Treatment and outcome for HER2 positive metastatic breast cancer patients: A Danish retrospective cohort.

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Word count: 4157

Abstract

Background:

Human Epidermal growth factor Receptor 2 positive metastatic breast cancer (HER2+ MBC) has a high tendency to develop central nervous system (CNS) metastases and is associated with a poor prognosis. However, in recent years, progress in systemic treatment has substantially improved survival. Danish real-world data describing treatment and outcomes, for this patient group, remains limited.

Methods:

We conducted a retrospective cohort study including 100 patients diagnosed with de novo or recurrent HER2+ MBC and treated with first-line double anti-HER2 treatment at Aalborg University Hospital between 2014–2024. Progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan–Meier methods. Univariable and multivariable Cox regression were used to evaluate prognostic factors including performance status (PS), tumor burden, estrogen receptor status, age, and CNS metastases.

Results:

Median PFS in first-, second-, and third-line therapy was 15.7, 7.7, and 4.5 months, respectively. Median OS for the full cohort was 49.3 months. High tumor burden, patients presenting with or developing CNS metastases, and patients in PS >0 were significantly associated with shorter PFS and OS. In the multivariable analysis, CNS metastases (HR 2.31), high tumor burden (HR 1.88), and PS 2 (HR 4.46) remained independent predictors of worse survival. Tumor burden predicted time to CNS metastases, however estrogen receptor status did not.

Conclusion:

The findings of this Danish cohort with HER2+ MBC patients were comparable to international real-world data and support the efficacy of the current treatment guidelines. CNS metastases, tumor burden, and PS had a major impact on survival and emphasizes the need for continued refinement of treatment for these patient groups in the future.

Table of contents

Background

The incidence of breast cancer in Denmark has been relatively stable the last 10 years, with an incidence of 5389 in 2024 [1]. However, the prevalence of women living with a breast cancer diagnosis has been rising from 56752 in 2011 to 80963 in 2024 [1, 2]. Although most of these patients get diagnosed with breast cancer in a non-metastatic stage, about 6% will be diagnosed in metastatic stages [3]. About 20% of patients with metastatic breast cancer (MBC) are Human Epidermal growth factor Receptor 2 positive (HER2+) [4]. The HER2 receptor belongs to a family of transmembrane tyrosine kinase receptors responsible for regulation of cell growth, vascular formations, and cell survival, thus HER2+ breast cancer is associated with faster tumor growth, earlier metastases, and worse prognosis [5]. In addition to conventional chemotherapy, anti-HER2 therapy has shown to significantly improve survival in both metastatic and non-metastatic HER2+ breast cancer. In addition, 20-25% of HER2+ patients develop central nervous system (CNS) metastases, associated with worse survival [6, 7].

Treatment of patients with metastatic HER2+ breast cancer

Advances in anti-HER2 therapy have substantially prolonged progression-free survival (PFS) and overall survival (OS) in HER2+ MBC patients [7, 8]. Prognosis remains modulated by factors such as age, performance status (PS), and tumor burden, including intracranial disease burden, with considerable inter-patient heterogeneity limiting precision of outcome prediction [3, 9-11].

A major milestone in the management of HER2+ MBC was the introduction of trastuzumab, which is a recombinant monoclonal antibody targeting HER2. In the M77001 study, patients with HER2+ MBC were randomized to docetaxel plus trastuzumab versus docetaxel alone. This study showed significant improvement in PFS (median PFS (mPFS) 11.7 vs 6.1 months) and OS (median OS (mOS) 31.2 vs 22.7 months) for patients receiving chemotherapy and trastuzumab compared to chemotherapy alone [12].

From 2013, pertuzumab, another anti-HER2 treatment, was added to the treatment regime due to the CLEOPATRA study, which was a randomized double blinded placebo-controlled study investigating the effect of the addition of pertuzumab to trastuzumab and chemotherapy compared to placebo, trastuzumab and chemotherapy [3, 13]. The study showed significantly improved OS for the patients treated with pertuzumab, trastuzumab, and chemotherapy. In their updated follow-up studies, the placebo group had an OS of 89.0%, 69.4%, and 50.4% 1, 2, and 3 years after treatment compared to the pertuzumab group with an OS of 94.4%, 80.7%, and 65.8% [13]. Thus, the results of the CLEOPATRA study, supported by other similar studies [6, 8-10, 14], underlined a more favorable patient outcome and since 2014, double blockade of HER2 in combination with

docetaxel, has been the first-line treatment of HER2+ MBC. However, in Denmark it is recommended to use vinorelbine instead of docetaxel due to the HERNATA study, which concluded that none of the two drugs had superior efficacy, but patients receiving vinorelbine experienced fewer adverse effects [15].

Today the treatment in subsequent lines has become more complex. Trastuzumab emtansine (T-DM1) has been the second-line treatment for several years [16, 17]. However, there has been a shift towards trastuzumab deruxtucan (T-DXd) in 2023 based on the evidence presented in the randomized DESTINY-breast-studies [18, 19]. These studies showed improved PFS (25.1 vs 7.2 months) and OS (12-month OS 94.1% vs 85.9%) for T-DXd compared to T-DM1 (previously treated with trastuzumab plus a taxane), although T-DM1 presented about 12% less side effects compared to T-DXd [3, 19].

Treatment of HER2+ patients with CNS metastases

Regarding patients with CNS metastases, the choice of systemic treatment is a challenge as neither trastuzumab, nor chemotherapy cross the blood-brain barrier (BBB). However, due to the destruction of the BBB by earlier treatment such as cranial surgery or radiotherapy, these treatments have shown to prolong OS [7]. In a double-blinded placebo-controlled study, HER2CLIMB, tucinatib (protein kinase inhibitor) in combination with capecitabine (chemotherapy) and trastuzumab has shown better survival (mOS 24.7 months) compared to the control of placebo plus capecitabine and trastuzumab (mOS 19.2 months) [20]. However, there is no guideline for systemic treatment of CNS metastases in Denmark. In addition to systemic treatment, it is recommended to obtain local control, which may include treatment such as surgery, stereotactic radiosurgery (SRS), or whole-brain radiotherapy (WBRT) depending on the number of lesions and size [3, 7].

Quality control

To ensure equal and updated treatment in Denmark the Danish Breast Cancer Group (DBCG) is responsible for continuously updating guidelines according to the newest evidence [3]. Additionally, to evaluate response to treatment, the patients are followed by routine imaging, most commonly, computed tomography (CT) scans with or without magnetic resonance imaging (MRI), and the disease burden is evaluated by the standard protocol of Response Evaluation Criteria in Solid Tumors (RECIST) [21].

Aim

The study by Artzi et al. in 2023 has already underlined the effect of treatment according to guidelines in the Danish patient HER2+ MBC group, by assessing the choices of first- and second-line treatment and their adherence to guidelines [6]. However, there are lacking studies investigating patients receiving first-line treatment according to guidelines, the subsequent treatment lines and detailed information regarding PFS and OS.

This study is a quality control study investigating the treatment, PFS, and OS in patients presenting with de novo or recurrent HER2+ MBC in the North Denmark Region, with a special focus on the treatment and survival of the patients developing CNS metastases.

Methods

This study is a historical, retrospective cohort study, of the population of HER2+ MBC patients treated with first-line treatment at the department of oncology at Aalborg University Hospital.

Patient identification and characteristics

Patients were identified using the online platform for ordination, MedOnc. For inclusion the patients needed to be diagnosed with de novo or recurrent HER2+ MBC and had received first-line treatment with double anti-HER2 blockade in combination with chemotherapy at the department of oncology at Aalborg University Hospital in the period 01.01.2014 - 31.12.2024. The end of follow-up was set on 01.09.2025. The patients had to have started first-line treatment no later than 1 month before the end of follow-up. In total, 112 patients were identified, and 100 patients were included in this study. Inclusion and exclusion flow is presented in figure 1.

Information about the primary diagnosis, disease burden, patient and treatment characteristics was retrieved from the patient record. The data was entered into REDCap [22, 23].
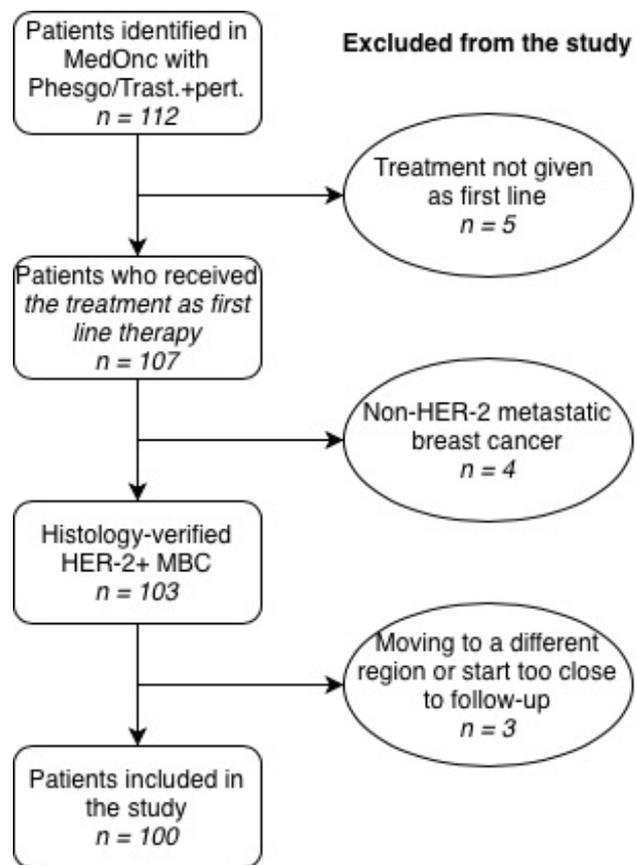

Figure 1: Study flowchart. Trast. = trastuzumab; pert. = pertuzumab; MBC = metastatic breast cancer.

Definitions

Baseline characteristics

Age was defined as the age of the patient on the day of diagnosis with MBC. PS was estimated by the clinician before the start of first-line treatment, using the ECOG performance status scale [24]. Histology with estrogen receptor (ER) and HER2 status was documented by the pathologists in patient records. Breast cancer recurrence was defined as a biopsy proven recurrence of the same type of histology verified cancer after completing treatment for the initial disease. To be in

accordance with other studies, the categorization of the initial metastatic site was defined as 1) visceral which included liver, lung, pancreas, heart, pleura, peritoneum, the gastrointestinal tract, kidney, endocrine glands, uterus, or ovaries, 2) non-visceral which included any other site such as bone and skin., and 3) brain.

Tumor burden was defined as the number of metastatic sites at the time of diagnosis. Lymph node involvement above the diaphragm was counted as one site, for instance involvement in the axil and the mediastinum was one site.

For patients with recurrent disease, systemic treatment for the primary breast cancer was registered.

CNS metastases

The treatment for CNS metastases was registered including the dose of radiation and number of fractions. The date of radiation was defined as the first day of treatment.

Dates for survival statistics

The date of diagnosis was defined as the day of the histopathological sampling concluding HER2+ MBC. For patients with recurrent MBC, the date of the primary breast cancer was defined as the day of initial histopathological sampling of the primary disease.

Progression was defined by the physician according to the RECIST criteria. The date of death was recorded in the patient record. The systemic treatment in each line was collected from MedOnc.

Statistical analyses

Baseline characteristics were described by number (N) and percentage for each variable, however for age, the median and range were presented.

PFS and OS were calculated using the Kaplan-Meier method. PFS was defined as the time from diagnosis of MBC to either the first progression (first-line treatment) or death. PFS for progression 2 and 3 (second- and third-line treatment), was the time from the previous progression to the next progression or death. Median PFS (mPFS) for first-line treatment was compared with log-rank test for patients in PS 0 versus 1+, tumor burden low versus high, and CNS metastases versus none. OS was defined as the time from diagnosis of de novo or recurrent MBC to either censoring at the last follow-up date or death. The mOS was also compared with a log-rank test according to patients treated in 2014-2018 versus 2019-2024, recurrent versus de novo disease, CNS metastases versus no CNS metastases, and tumor burden low versus high, PS 0 versus 1+, and ER status.

These variables were furthermore tested with Cox regression analysis, both univariable and multivariable, presented with the Hazard Ratio (HR) and 95% confidence intervals (CI). In the multivariable analysis, variables were adjusted for age, tumor burden, PS, and ER status.

Kaplan–Meier analysis was used to assess whether tumor burden or ER status predicted time from diagnosis to CNS metastasis or censoring, with CNS metastasis defined as the event.

For a test to be statistically significant, the p-value should be < 0.05. All statistics were carried out in Stata v. 17.0 (StataCorp. 2025. Stata Statistical Software: Release 19. College Station, TX: StataCorp LLC.).

Results

Baseline characteristics

The baseline characteristics of the 100 patients included in this study is presented in table 1. Median age was 59.5 (range 25-83). Most patients were in PS 0-2 (84%), but 2% were in PS 3-4 and for 14% of the patients the PS was not specified. The most common histology subtype was invasive ductal carcinoma (90%) and 68% of the patients had an ER positive disease.

Baseline Characteristics				
	n = 100, (%)			**n = 100, (%)**
Age, Median (range)	*59.5 (25-83)*	**Tumour burden****		
Performance status		1, Low		*24 (24%)*
0	*45 (45%)*	2, Low		*33 (33%)*
1	*30 (30%)*	3+, High		*43 (43%)*
2	*9 (9%)*	**Earlier treatment**		
3	*1 (1%)*	None***		*35 (35%)*
4	*1 (1%)*	Anti-HER2 + chemo		*15 (15%)*
Not specified	*14 (14%)*	Anti-HER2 + chemo + anti-hormone		*35 (35%)*
Histology		Anti-hormone		*15 (15%)*
Ductal	*91 (91%)*			
Lobular	*6 (6%)*			
Other*	*3 (3%)*			
Estrogen receptor status		**Local CNS treatment characteristics**		**n = 32, (%)**
Positive	*68 (68%)*	**CNS metastases treatment type**		
Negative	*32 (32%)*	WBRT		*21 (65.6%)*
Presentation		SRS		*5 (15.6%)*
De novo	*33 (33%)*	Surgery + WBRT		*4 (12.5%)*
Recurrent	*67 (67%)*	Surgery + SRS		*2 (6.3%)*
Initial metastatic site		**Radiotherapy (Gray/Fractions)**		
Visceral	*48 (48%)*	WBRT: 30/10, 30/3, 20/5, 20/4		*25 (78.1%)*
Non-visceral	*45 (45%)*	SRS: 27/3, 20/1		*7 (21.9%)*
Brain	*7 (7%)*			

Table 1: Baseline Characteristics and Local CNS treatment characteristics. WBRT = Whole Brain Radiotherapy, SRS = Stereotactic Radiosurgery.
*Histology types such as tubular
**Number of metastatic sites
***Represents 33 patients with de novo disease and the patients who had declined treatment.

In total, 33% of the patients were diagnosed with de novo disease while 67% had recurrence of breast cancer. The most common metastatic sites were visceral (48%) or non-visceral (45%), however, 7% of the patients presented with brain metastases. As presented in table 1, 57% of the patients had a low tumor burden (24% with 1 and 33% with 2 metastatic sites) while 43% of patients had a high tumor burden with 3 or more metastatic sites. Moreover, 32% of the patients presented with or developed CNS metastases during follow-up. Of these, 21 (65.6%) received whole brain radiotherapy (WBRT), 5 (15.6%) were treated with stereotactic radiosurgery (SRS), 4 (12.5%) with surgery and WBRT, and 2 (6.3%) with surgery and SRS. WBRT was delivered with 30-20 Gray in 10-3 fractions while SRS was delivered with 27-20 Gray in 3-1 fractions.

No prior treatment was given to 35% of patients before being diagnosed with MBC. Of these 33% were diagnosed with de novo MBC and 2% had declined treatment in relation to their primary disease. For the patients with recurrence, 50% received anti-HER2 treatment and chemotherapy with or without anti-hormone treatment, while 15% received anti-hormone treatment alone, prior to the diagnosis with MBC.

Treatment lines

Of the total cohort, 58 patients received second-line treatment. Almost half of these patients also received further lines of treatment. In total, 6 patients received up to 8 lines of treatment with varying types as presented in table 2. Most of the patients had been treated with T-DM1 or T-DXd as second-line treatment. During subsequent treatments, anti-HER2 treatment as a single (trastuzumab) or double blockade (trastuzumab and pertuzumab) with chemotherapy or anti-hormone was the most common choice of treatment. The use of lapatinib in combination with trastuzumab or capecitabine was also relatively common, however only few patients received the presently recommended third-line treatment with trastuzumab, capecitabine, and tucatinib.

	Line of treatment							
	2	3	4	5	6	7	8	n
T-DM1	35	2		1				38
T-DXd	9	4	1	1	1	1	1	18
Trastuzumab, Capecitabine, Tucatinib		2	1					3
Capecitabine, Lapatinib	1	4	4	1				10
Trastuzumab, Lapatinib		1		2	3		1	7
Trastuzumab		2	3			1	2	8
Anti-HER2 and chemotherapy*	3	10	8	7	3	4	1	36
Anti-HER2 and anti estrogen*	5	3	1			1		10
Other**	5	2	1	1	4	1	1	15
Sum	58	30	19	13	11	8	6	145

Table 2: Type of treatment per line. T-DM1 = Trastuzumab Emantasine, T-DXd = Trastuzumab Deruxtecan, HER2 = Human Epidermal Growth Factor Receptor 2.
*Single or double anti-HER2 treatment
**Single line chemotherapy or anti-hormone

Survival analyses

The median follow-up time in the study was 65.1 months, and during this time 54 of the patients had died.

For all patients the mPFS in the first line of treatment were 15.7 months (95% CI: 12.5 - 20.7), in the second line 7.7 months (95% CI: 5.3 - 12.6), and in the third line 4.5 months (95% CI: 3.2 - 6.2), as presented in figure 2. In the first line of treatment the mPFS for patients in PS 0 was 23.7 months (95% CI 15.3 - 30.4) and for patients in PS 1+ 12.2 months (95% CI 7.56 - 23.5), which

was significantly different: p = 0.026. The mPFS for low versus high tumor burden was also significantly different with 25.3 months (95% CI 15.3 - 29.4) versus 11.4 months (95% CI 9.10 - 15.3) respectively (p < 0.000). The mPFS for patients presenting with or developing CNS metastases was 11.3 months (95% CI 6.27 - 17.0) and 20.3 months (95% CI 13.2 - 27.3) for those without (p = 0.004).

The PS 1+ group progressed significantly faster compared to patients in PS 0 (HR = 1.80, 95% CI: 1.08 - 3.01, p = 0.024). Patients with a high tumor burden progressed significantly faster than those with a low tumor burden (HR = 2.39, 95% CI: 1.49 - 3.83, p < 0.001). Patients presenting with or developing CNS metastases also progressed significantly faster than those without (HR = 2.04, 95% CI: 1.28 - 3.25, p = 0.003).
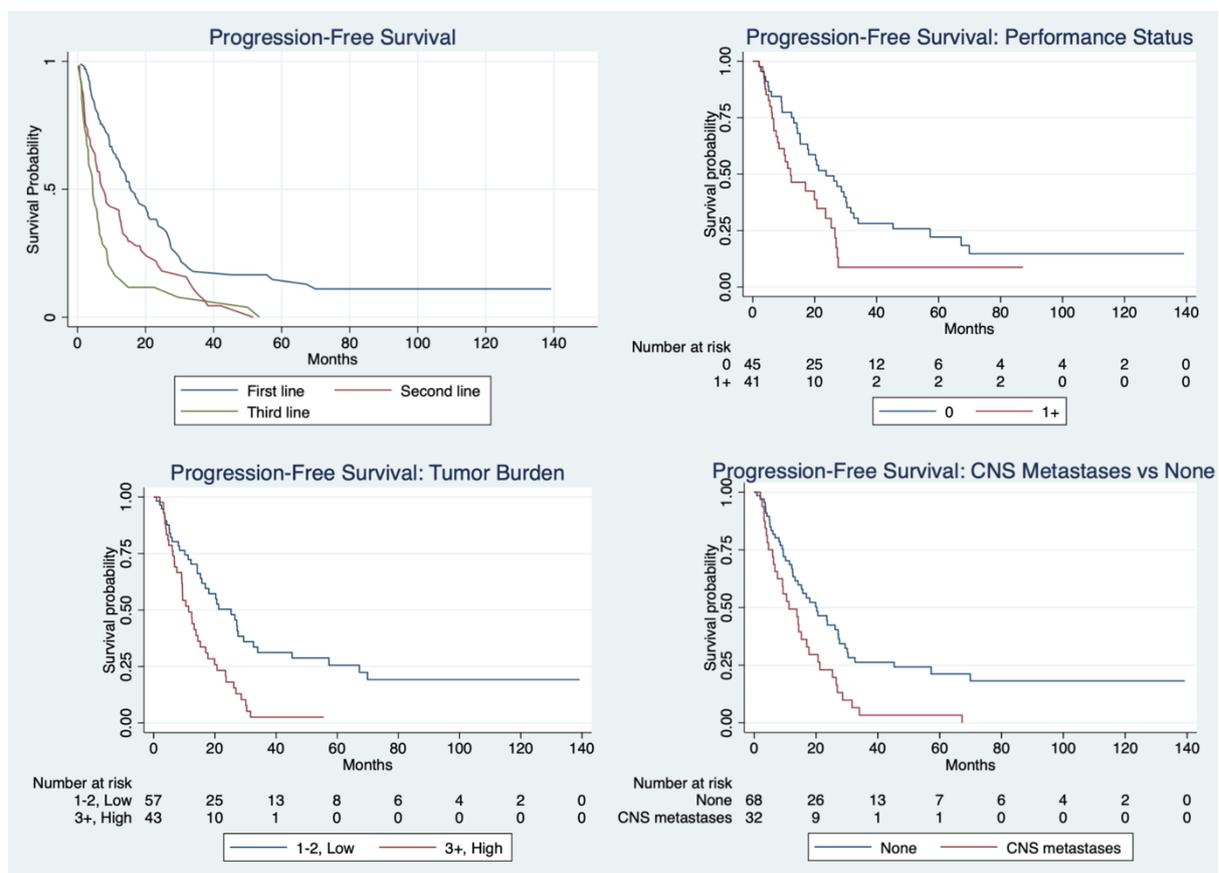

Figure 2: Kaplan-Meier plots of Progression-Free Survival in first-, second-, and third-line treatment; Performance status 0 versus 1+; Tumor burden low versus high; CNS metastases versus none.

For all the included patients, the mOS was 49.3 months (95% CI: 39.2 - 67.2). By comparing patients treated in 2014-2018 to 2019-2024, no significant result was observed in the log-rank test (p = 0.783). Patients in PS 1+ had a mOS of 32.8 months, being significantly lower compared to patients in PS 0 (p < 0.001) as presented in figure 3. mOS was 72.7, 42.1, 27.7, and 15.5 months for patients in PS 0, 1, 2, and "not specified" respectively. In general, patients presenting with or developing CNS metastases during treatment, had a mOS at 39.1 months (95% CI: 29.2 - 49.3),

whereas mOS from the time of the diagnosis of CNS metastasis until death or censoring was only 14.1 months (95% CI: 7.3 - 23.4).
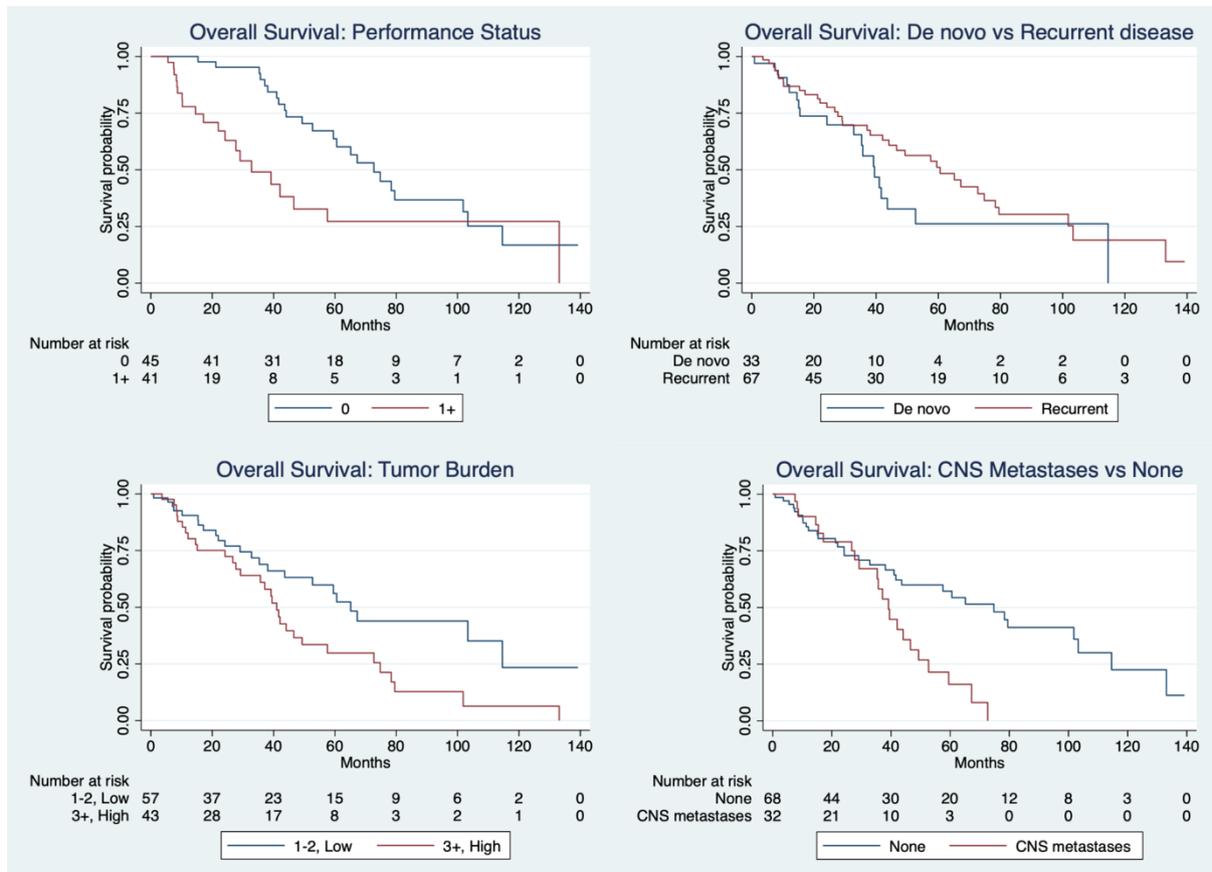

Figure 3: Kaplan-Meier overall survival plots. Performance status 0 versus 1+; De novo versus recurrent disease; CNS metastases versus none; Tumor burden low versus high.

When adjusting for age, ER status, and tumor burden, the OS for patients in PS 1 compared to patients in PS 0 did not significantly differ (HR = 1.87, 95% CI: 0.90 - 3.88, p = 0.094), however when comparing patients in PS 2 and patients in PS 0 a significant difference was observed (HR = 4.46, 95% CI: 1.68 - 11.8, p = 0.003). ER status (HR = 1.07, 95% CI: 0.61 - 1.88, p = 0.805) and age (HR = 1.02, 95% CI: 1.00 - 1.04, p = 0.120) had no significant impact on survival as presented in table 3.

	Unadjusted model			Adjusted model*		
	Hazard Ratio	95% Confidence interval	p-value	Hazard Ratio	95% Confidence interval	p-value
Age	1.02	1.00 1.04	0.120	1.00	0.98 1.04	0.666
Estrogen receptor status	1.07	0.61 1.88	0.805	1.05	0.54 2.04	0.896
Performance status						
1 vs 0	1.95	0.93 4.09	0.076	1.87	0.90 3.88	0.094
2 vs 0	3.01	1.11 8.19	**0.031**	4.46	1.68 11.8	**0.003**
Tumor burden (high vs low)	1.96	1.14 3.37	**0.016**	1.88	1.01 3.52	**0.047**
De novo vs Recurrent disease	0.67	0.38 1.18	0.166	0.65	0.32 1.33	0.238
CNS metastases vs none	2.26	1.26 4.07	**0.006**	2.31	1.10 4.85	**0.027**

Table 3: Univariable and multivariable cox regression analysis for overall survival.
*Adjusted for age, estrogen receptor status, performance status, and tumor burden. De novo versus recurrent disease and CNS metastases are only adjusted for in their separate analyses.

There was no statistically significant difference in OS when comparing patients with de novo versus recurrent disease (HR = 0.67, 95% CI: 0.38 - 1.18, p = 0.17). In addition, there was no significant result in the adjusted model. Having a higher tumor burden showed statistically significant decreased survival compared to having low tumor burden (HR = 1.96, 95% CI: 1.14 - 3.38, p = 0.016). This was also significant in the adjusted model (HR = 1.88, 95% CI: 1.01 - 3.52, p = 0.047). Patients with CNS metastases had significantly decreased survival compared with the patients without CNS metastases during follow-up (HR = 2.26, 95% CI: 1.26 - 4.07, p = 0.006). Moreover, a statistically significant result in the adjusted model was found (HR = 2.31, 95% CI: 1.10 - 4.85, p = 0.027).

In the survival analysis investigating if ER status or tumor burden could be used as a predictor for time to CNS metastases (CNS metastases as an event), no significant result was found for ER status (HR = 0.65, 95% CI: 0.29 - 1.45, p = 0.295), however tumor burden was a significant predictor in time to develop CNS metastases (HR = 2.37, 95% CI: 1.14 - 4.96, p = 0.021).

Discussion

In this study of 100 patients with HER2+ MBC treated with first-line treatment, consisting of double anti-HER2 blockade in combination with chemotherapy, 58% received second-line treatment and 30% third-line treatment. It is slightly lower than the findings of Artzi et al. with 69% of patients receiving second-line and 41% third-line treatment [6] however, the results were in line with Di Maio et al.; 56% received second-line treatment and 34% third-line treatment [8]. The majority of patients followed the national guidelines for second-line treatment in the investigated period from 2014-2024. In total, 35 (60.3% in second-line treatment) patients received T-DM1 which has been recommended since the mid-2010s (European market approval 2013) and 9 (15.5% in second-line treatment) patients received T-DXd, which has been recommended as second-line treatment since 2023. In Artzi et al. 45% of the patients received the recommended second-line treatment, thus higher compliance with the guidelines is found in our study. Artzi et al. could not explain the relatively low compliance, as the tolerance for T-DM1 was relatively high [6].

In our study, only 2 patients received the recommended third-line treatment (tucatinib plus capecitabine and trastuzumab), which is not surprising as this combination was included in the national guidelines in 2023. A majority of the patients received single or double anti-HER2 blockade with chemotherapy in third-line treatment, which was standard practice before the current guidelines. This is a treatment pattern that continues in later lines of treatments as well. The choices in the later lines of treatment may represent complexity of treatment, due to the patient's performance status and progressing disease, and the toxicity of previous treatments, which affect the treatment choice. Of note, T-DXd and tucatinib is not recommended to be administered to patients in PS >1, which also could explain the low numbers.

The mPFS in our study in first-, second-, and third-line treatment was 15.7, 7.7, and 4.5 months respectively. This reflects the disease progression and the decreasing efficacy of the treatment with each line of treatment. The results are in line with other real-world studies such as Artzi et al., which found a mPFS of 13.4, 6.6, and 5.8 months for first-, second-, and third-line treatment respectively [6]. Di Maio et al. found that mPFS in 2000-2013 versus 2014-2020 was 16.5 versus 19.5 months for first-line treatment, and for overall second-line therapy the mPFS was 9.6 months [8]. These numbers are slightly higher than those presented in our study.

In our study, patients with PS 1+, high tumor burden, and/or CNS metastasis had disease progression 12 months earlier than patients in PS 0, low tumor burden, and without CNS metastasis. This could be explained by the already weakened body status in patients in PS 1 at

treatment start compared to patients in PS 0. High tumor burden decreases the mPFS significantly and could be explained by the tumor having a high proliferation rate and aggressive growth characteristics leading to rapid spread to multiple locations. Patients presenting with or developing CNS metastases progress faster, which could be due to a more aggressive phenotype as well.

The mOS of 49.3 months found in our study was in line with findings of other studies investigating the impact of the current first-line treatment on survival, such as Artzi et al. with a mOS of 42.3 months [6]. Furthermore, a Dutch study by Ding et al. had similar findings looking at only de novo HER2+ MBC patients. In that study, the mOS improved from 30.9 months for patients treated between 2008-2009 to 57.3 months for patients treated between 2016-2017, showing the improvement of treatment over time [10]. The mOS was slightly higher compared to the findings in this present study. Our study could not conclude any significant difference in mOS between time periods (2014-2018 versus 2019-2024), as there were no significant changes in treatment strategy before 2023. On the other hand, it could also be explained by the relatively small sample size of this study. Comparing our data with an older study, M77001 (mOS 31.2 months for trastuzumab plus docetaxel), it is clear that the current treatment standards with double anti-HER2 drugs are superior to a single blockade, which became part of the standard first-line treatment after the CLEOPATRA study in 2013 [12, 13].

The CLEOPATRA study found a slightly higher mOS of 57.1 months, compared to this study [25]. This is expected, as real-world data is less controlled compared to that of clinical trials. The patients selected for clinical trials are often younger, in better PS, and with low comorbidities. Although comorbidities were not included in this study, it is an interesting variable to explore in future studies, as some comorbidities may have an impact on prognosis and treatment choice.

PS proved to be one of the most significant prognostic markers, solidifying its importance in the planning of treatment and patient prognosis. The mOS of PS 0, 1, and 2 was 72.7, 42.1, and 27.7 months respectively. PS 1 vs 0 had a nonsignificant adjusted HR of 1.87, $p = 0.094$, however, PS 2 vs 0 showed significant adjusted HR of 4.46, $p = 0.003$. This showed that PS 2 is an important predictor of OS and an independent predictor for the progression of the disease. These findings are in line with other studies such as Gamucci et al., finding a significant decrease in PFS in patients with higher PS [26].

In the guidelines it is not recommended to treat patients above PS 2, however in our study some patients with PS >2 were treated. These patients must have had potential benefits outweighing the

PS. As addressed earlier, it is important to assess the PS of the patients, to discuss the advantages and disadvantages of treatment including potential side effects.

This study did not find a significant difference in the survival between patients with ER negative versus ER positive patients with an adjusted HR of 1.05, p = 0.896. The influence of ER status on survival in this patient group is also questioned in other studies [27]. It could be argued that the HER2 receptor pathway is the main driver of tumor growth and aggressiveness, while the ER pathway plays a smaller role.

Tumor burden represents both a predictor for OS as well as time to CNS metastases. In our study low versus high tumor burden was significant in survival, with the adjusted HR of 1.88, p = 0.047. This reflects a more aggressive tumor biology.

The total mOS for patients developing CNS metastases during treatment was 39.1 months, which is in line with other studies, such as Artzi et al. with 26.3 months, although our result is slightly higher [6]. An Australian study by Tung et al., found a longer mOS for patients developing CNS metastases of 58.9 months, however their mOS for patients never developing CNS metastases were also longer compared to our data with 96.1 months [28]. This longer mOS, could demonstrate international differences in treatment.

In our study CNS metastases had a large impact on survival, with a mOS after diagnosis with CNS metastasis of 14.1 months. This poor survival is in line with Hurvitz et al., who found a mOS of 20.1 months for patients with CNS-only metastasis at MBC diagnosis [29]. Furthermore, in our Kaplan-Meier survival model with CNS metastases being the event, tumor burden was a significant predictor of time to CNS metastases.

The poor survival of patients presenting with or developing CNS metastases highlights the possible benefits of early CNS evaluation and incorporation of targeted treatments for these patients, such as tucatinib, lapatinib, and T-DXd which have shown intracranial efficacy [30].

Strengths and limitations

The strength of this study is the detailed investigation of the HER2+ MBC patient group in the North Denmark Region, which gives valuable insights on the clinical practice in the time from 2014-2024. The Danish healthcare system provides highly comprehensive follow-up and survival data. In addition, the MedOnc database contains very detailed information of the treatments administered for the patients, resulting in consistent data.

However, one of the limitations is the retrospective design. Due to this design, typing errors may occur, compromising data integrity. This study has a good sample size for a regional study; however, a larger sample size and longer follow-up could have made it possible to further investigate the effect of newer treatments such T-DXd. Lastly, due to the information being entered by clinicians into patient records, there is risk of missing values such as PS.

Conclusion

In conclusion, this study demonstrates that PFS and OS for patients with HER2+ MBC in the North Denmark Region are comparable to similar international studies and emphasizes the need for continued refinement of treatment protocols for patients in high risk of poorer outcomes, especially those presenting with high tumor burden, high performance status or CNS involvement or development. To help clarify the impact of newer HER2-targeted treatments and treatment strategies for patients with CNS involvement in the Danish population, future studies with larger sample sizes and prospective designs are needed.

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