. Given the low frequency of early-stage HER2-positive breast cancer in males and this study's sample size, including such patients would have provided little evidence from which to withdraw any relevant conclusions.

T-DM1 adjuvant treatment was well tolerated. No grade 4 or grade 5 AEs occurred after a median of 6 cycles of treatment. Grade 3 AEs related to treatment showed low incidence, mainly neutropenia (1.8 %), thrombocytopenia (0.9 %), and peripheral neuropathy (0.9 %). Thrombocytopenia and peripheral neuropathy could have been associated with the taxane- and/or platinum-based neoadjuvant therapy since 17.5 % of patients experienced peripheral neuropathy before the first cycle of T-DM1, and the resolution rate of thrombocytopenia was higher in patients who did not receive platinum-based neoadjuvant therapy. Our safety findings are consistent with those reported in the KATHERINE study, where more than 70 % of the patients completed 14 cycles of treatment: grade 3 or higher toxicities included a decreased platelet count (5.7 %), hypertension (2 %), sensory neuropathy (1.4 %), and decreased neutrophil count (1.2 %) [19]. Thus, our study confirmed the safety of T-DM1 as showing a tolerable and manageable profile. Nevertheless, safety data should be interpreted within the context of a retrospective study conducted under the conditions of routine clinical practice.

Adverse events leading to premature treatment withdrawal occurred in 8 (7.0 %) patients compared to 18 % of patients treated with T-DM1 in the KATHERINE trial [19]. Additionally, about 10 % of patients required at least one dose reduction, similar to the T-DM1-treated populations in the KATHERINE study. The low discontinuation rate may suggest a moderate impact of toxicity and manageable dose adjustments in these patients in the real-world setting.

This study has limitations that should be acknowledged. The retrospective nature of the study determined the data availability, implying data generation according to routine clinical practice and a lack of systematically collected data. According to the TDM-1 label and guidelines, the recommended adjuvant treatment comprises 14 cycles. Due to the study design and that patients receiving at least one dose were included, the median number of T-DM1 treatment cycles in this study was only 6. Consequently, 70.2 % of patients were still under adjuvant treatment at the time of analysis.

Conclusion

The KARMA study describes the sociodemographic and clinicopathological characteristics of patients with HER2-positive EBC with residual disease after neoadjuvant treatment and the real-life management of treatment with adjuvant trastuzumab emtansine. At breast cancer diagnosis, over 70 % of the patients have tumours at operable clinical stages. There is also a high frequency of infiltrating ductal carcinoma, mainly grade 2, and HR-positive tumours, and most of the patients receive neoadjuvant treatment with trastuzumab plus pertuzumab in combination with anthracyclines and taxanes-based chemotherapies. This study also supports the manageable safety profile of the adjuvant T-DM1 regimen, with a low discontinuation rate.

Clinical practice points

Trastuzumab emtansine (T-DM1) significantly improves invasive disease-free survival and reduces the risk of recurrence in HER2-positive (HER2+) early breast cancer (EBC) patients with residual disease (RD) at the time of surgery after neoadjuvant treatment. A better characterization of patients with RD after neoadjuvant treatment might improve the clinical management of these patients and address the increased risk of recurrence and worse prognosis of their disease.

Our study was conducted in patients with HER2-positive EBC with RD following neoadjuvant treatment who had received ≥1 dose of T-DM1 as adjuvant treatment. At diagnosis, most patients had infiltrating ductal carcinoma (IDC), grade 2, and hormone receptor-positive (HR+) tumours, and their disease was in operable clinical stages (T1-3 N0-1). Most patients received trastuzumab plus pertuzumab as neoadjuvant therapy, and one-fourth achieved radiological complete response. Breast-conserving surgery was performed in about half of the patients. Surgical specimens showed that most patients had RD classified as moderate. Grade 3 treatment-related adverse events occurred in 5.3 % of patients, and no grade 4/5 treatment-related adverse events were reported.

The KARMA study describes the characteristics of HER2+ EBC patients with RD after neoadjuvant treatment and the real-life management of a T-DM1 adjuvant regimen. This study supports the manageable safety profile of the adjuvant T-DM1 regimen.

Author contribution

Silvia Antolín Novoa, Santiago Escrivá de Romaní, and Lucia Gonzalez-Cortijo have contributed to the Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing - original draft and Writing - review and editing. Pablo Tolosa Ortega, Lucía Oliva Fernández, Rafael López López, Ana López González, Pilar de la Morena Barrio, Isabel Echavarria Díaz-Guardamino, José Enrique Alés Martinez, and Zita Garate have contributed to the Data curation, Investigation, Visualization and Writing - review and editing. All authors approved the final version of the manuscript.

Funding

This work was funded by Roche Farma SA (Spain). The sponsor was involved in the study design, collection, analysis, and interpretation of data, writing of the report, and in the decision to submit the article for publication.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Silvia Antolín Novoa declares consulting fees from Roche, Daiichi Sankyo, Pierre Fabre, and Lilly; and fees for non-continuing medical education (CME) services received directly from commercial interest or their agents from Roche, Pierre Fabre, and Pfizer. Santiago Escrivá de Romaní Muñoz declares consulting fees from F. Hoffmann-La Roche Ltd, Pierre-Fabre, AstraZeneca/Daiichi-Sankyo, and Seagen; fees for non-CME services received directly from commercial interest from F. Hoffmann-La Roche Ltd, Pierre-Fabre, Novartis, AstraZeneca/Daiichi-Sankyo, and Seagen; and contracted research (for the institution) from F. Hoffmann-La Roche Ltd, AstraZeneca/Daiichi-Sankyo, Byondys, Zymeworks, MedSir, and Solti. Pablo Tolosa Ortega declares consulting fees from AstraZeneca, Daiichi-Sankyo, Novartis, and Seagen; and fees for non-CME services received directly from commercial interest from Pfizer, Novartis, Lilly, AstraZeneca, Daiichi-Sankyo, and Seagen. Rafael López López has received honoraria for participation in Advisory Boards from Roche, AstraZeneca, Merck, MSD, Bayer, BMS, Novartis, Janssen, Lilly, Pfizer, and Leo; travel, accommodations, and expenses from

Pharmamar, Roche, BMS, and Pierre Fabre; research funding from Roche and Merck; and is co-founder and shareholder in Nasasbiotech, Diversa Technologies. Ana López González has received consulting fees from Pfizer, Lilly, and Seagen; and non-CME services directly from commercial interest from Pfizer, Novartis, Lilly, and Roche. Pilar de la Morena Barrio declares expert testimony fees from Roche and GSK and honoraria from GSK. Isabel Echavarria Díaz-Guardamino has received fees from Lilly and Astra Zeneca; and fees for non-CME services received directly from commercial interest or their agents from Roche, Pierre Fabre, Novartis, Lilly, and Pfizer. Lucia González-Cortijo declares consulting fees from MSD and GSK; and fees for non-CME services received directly from Roche, MSD, GSK, and Gilead. Lucía Oliva Fernández and José Enrique Alés Martinez declare no conflicts of interest. Zita Garate is a Roche Pharma employee.

Acknowledgements

Medical writing support was provided by Alberto García Mariscal at Dynamic Science SLU (Evidenze Clinical Research), and it was funded by Roche Farma SA (Spain).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2023.100772.

References

[1] H. Sung, J. Ferlay, R.L. Siegel, et al., Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 71 (2021) 209–249.
[2] R.M. Sareyeldin, I. Gupta, I. Al-Hashimi, et al., Gene expression and miRNAs profiling: function and regulation in human epidermal growth factor receptor 2 (HER2)-positive breast cancer, Cancers (Basel) (2019) 11.
[3] A.M. Chen, F. Meric-Bernstam, K.K. Hunt, et al., Breast conservation after neoadjuvant chemotherapy: the MD Anderson cancer center experience, J. Clin. Oncol. 22 (2004) 2303–2312.
[4] B.K. Killelea, V.Q. Yang, S. Mougalian, et al., Neoadjuvant chemotherapy for breast cancer increases the rate of breast conservation: results from the National Cancer Database, J. Am. Coll. Surg. 220 (2015) 1063–1069.
[5] P. Cortazar, L. Zhang, M. Untch, et al., Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis, Lancet 384 (2014) 164–172.
[6] M. Untch, P.A. Fasching, G.E. Konecny, et al., Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups, J. Clin. Oncol. 29 (2011) 3351–3357.
[7] E. de Azambuja, A.P. Holmes, M. Piccart-Gebhart, et al., Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response, Lancet Oncol. 15 (2014) 1137–1146.
[8] L. Gianni, W. Eiermann, V. Semiglazov, et al., Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort, Lancet Oncol. 15 (2014) 640–647.
[9] A. Schneeweiss, S. Chia, T. Hickish, et al., Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer, Eur. J. Cancer 89 (2018) 27–35.
[10] M. Ban, B. Petrić Miše, E Vrdoljak, Early HER2-positive breast cancer: current treatment and novel approaches, Breast Care (Basel) 15 (2020) 560–569.
[11] F. Cardoso, S. Kyriakides, S. Ohno, et al., Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†, Ann. Oncol. 30 (2019) 1194–1220.
[12] L. Gianni, T. Pienkowski, Y.H. Im, 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. 13 (2012) 25–32.
[13] S. Loibl, C. Jackisch, A. Schneeweiss, et al., Dual HER2-blockade with pertuzumab and trastuzumab in HER2-positive early breast cancer: a subanalysis of data from the randomized phase III GeparSepto trial, Ann. Oncol. 28 (2017) 497–504.
[14] S.M. Swain, M.S. Ewer, G. Viale, 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. 29 (2018) 646–653.
[15] J. Hong, Y.H. Park, Perioperative HER2 targeted treatment in early stage HER2-positive breast cancer, Ther. Adv. Med. Oncol. 14 (2022), 17588359221106564.
[16] J. Gavila, M. Oliveira, T. Pascual, et al., Safety, activity, and molecular heterogeneity following neoadjuvant non-pegylated liposomal doxorubicin, paclitaxel, trastuzumab, and pertuzumab in HER2-positive breast cancer (Opti-HER HEART): an open-label, single-group, multicenter, phase 2 trial, BMC Med. 17 (2019) 8.
[17] Kadcyla: European public assessment report - product information: European Medicines Agency 2021.
[18] T.T. Junttila, G. Li, K. Parsons, G.L. Phillips, M.X. Sliwkowski, Trastuzumab-DM1 (T-DM1) retains all the mechanisms of action of trastuzumab and efficiently inhibits growth of lapatinib insensitive breast cancer, Breast Cancer Res. Treat. 128 (2011) 347–356.
[19] G. von Minckwitz, C.S. Huang, M.S. Mano, et al., Trastuzumab emtansine for residual invasive HER2-positive breast cancer, N. Engl. J. Med. 380 (2019) 617–628.
[20] J. Delgado, C. Vleminckx, S. Sarac, et al., The EMA review of trastuzumab emtansine (T-DM1) for the adjuvant treatment of adult patients with HER2-positive early breast cancer, ESMO Open 6 (2021), 100074.
[21] M.C. Liefaard, E.H. Lips, J. Wesseling, et al., The way of the future: personalizing treatment plans through technology, Am. Soc. Clin. Oncol. Educ. Book 41 (2021) 1–12.
[22] E.A. Eisenhauer, P. Therasse, J. Bogaerts, et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), Eur. J. Cancer 45 (2009) 228–247.
[23] K.N. Ogston, I.D. Miller, S. Payne, et al., A new histological grading system to assess response of breast cancers to primary chemotherapy: prognostic significance and survival, Breast 12 (2003) 320–327.
[24] W.F. Symmans, F. Peintinger, C. Hatzis, et al., Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy, J. Clin. Oncol. 25 (2007) 4414–4422.
[25] T. Hyder, S. Bhattacharya, K. Gade, A. Nasrazadani, A.M. Brufsky, Approaching neoadjuvant therapy in the management of early-stage breast cancer, Breast Cancer (Dove Med Press) 13 (2021) 199–211.
[26] M.S. van Ramshorst, E. van Werkhoven, I.A.M. Mandjes, et al., Trastuzumab in combination with weekly paclitaxel and carboplatin as neo-adjuvant treatment for HER2-positive breast cancer: the TRAIN-study, Eur. J. Cancer 74 (2017) 47–54.
[27] A. Schneeweiss, S. Chia, T. Hickish, 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. 24 (2013) 2278–2284.
[28] M.S. van Ramshorst, A. van der Voort, E.D. van Werkhoven, et al., Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial, Lancet Oncol. 19 (2018) 1630–1640.
[29] Early Breast Cancer Trialists' Collaborative G, Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials, Lancet Oncol. 19 (2018) 27–39.
[30] G.V. Minckwitz, M. Kaufmann, S. Kuemmel, et al., Correlation of various pathologic complete response (pCR) definitions with long-term outcome and the prognostic value of pCR in various breast cancer subtypes: results from the German neoadjuvant meta-analysis, J. Clin. Oncol. 29 (2011) 1028. -1028.
[31] S. Loibl, C.-S. Huang, M.S. Mano, et al., Adjuvant trastuzumab emtansine in HER2-positive breast cancer patients with HER2-negative residual invasive disease in KATHERINE, npj Breast Cancer 8 (2022) 106.
[32] E.A. Mittendorf, Y. Wu, M. Scaltriti, et al., Loss of HER2 amplification following trastuzumab-based neoadjuvant systemic therapy and survival outcomes, Clin. Cancer Res. 15 (2009) 7381–7388.
[33] V. Guarneri, M.V. Dieci, E. Barbieri, et al., Loss of HER2 positivity and prognosis after neoadjuvant therapy in HER2-positive breast cancer patients, Ann. Oncol. 24 (2013) 2990–2994.
[34] F.P. Branco, D. Machado, F.F. Silva, et al., Loss of HER2 and disease prognosis after neoadjuvant treatment of HER2+ breast cancer, Am. J. Transl. Res. 11 (2019) 6110–6116.
[35] N. Niikura, A. Tomotaki, H. Miyata, et al., Changes in tumor expression of HER2 and hormone receptors status after neoadjuvant chemotherapy in 21,755 patients from the Japanese breast cancer registry, Ann. Oncol. 27 (2016) 480–487.
[36] L. Ottini, D. Palli, S. Rizzo, M. Federico, V. Bazan, A. Russo, Male breast cancer, Crit. Rev. Oncol. Hematol. 73 (2010) 141–155.
[37] F. Cardoso, J.M.S. Bartlett, L. Slaets, et al., Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program, Ann. Oncol. 29 (2018) 405–417.
[38] E. Adrienne, A. Elizabeth, O. Hayrettin, L.T Patty, Characteristics, treatment and outcomes of HER2 positive male breast cancer, Am. J. Surg. (2022).