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Anti-Her2 therapy patterns in metastatic breast cancer—Real-world data suggest undertreatment

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Abstract

Treatment efficacy of anti-HER2 therapies for metastatic breast cancer (mBC) has been demonstrated in clinical trials, but real-world data are lacking. In particular, it is unclear whether patients in clinical practice receive treatment as recommended. We took advantage of population-based registries in Norway to assess anti-HER2 therapy patterns in real-world data, with specific attention to the treatment of vulnerable groups. We included 715 patients with HER2+ mBC diagnosed from 2012 to 2021. Median age was 60 years, 473 (66%) had relapsed from early-stage BC, and 440 (62%) had hormone receptor positive (HR+) disease. Anti-HER2 therapy patterns aligned with national recommendations. Median treatment duration for first line therapy was 7.2 months, where 261 patients (55%) used trastuzumab and pertuzumab (±chemotherapy), followed by monotherapy with trastuzumab (195 patients, 41%). Second line therapy was initiated by 206 patients (43%), with a median duration of 7 months, where trastuzumab emtansine was the most prevalent therapy, used by 84 patients (41%). Third line therapy was initiated in 119 patients (25%) and 55 patients (11%) proceeded to fourth line therapy. The 182 patients (28%) who did not receive any anti-HER2 therapy were older (74 years vs. 55 years) and had more comorbidity compared to treated patients. Among patients ≤75 years and healthy, 15% did not receive anti-HER2 therapy. Patient characteristics strongly influence anti-HER2 treatment patterns, and although numerous treatment options are available, a substantial proportion of HER2+ mBC patients did not receive targeted therapy. Undertreatment may be present.

KEYWORDS

HER2+ metastatic breast cancer, population-based cohort, real-world data, vulnerable patient groups

Abbreviations: ADC, antibody drug conjugate; ATC-code, Anatomical Therapeutic Chemical code; BC, breast cancer; CRN, Cancer Registry of Norway; CVD, coronary vascular disease; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HER2+, human epidermal growth factor receptor 2 positive; ICD, International Classification of Disease; ICD-10, International Classification of Disease version 10; mBC, metastatic breast cancer; NCDNOR-project, non-communicable diseases in Norway project; NorPD, Norwegian Prescribed Drug Registry; NPR, Norwegian Patient Registry; PRI, Patient Registry Index; RWD, real-world data; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

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What's New?

Although human epidermal growth factor 2-positive (HER2+) breast cancer is an aggressive malignancy, significant survival benefits are possible with targeted anti-HER2 therapies. Whether these therapies are used as recommended, however, is unknown. Here, the authors investigated data from population-based registries in Norway to assess anti-HER2 therapy utilization. Patterns of anti-HER2 therapy use followed national recommendations. However, analyses indicate that a substantial proportion of metastatic HER2+ patients do not receive anti-HER2 therapy. Notably, older patients with comorbidities are less likely to undergo anti-HER2 therapy than younger patients. The data highlight variations in clinical use of anti-HER2 therapies in metastatic HER2+ patients.

1 | INTRODUCTION

Human epidermal growth factor 2 positive (HER2+) breast cancer (BC) accounts for 15%–20% of BC cases,[1] of which 12%–24% will develop metastatic disease (mBC).[1,2] This subgroup of BC is inherently aggressive in nature and was, prior to the "HER2 era" of BC therapy, associated with rapid disease progression and poor overall survival.[3] During the last 25 years, there has been a gradual introduction of targeted anti-HER2 therapies resulting in significant improvements in survival.[4] These therapies include HER2 monoclonal antibodies (i.e., trastuzumab and pertuzumab), tyrosine kinase inhibitors (i.e., lapatinib, neratinib, tucatinib) and antibody-drug conjugates (ADCs) (i.e., trastuzumab deruxtecan (T-DXd) and trastuzumab emtansine (T-DM1)). At present, Norwegian and international treatment guidelines recommend trastuzumab, pertuzumab, and a taxane-based chemotherapy as first-line therapy, T-DXd as second-line therapy, and T-DM1 or different combinations of chemo- and anti-HER2 therapy in third and subsequent lines.[5,6] Treatment algorithms for mBC do not consider patients' age, comorbidities, or performance status, leaving it up to the clinician to individualize therapy as needed.

The clinical trials which demonstrated significant survival benefits for targeted anti-HER2 therapies were based on smaller and selected groups of patients. These patients were younger, had better general health, and were more likely to experience favorable outcomes and less toxicity compared to patients treated in clinical practice.[7–9] When clinicians are faced with older and comorbid patients, treatment decision-making is challenging, weighing the risk of toxicity against the potential therapeutic effect. Real-world data (RWD) from nationwide cancer registries may complement the evidence derived from clinical trials and increase our knowledge of the extent to which these therapies are used in clinical practice. Within a setting where cancer care is free of charge and universally accessible in public hospitals, such data enables identification of vulnerable patient groups that may be at risk of undertreatment, ultimately improving the quality of cancer care.

In this study, we took advantage of population-based registries to explore treatment patterns in a nationwide cohort of HER2+, mBC patients. Over a 10-year period, we characterize patients and anti-HER2 therapy patterns across the metastatic disease trajectory.

2 | MATERIALS AND METHODS

2.1 | Study population

This population-based cohort study included women aged 18 years and older at the time of diagnosis, registered with HER2+ BC (ICD-10 codes C50.0–C50.9) in the Cancer Registry of Norway (CRN) from 2012 to 2021. The CRN is based on mandatory reporting of all new cancer cases and is practically complete.[10] Data from the CRN was merged with data from the National Patient Registry (NPR), the Norwegian Cause of Death Registry, and the Norwegian Prescribed Drug Registry (NorPD) using the unique personal identification number assigned to all inhabitants at birth. These registries are all population-based. The NPR includes treatment data from all public hospitals from 2008 and onwards, and reporting is mandatory.[11]

From 2012 to 2021, there were 4692 females registered in the CRN with invasive HER2+ BC (13% of total number of BC cases), of whom 804 women had metastatic disease (Figure S1; flowchart). Metastatic disease included women diagnosed with metastasis at primary diagnosis or during the first 4 months after primary diagnosis (classified as de novo mBC), and women who experienced distant recurrence after a disease-free interval. We excluded women with BC stage I–III at diagnosis who did not relapse during follow-up ($n = 3888$), and 89 women with mBC based on the following exclusion criteria: previous cancer (other than non-melanoma skin cancer) ($n = 80$), assumed previous cancer from treatment information ($n = 5$), other cancer diagnosis (than breast or non-melanoma skin cancer) at the date of first breast cancer diagnosis ($n \leq 5$), missing information on hormone receptor status ($n \leq 5$), and patients diagnosed at autopsy, or who were dead or lost to follow-up at the date of diagnosis (for de novo patients)/metastatic presentation (for relapsed patients) ($n \leq 5$) (Figure S1, flowchart). Thus, the final study sample included 715 women with HER2+ mBC. Patients were followed from the date of metastatic disease to the date of death, or other cancer diagnosis or June 2023, whichever happened first.

2.2 | Clinical variables

The CRN, including the Incidence Database[12] and the Norwegian Breast Cancer Registry,[13] provided information on the date of

metastasis and tumor characteristics, including hormone receptor status. If patients had two or more BC diagnoses with different receptor statuses registered on the same day, classification was made according to the most aggressive histology. We used the time of diagnosis to calculate the time from primary to metastatic disease. Information on metastatic disease was obtained from pathology- or clinical reports in the CRN and supplemented with ICD-10 codes C77–79 registered in the NPR. As brain metastasis may be diagnosed without biopsy, patients who had received radiation therapy to the brain (both whole brain radiotherapy and stereotactic radiation) were registered as having brain metastasis. Time and cause of death were obtained from the Norwegian Cause of Death Registry and used to calculate months from metastasis to death.

2.3 | Treatment variables

Information on chemotherapy and anti-HER2 therapy was retrieved from the systemic anti-cancer treatment database in the CRN, which includes data on all cancer therapies given during 2019–2021 in Norwegian public hospitals, except for northern Norway. For 2019–2021, the completeness of these data was reported to be above 90%.[14] For treatment prior to 2019 and for northern Norway, treatment data were obtained from the NPR (cancer therapy given in hospitals) and the NorPD (endocrine treatment and orally administered cancer therapy dispensed from pharmacies).

We considered a patient as having received anti-HER2 therapy if they had at least one registration of trastuzumab, trastuzumab and pertuzumab, T-DM1, T-DXd, or lapatinib (the only tyrosine kinase inhibitor available in Norway during the study period) after metastatic diagnosis. Patients were considered as having received any systemic antineoplastic treatment if they had any registration of anti-HER2 therapy, chemotherapy, or endocrine therapy (ATC group L01 or L02) after metastatic diagnosis.

In the NPR, 2.8% of treatments were registered with an unspecific code labelled "medical treatment against tumors" only (hereafter referred to as unspecific treatment codes). Yet, 33.5% of the patients had at least one such unspecific treatment code registered during the period. Metastatic treatment lines were defined according to the drug specific algorithm presented by Sørup et al.,[15] where a treatment line was defined as a series of treatments with the same drug, and a change or addition of a drug indicated a new treatment line. If less than 48 days passed between a specific and an unspecific treatment code, they were defined as being part of the same treatment line. If the unspecific treatment code occurred with more than 48 days to another treatment, it remained unspecified. As opposed to the data used by Sørup et al., our data did not allow us to distinguish between antineoplastic treatment and treatment with bisphosphonates when only unspecific treatment codes were used. Therefore, we did not count treatment lines for patients who had treatment that remained unspecified after the application of the algorithm.

2.4 | General health variables

Information on the main non-communicable diseases was based on specific ICD codes from the NPR (registered during the last 4 years prior to metastatic diagnosis) or registered as reimbursement codes from the NorPD (during the last year before metastatic diagnosis). Prevalence estimates for cardiovascular disease, chronic obstructive pulmonary disease, and diabetes were obtained using definitions from the Non-communicable Diseases in Norway (NCDNOR) Project,[16] while dementia and kidney failure were defined through ICD codes (F00-3 or G30 and N17–19 respectively). Additionally, the Patient Registry Index was applied, which is based on NPR data covering the last 4 years prior to the metastatic BC diagnosis. A value above zero indicates hospital admissions for one or more comorbidities (cancer diagnosis not included).[11] This is a modified version of the Charlson comorbidity index developed specifically for NPR data with high reported validity.[11]

2.5 | Sociodemographic variables

Age at diagnosis was provided from the CRN and used to categorize patients as pre- (≤55 years) and post-menopausal (>55 years). Statistics Norway provided information on educational attainment, categorized into compulsory (elementary school), secondary (high school) and tertiary education (university), and household income, categorized in quintiles according to median household income for the general Norwegian population at year of diagnosis.

2.6 | Statistical methods

We used descriptive statistics to present baseline characteristics for the patient population, and timelines for anti-HER2 therapies used in Norway during 2012–2021. To visualize anti-HER2 therapy patterns across the metastatic trajectory, a Sankey diagram was created.[17] Anti-HER2 therapy was categorized as trastuzumab; trastuzumab and pertuzumab; lapatinib; trastuzumab + lapatinib (each of these including monotherapy and/or combination with chemotherapy); T-DM1 and T-DXd. Descriptive statistics were applied to characterize patients who did not receive any systemic antineoplastic treatment.

We used the Pohar Perme estimator[18] to estimate relative survival for HER2+ patients according to age at metastasis. Patients were categorized into four age categories: <50 years, 50–59 years, 60–74 years, and ≥75 years. Relative survival is an estimate of the patients' survival if breast cancer were the only possible cause of death. It is calculated as the observed survival among the HER2+ mBC patients divided by the expected survival of women in the general Norwegian population of the same age and calendar year. All analyses were performed in STATA (Stata Corp. 2023. Stata Statistical Software: Release 18. College Station, TX: Stata Corp LLC), including the Sankey package (version 1.73)[17] and the stpp package to model relative survival.[19]

TABLE 1 Baseline characteristics of patients with HER2+ metastatic breast cancer in Norway from 2012 to 2021.

	Total
n	715
Age at metastatic disease, years	
Mean (SD), range	59.7 (15.2)
<50	212 (29.7%)
50–59	166 (23.2%)
60–69	132 (18.5%)
70–79	125 (17.5%)
80+	80 (11.2%)
Year of metastatic disease	
2012–2016	255 (35.7%)
2017–2022	460 (64.3%)
Missing	0
Time to metastatic disease	
De novo	242 (33.8%)
≤1 year	178 (24.9%)
>1–5 years	253 (35.4%)
>5 years	42 (5.9%)
Hormone receptor status	
Positive	440 (61.5%)
Negative	275 (38.4%)
Educational attainment	
Compulsory	163 (23.1%)
Secondary	308 (43.7%)
Higher	234 (33.2%)
Missing	10
Household income	
Lowest quintile	197 (27.8%)
Middle quintiles	390 (55.1%)
Highest quintiles	121 (17.1%)
Missing	7
Comorbidity at metastatic disease[a]	
Patient registry index >0[b]	135 (18.9%)
Dementia	10 (1.4%)
Chronic obstructive pulmonary disease	41 (5.7%)
Heart disease	202 (28.3%)
Diabetes	61 (8.5%)
Kidney failure	32 (4.5%)
Menopausal status	
Pre-menopausal (≤55 years)	314 (43.9%)
Post-menopausal (>55 years)	401 (56.1%)
Deaths	349 (48.8%)
Months from metastatic disease to death, mean (range 1st to 3rd quartile)	14 (3–31)
Endocrine therapy	
Any	316 (44.2%)
Aromatase inhibitors	235 (32.9%)
Tamoxifen	120 (16.8%)
Goserelin	49 (6.9%)
Fulvestrant	47 (6.6%)
CDK4/6-inhibitors	27 (3.8%)

[a]Defined as diagnosed before metastatic disease (specific conditions were registered in the NPR during the last 4 years and/or in the NorPD during the last year prior to mBC diagnosis).
[b]Patient registry index (PRI) where a value above 0 indicates hospital admission for one or more comorbidities (the cancer diagnoses are not included), calculated from the 4 years before metastatic disease.

3 | RESULTS

3.1 | Patient characteristics

Of the 715 patients diagnosed with HER2+ mBC from 2012 to 2021, 440 (62%) were HR+. The median age at metastatic diagnosis was 60 years. Six out of 10 patients (64%) were diagnosed during 2017–2022. There were 242 patients (33%) with de novo metastatic disease, while the rest had relapsed from early-stage BC. Among relapsed patients, 60% relapsed within the first 5 years. Household income was in the lowest quintile for 28% of the patients. Comorbidities (based on the comorbidity index) were present for 135 patients (19%), and cardiovascular disease was the most prevalent comorbid condition, affecting 28%. Aromatase inhibitors were used by 33% of the patients. There were 349 deaths (49%) during the study period. Median months from metastatic diagnosis to death for these patients were 14 months (interquartile range 3–31) (Table 1).

3.2 | Treatment patterns

Among treated patients with only specific treatments registered ($n = 661$) we observed a clear shift from 2014 in treatment practices from primarily monotherapy with trastuzumab to combination therapy with pertuzumab (±chemotherapy), and an increasing use of ADCs towards the end of the study period (Figure 1). Among patients who received anti-HER2 therapy ($n = 479$), the median treatment duration in the first line was 7.2 months. Of them, 261 (55%) received trastuzumab + pertuzumab (±chemotherapy), while 195 (41%) received monotherapy with trastuzumab. Two hundred and six (43%) transitioned to a second line of anti-HER2 therapy with a median treatment duration of 7 months. Trastuzumab emtansine was most frequently used in the second line (84 patients, 41%). At the start of second line therapy, 19% of the patients had died, and 36% had their last follow-up. One hundred and nineteen patients (25%) transitioned to a third line therapy with a median treatment duration of 6.8 months, and 55 patients (11%) to a fourth line, with a treatment duration of 3.9 months (Figure 2).

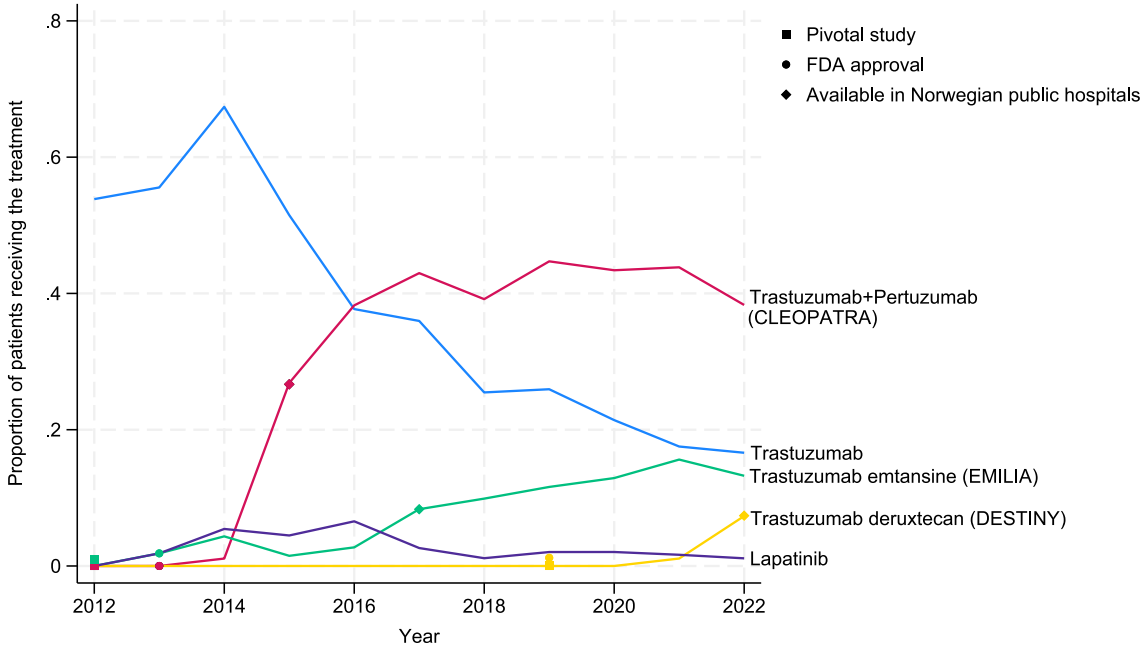


FIGURE 1 Proportion of patients receiving different anti-HER2 therapies in Norwegian public hospitals from 2012 to 2022, according to the publication year of pivotal clinical study, and the year of international (FDA)- and national approval in Norway.

3.3 | The "untreated"

One hundred and five patients (16%) did not receive any anti-neoplastic therapy (including endocrine therapy). One hundred and eighty-two patients (28%) did not receive any anti-HER2 therapy, and 247 (38%) did not receive chemotherapy. Patients who did not receive any anti-HER2 therapy were older compared to treated patients (median 74 years vs. 55 years); 63% had HR+ disease, and 76% had relapsed after early-stage BC. Untreated patients had a higher prevalence of all examined comorbid conditions, including dementia, diabetes, and cardiovascular diseases, and the median number of months from metastasis to death in this patient group was 3 months (interquartile range 1.1–11.8) compared to 21 months (interquartile range 8.3–38.3) among treated patients. Fifteen patients (16%) received palliative radiation therapy to any site and no anti-neoplastic therapy (Figure 3). Among patients younger than 76 years without comorbidity, 15% did not receive anti-HER2 therapy, and 40% of these were in the lowest household income quintile (Figure S2).

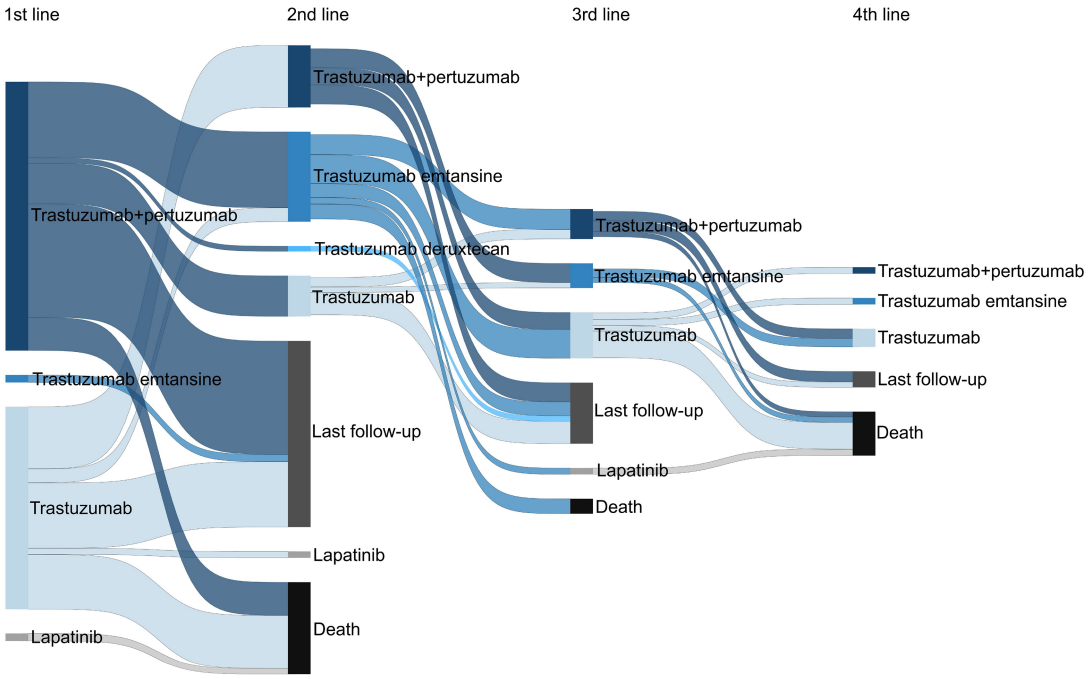
3.4 | Survival

Compared to women of the same age without BC, relative survival for HER2+ mBC patients declined with increasing patient age and time since diagnosis. The observed difference between age groups was more pronounced for the first year following metastatic diagnosis, where patients ≥75 years of age had a relative survival of approximately 55% compared to 90% among patients aged 50–59 years. Five years after metastatic diagnosis, relative survival was 20% among the oldest patients compared to 60% for the youngest age category (Figure 4).

4 | DISCUSSION

This is the first study to present comprehensive anti-HER2 therapy data for the Norwegian mBC population. Our findings demonstrate that even though cancer care is free of charge, available in public health care, and an increasing number of targeted drugs are available, a substantial proportion of patients do not receive state-of-the-art targeted anti-HER2 therapy. This finding was not limited to elderly, comorbid patients, suggesting that undertreatment may be present.

Therapy patterns from 2012 to 2021 reflect the gradual introduction of different targeted anti-HER2 therapies into clinical practice. Specific treatment choices were in alignment with guidelines at the time, but there were substantial delays from international approval of a new drug to implementation in clinical practice. Only 72% of these patients received first-line anti-HER2 therapy. This is lower than reported in a recent multi-country cohort study, where 93% of patients received first-line anti-HER2 therapy.[20] Patient and clinical characteristics in that study were comparable to our data, but they included women from 2017 to 2021, which may in part account for the observed difference. They did, however, observe the same treatment pattern as we did; the number of patients who transitioned from one therapy line to the next was almost halved for each new line of therapy, and attrition was primarily due to patient death and loss to follow-up.[20] This was also the case in a large French study from 2020, which included 6030 HER2+



	1st line		2nd line		3rd line		4th line	
	n (%)	median line duration in days (1st;3rd quartile)*	n (%)	median line duration in days (1st;3rd quartile)*	n (%)	median line duration in days (1st;3rd quartile)*	n (%)	median line duration in days (1st;3rd quartile)*
Total treated	479	215 (89;446)	206	204 (84;441)	119	204 (96;343)	55	118 (68;305)
Trastuzumab	195 (40.7%)	170 (69;427)	40 (19.4%)	318 (224;593)	47 (39.5%)	241 (111;400)	18 (32.7%)	190 (92;391)
Trastuzumab+pertuzumab	261 (54.5%)	232 (111;447)	62 (30.1%)	270 (85;728)	29 (24.4%)	128 (70;286)	13 (23.6%)	109 (90;232)
Trastuzumab emtansine	15 (3.1%)	-	84 (40.8%)	142 (67;308)	26 (21.8%)	330 (113;519)	11 (20.0%)	214 (68;539)
Trastuzumab deruxtecan	<5	-	6 (2.9%)	-	<5	-	6 (10.9%)	-
Lapatinib	7 (1.5%)	-	10 (4.9%)	124 (92;215)	12 (10.1%)	120 (65;182)	5 (9.1%)	-
Trastuzumab+lapatinib	0 (0.0%)	-	<5	-	<5	-	<5	-
Death			92		28		42	
Last follow-up			174		57		22	
Censored due to other cancer			7		<5		0	

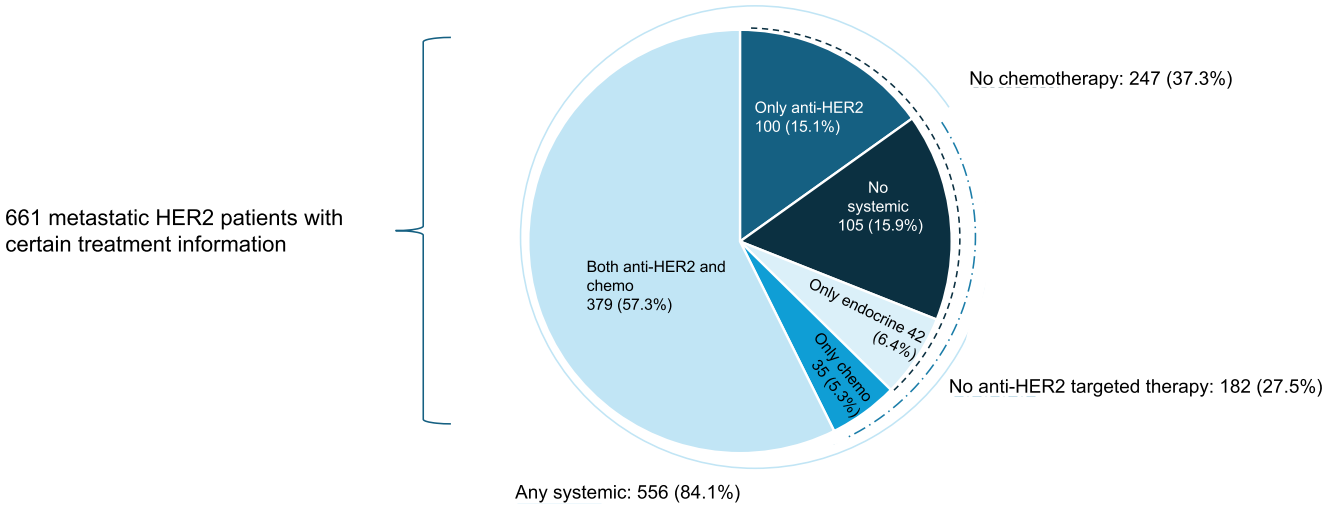
*calculated for those who progress to the next treatment line or die after the present treatment line
-median not shown if less than 10 patients progress to the next treatment line or die after the present treatment line

FIGURE 2 Sankey diagram of anti-HER2 therapy user patterns for 2012–2022 (not including endocrine or chemotherapy) (*n*: 479), according to treatment line[1–4] with corresponding table showing number of patients starting each line of therapy (in total and according to specific therapy), median treatment duration in days (in total and according to specific therapy), and number of patients who are lost to follow-up, censored due to cancer or die before the next line of therapy.

mBC patients from 2011 to 2018.[21] They reported that while 80% of patients received first-line anti-HER2 therapy, only 40% transitioned to a second line, and 23% to a third line. Combined, these results suggest that there is potential for improvements in the treatment strategies for HER2+ mBC, especially after first-line therapy.

The median treatment duration for first line therapy with trastuzumab and pertuzumab was approximately 8 months (232 days) in this cohort, which is clearly shorter than reported in the CLEOPATRA trial[8] but comparable to the above-mentioned multi-country RWD-cohort study,[20] highlighting the differences between clinical trials and clinical practice. We observed that the median treatment duration on second line therapy was as long as that for first line therapy, which may be due to the relatively large number of patients receiving trastuzumab monotherapy in the first line and transitioning to a more effective treatment option in the second line.

Patients who did not receive any anti-HER2 therapies were on average 20 years older than those treated. As expected, relative survival for the oldest patients (≥75 years) was markedly reduced compared to healthy women of the same age, especially during the first year after metastatic diagnosis. This may reflect a very frail subgroup of patients who die within the first months following diagnosis, perhaps of other causes than BC. This is supported by the observation that untreated patients more often died in other health care institutions than hospitals, such as nursing homes, and more often of other causes than BC compared to treated patients. However, after the first 6 months, the survival curve is relatively parallel to that of other age groups, indicating less survival disadvantage in the oldest patients thereafter if they survive the initial phase of the disease. We know from previous studies that older age is associated with de-escalated cancer therapy strategies, likely due to the increased risk of toxicity and complications compared to younger patients.[22,23] Reviews have however recommended the use of anti-HER2 therapy for the geriatric cancer population, considering the survival benefits and favorable safety profile observed also for patients above 65 years.[24] Monotherapy with trastuzumab is reported to increase survival without reducing quality of life and with low risk of cardiac toxicity for older



	Any systemic	No systemic*	No anti-HER2	No chemo
Age at metastasis**	55.1 (46.7-67.0)	77.4 (68.3-82.0)	73.8 (60.2-81.2)	71.8 (55.0-81.0)
Distant recurrence	62.1%	76.2%	75.8%	78.5%
Hormone receptor positive	62.1%	49.5%	62.6%	62.8%
Comorbidity at metastasis				
Patient Registry Index>0	14.6%	43.8%	39.0%	33.6%
Cardiovascular disease	24.1%	53.3%	50.5%	44.9%
COPD	4.7%	12.4%	13.7%	8.9%
Dementia	0.4%	7.6%	5.5%	4.0%
Diabetes	7.9%	14.3%	15.4%	13.0%
Among the 334 patients who died				
Months from metastasis to death**	20.1 (8.3-38.3)	1.7 (0.6-4.4)	2.8 (1.1-11.8)	3.2 (1.2-16.1)
Died at other health care facility	50.7%	58.4%	57.9%	62.0%
Died from other cause than breast cancer	7.4%	13.0%	14.9%	10.9%

*here 15 have received radiation **median (1st ; 3rd quartile)

FIGURE 3 Overview of patients who received and who did not receive systemic cancer therapy (including chemo-, endocrine- and anti-HER2 therapy) among 661 patients registered with certain treatment information from 2012 to 2021, and corresponding patient characteristics.

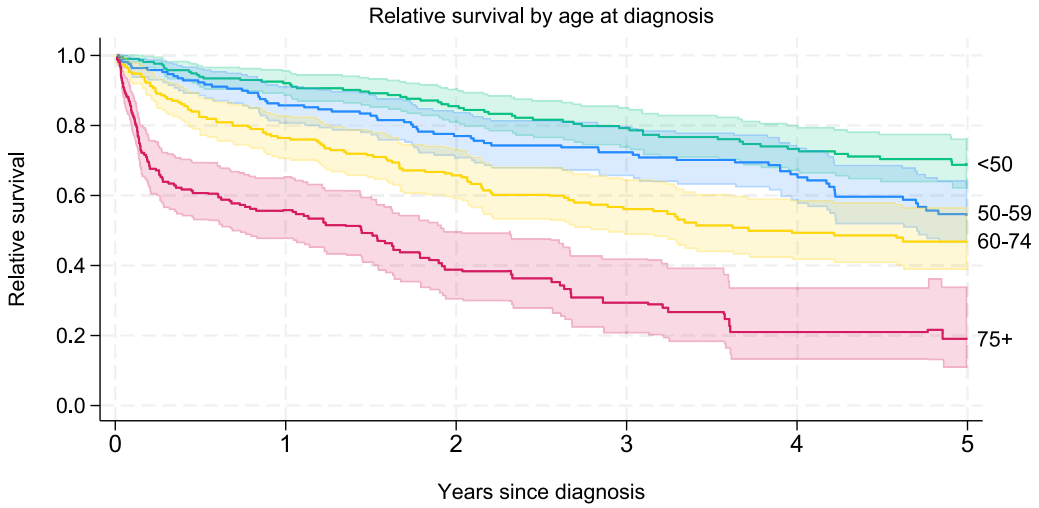


FIGURE 4 Relative survival for all patients with HER2+ mBC according to age group at metastatic diagnosis and years since metastatic diagnosis.

patients.[25] A large German observational study reported comparable clinical effect of trastuzumab for patients above 65 years compared to younger patients, and adverse effects were rare.[26] Chronological age should be evaluated alongside factors such as frailty and daily function when deciding which patients are unfit for anti-HER2 therapy, preferably through a comprehensive geriatric assessment.[27]

Interestingly, not receiving anti-HER2 therapy was not restricted to older, comorbid patients. Among healthy, younger patients, there were still 15% who did not receive anti-HER2 therapy. Younger age is associated with more aggressive disease presentation, including a higher metastatic burden,[28] which may exclude some patients from receiving therapy. Patients who had relapsed after early-stage BC seemed more vulnerable to not receiving therapy compared to de novo mBC patients. These patients are known to have poorer prognosis,[29] most likely due to toxicity from adjuvant systemic therapy, being more therapy resistant, or having aggressive disease.[30] Further, we observed that almost half of these patients had low household income. To conclude that there is a financial gradient to receiving therapy based on this finding alone is, however, too bold, as household income is influenced by other important factors such as working status, age, and number of people in the household. We found no differences in treatment patterns across the different health regions of Norway, indicating equal access to health care.

5 | STRENGTHS AND LIMITATIONS

The major strength of this study is the population-based sample, resulting in an unselected cohort of HER2+ mBC patients who principally have equal access to cancer therapy. Prospective collection of therapy data enabled us to assess long-term therapy patterns. Variables applied from the CRN and NPR are structured and validated, resulting in excellent internal validity. These findings may be generalizable to other countries with a similar health care system as in Norway.

There are weaknesses that need to be addressed. Firstly, the study period did not include the introduction period for trastuzumab in clinical practice. This was because the registration of systemic oncological therapy in the CRN was incomplete prior to 2012. Data on T-DXd was very limited as this drug was approved in Norway in 2022. Cancer therapies given in private health care facilities are not included in this study. As cancer care is publicly funded, very few patients in Norway receive cancer therapy outside public hospitals. In 2023, approximately 100 cancer patients, including all cancer types, received treatment in private health care.[31] In comparison, 38,000 patients were diagnosed with cancer during that year. We cannot rule out that some patients received therapy in private health care while specific drugs were awaiting national approval. This applies to pertuzumab during 2013–2015 and T-DM1 during 2013–2017. However, these patients would most likely shift to public health care once the drug was approved—and consequent use would be registered in the NPR. Further, if patients received specific drugs privately, for instance pertuzumab, they would likely receive approved drugs (trastuzumab and chemotherapy) in the public hospitals. As such, they would be classified as treated in our study. We cannot know why individual patients did not receive systemic therapy, or if their prognosis was poor due to lack of therapy, or if poor prognosis resulted in lack of therapy. Having access to patient records in hospitals with measurements of overall function and patient preference was unfortunately not available to us. Information on metastatic burden (visceral vs. non-visceral metastasis and number of metastatic sites), which may impact treatment decisions, is also lacking in the CRN. Finally, although we used previously validated methods to define therapy and therapy lines, we cannot rule out the risk of misclassifications of therapy. Such a risk is likely to be higher when exploring therapy given beyond the first line of anti-HER2 therapy, as reported by Sørup et al.[15]

6 | CONCLUSION

Although anti-HER2 targeted therapy options are numerous for HER2+ mBC, patient characteristics clearly influence clinicians' treatment planning. Among patients who received treatment, national treatment guidelines were followed. There was, however, a high proportion of untreated patients in this population-based cohort, which was not restricted to old and comorbid patients. This may reflect undertreatment and highlight the potential of improving anti-HER2 therapy strategies for BC patients with metastatic disease.

AUTHOR CONTRIBUTIONS

Kathrine F. Vandraas: Writing – original draft; writing – review and editing; conceptualization; investigation; project administration. **Sarah Hjorth:** Writing – review and editing; methodology; project administration; data curation. **C.B. Trewin-Nybråten:** Writing – review and editing; project administration. **Giske Ursin:** Writing – review and editing. **Edoardo Botteri:** Writing – review and editing. **Bettina Kulle Andreassen:** Conceptualization; writing – review and editing. **Kristin V. Reinertsen:** Writing – review and editing. **Egil S. Blix:** Writing – review and editing. **Bjørn Naume:** Writing – review and editing. **Nathalie C. Støer:** Conceptualization; funding acquisition; writing – review and editing; project administration; supervision.

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CONFLICT OF INTEREST STATEMENT

Egil Blix has a consulting or advisory board role in AstraZeneca, Daiichi Sankyo, Eli Lilly, Novartis, Pfizer, and Roche. The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data are available in the Cancer Registry of Norway. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

This research was performed in compliance with relevant laws and institutional guidelines and has been approved by the Regional Committees for Medical and Health Research Ethics, Southeast Norway (nr 2018/775).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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