Therapy landscape of patients with metastatic, HER2 positive breast cancer – data from the real world breast cancer registry PRAEGNANT

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BACKGROUND

Overexpression of human epidermal growth factor receptor 2 (HER2) or amplification of the *HER2* gene is seen in approximately 15–25% of breast cancer (BC) patients [1]. Adding the monoclonal anti-HER2 antibody trastuzumab to standard chemotherapy resulted in a significant improvement in the progression-free survival (PFS) and overall survival (OS) in patients with metastatic HER2-positive BC [2]. These results led to the approval of trastuzumab for the treatment of patients with HER2-positive metastatic BC.

Later, the dual tyrosine kinase inhibitor lapatinib was also analyzed in this group of patients. Women whose cancers had progressed after treatment with an anthracycline, a taxane, and trastuzumab were randomly assigned to therapy with capecitabine plus lapatinib or capecitabine alone. In contrast to the monotherapy, the combination treatment led to a significantly longer PFS, and lapatinib therefore became the standard of second-line treatment in the early 2000s [3,4].

The CLEOPATRA study demonstrated an additional improvement in survival outcomes in treatment naïve HER2-positive patients with metastatic BC. The improved survival results led to pertuzumab being approved for the first-line treatment setting [5, 6].

Another HER2-targeted approved drug is trastuzumab emtansine (T-DM1), which was designed as an antibody-drug conjugate to target specifically HER2-enriched tumor cells and in this way reduce side effects in non-targeted tissue [7].

The **objective** of this study was to describe comprehensive real world evidence on the use of trastuzumab, pertuzumab, lapatinib and T-DM1 in patients with HER2-positive metastatic BC.

STUDY DESIGN AND METHODS

The PRAEGNANT study is an ongoing, prospective BC registry. The aims of PRAEGNANT are the assessment of treatment patterns and quality of life and to identify patients who may be eligible for clinical trials or specific targeted treatments [8]. Patients can be included at any time point during the course of the disease. All patients included in the present study provided informed consent, and the study was approved by the relevant ethics committees.

Data collection

The data were collected by trained stuff and documented in an electronic case report form. The data were monitored using automated plausibility checks and on-site monitoring. Data that are not usually documented as part of routine clinical work are collected prospectively using structured questionnaires completed on paper.

Statistical considerations

The analysis and reporting of treatments are descriptive. The total numbers of treatments for each of the following four therapy lines are provided: trastuzumab (TZM), pertuzumab (PTZ), lapatinib (LAP), and trastuzumab emtansine (T-DM1). It was also analyzed whether patients who had already completed a specific number of therapy lines (1–4) received these four anti-HER2 therapies in any therapy line. Similarly, the frequencies of usage of PTZ → T-DM1 and T-DM1 → PTZ therapy sequences were analyzed regardless of whether these therapies followed each other directly.

It was also analyzed whether the patients' characteristics were associated with the frequency of utilization of the PTZ → T-DM1 sequence in the first four therapy lines, again regardless of whether these therapies followed each other directly.

Table 1: Patients' characteristics at baseline

Characteristic		n or mean	% or SD
Age at study entry		57.9	13.0
BMI		26.0	5.3
Time from diagnosis to metastasis (days)		1177.8	1743.0
Therapy situation at study entry	First-line	223	53.5
	Second-line	70	16.8
	Third-line	53	12.7
	Fourth-line	26	6.2
	Fifth-line and higher	34	8.2
Therapy situation at database closure	First-line	171	41.0
	Second-line	82	19.7
	Third-line	47	11.3
	Fourth-line	17	4.1
	Fifth-line and higher	59	14.1
Hormone receptor status	Negative	93	22.3
	Positive	324	77.7
ECOG	0	196	47.0
	1	155	37.2
	2	35	8.4
	3	12	2.9
	4	2	0.4
Metastasis site at study entry	Brain	79	18.9
	Visceral	222	53.2
	Bone only	58	13.9
	Other	50	12.0
Metastatic at time of diagnosis	No	244	58.5
	Yes	173	41.5

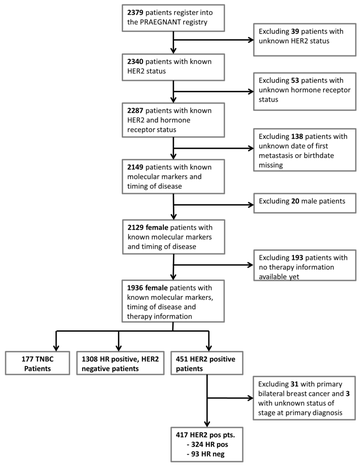

Figure 1: Patient selection

RESULTS

Patients' and disease characteristics

A total of 451 (23.3%) patients in the registry had HER2-positive metastatic breast cancer **(Fig. 1)**. The final study population comprised 417 patients, 324 of whom were hormone receptor-positive and 93 hormone receptor-negative.

While the HER2 status was positive in 37% of all patients with metastases who were treated up to 2006, HER2 positivity was seen in 25% and 22% of patients diagnosed with metastases in 2007-2013 and after 2013, respectively **(Fig. 2)**.

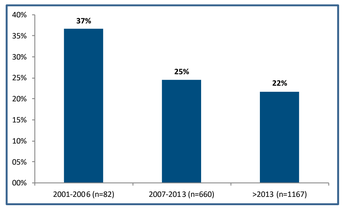

Figure 2: Frequency of HER2-positive patients relative to the year in which the metastases were diagnosed

The characteristics of the patients and diseases are listed in **Table 1.** Most patients entered the study in the first-line setting, had Eastern Cooperative Oncology Group (ECOG) score of 0, and had visceral metastases. Approximately 40% of the patients had metastases at the time of diagnosis.

Therapies

Across all therapy lines, 241 of the 417 patients were treated with TZM without any additional anti-HER2 therapy, 237 with PTZ/ TZM, 85 with lapatinib, and 125 with T-DM1. The respective figures up to therapy line four are 236, 220, 79, and 108 patients.

Table 2 shows patterns of therapy utilization relative to patient group according to the number of documented therapy lines. Trastuzumab, either as a single anti-HER2 therapy or together with pertuzumab, was already administered in over 80% of the patients for whom only the first line was documented. PTZ/ TZM utilization increased across the different time periods, with approximately 60-70% of all patients already receiving this treatment as first-line therapy.

T-DM1 utilization also increased across the time periods, although patients with a larger number of documented therapy lines had a higher frequency.

Lapatinib use did not change across the time periods and was mainly administered in later therapy lines.

The sequence of PTZ/TZM followed by T-DM1 (PTZ/ TZM → T-DM1) was administered in 51 patients (12%) throughout all therapy lines and in 50 patients in lines 1 to 4 **(Table 3)**. Eleven patients received a sequence of T-DM1 → PTZ/ TZM, eight of whom were treated within the first four therapy lines.

Table 2: Frequencies of patients who received the respective treatments; n (%)

Therapy	Patients treated before 2012: Not treated	Patients treated before 2012: Treated	Patients treated crossing 2013: Not treated	Patients treated crossing 2013: Treated	Patients treated after 2013: Not treated	Patients treated after 2013: Treated
Trastuzumab (TZM)						
Patients with only 1st line	4 (19)	17 (**80.9**)	0 (0)	6 (**100**)	28 (20.4)	109 (**79.5**)
Patients with 1st – 2nd line	0 (0)	6 (**100**)	2 (13.3)	13 (**86.6**)	11 (15)	62 (**84.9**)
Patients with 1st – 3rd line	0 (0)	4 (**100**)	3 (15.7)	16 (**84.2**)	6 (15.3)	33 (**84.6**)
Patients with 1st – 4th line	3 (20)	12 (**80**)	8 (18.1)	36 (**81.8**)	7 (18.4)	31 (**81.5**)
Trastuzumab + Pertuzumab (TZM/ PTZ)						
Patients with only 1st line	19 (90.4)	2 (**9.5**)	3 (50)	3 (**50**)	51 (37.2)	86 (**62.7**)
Patients with 1st – 2nd line	6 (100)	0 (**0**)	11 (73.3)	4 (**26.6**)	21 (28.7)	52 (**71.2**)
Patients with 1st – 3rd line	4 (100)	0 (**0**)	13 (68.4)	6 (**31.5**)	12 (30.7)	27 (**69.2**)
Patients with 1st – 4th line	15 (100)	0 (**0**)	28 (63.6)	16 (**36.3**)	14 (36.8)	24 (**63.1**)
Lapatinib (LAP)						
Patients with only 1st line	20 (95.2)	1 (**4.7**)	5 (83.3)	1 (**16.6**)	134 (97.8)	3 (**2.1**)
Patients with 1st – 2nd line	6 (100)	0 (**0**)	12 (80)	3 (**20**)	65 (89)	8 (**10.9**)
Patients with 1st – 3rd line	3 (75)	1 (**25**)	15 (78.9)	4 (**21**)	30 (76.9)	9 (**23**)
Patients with 1st – 4th line	8 (53.3)	7 (**46.6**)	22 (50)	22 (**50**)	18 (47.3)	20 (**52.6**)
Trastuzumab emtansine (T-DM1)						
Patients with only 1st line	21 (100)	0 (**0**)	6 (100)	0 (**0**)	131 (95.6)	6 (**4.3**)
Patients with 1st – 2nd line	6 (100)	0 (**0**)	10 (66.6)	5 (**33.3**)	49 (67.1)	24 (**32.8**)
Patients with 1st – 3rd line	4 (100)	0 (**0**)	8 (42.1)	11 (**57.8**)	21 (53.8)	18 (**46.1**)
Patients with 1st – 4th line	14 (93.3)	1 (**6.6**)	21 (47.7)	23 (**52.2**)	18 (47.3)	20 (**52.6**)

Table 3: Frequencies of patients who were treated with the respective treatment sequence, irrespective of wether the sequences were administered directly after each other ; n (%)

Therapy	Patients treated before 2012: Not treated	Patients treated before 2012: Treated	Patients treated crossing 2012: Not treated	Patients treated crossing 2012: Treated	Patients treated after 2012: Not treated	Patients treated after 2012: Treated
Pertuzumab/ trastuzumab → trastuzumab emtansine (PTZ/ TZM → T-DM1)						
Patients with only 1st line	21 (100)	0 (**0**)	6 (100)	0 (**0**)	137 (100)	0 (**0**)
Patients with 1st – 2nd line	6 (100)	0 (**0**)	14 (93.3)	1 (**6.6**)	59 (80.8)	14 (**19.1**)
Patients with 1st – 3rd line	4 (100)	0 (**0**)	17 (89.4)	2 (**10.5**)	27 (69.2)	12 (**30.7**)
Patients with 1st – 4th line	15 (100)	0 (**0**)	39 (88.6)	5 (**11.3**)	22 (57.8)	16 (**42.1**)

Predictors of the use of a therapy sequence of PTZ/ TZM followed by T-DM1

Several patient and disease characteristics were analyzed in relation to their influence on the utilization of the therapy sequence PTM/ TZM → T-DM1 **(Table 4)**. Worse ECOG, negative hormone receptor status, and visceral or brain metastases were associated with a more frequent use of this therapy sequence. All patients who had at least two documented therapy lines in whom all treatments started after 2013 are included.

Table 4: Frequency of patients who received the treatment sequence PTZ/ TZM → T-DM1, irrespective of wether the sequences were administered directly after each other; n (%)

Characteristic		PTZ/ TZM → T-DM1: No	PTZ/ TZM → T-DM1: Yes
Age	< 50	28 (65.1)	15 (34.9)
	50-65	53 (72.6)	20 (27.4)
	> 65	27 (79.4)	7 (20.6)
Eastern Cooperative Oncology Group (ECOG) score	0	59 (79.7)	15 (20.3)
	1	34 (63.0)	20 (37.0)
	2	6 (60.0)	4 (40.0)
	3	5 (100)	0 (0)
Metastasis site at study entry	Brain	14 (58.3)	10 (41.7)
	Visceral	56 (68.3)	23 (31.7)
	Bone only	16 (94.1)	1 (5.9)
	Other	19 (82.6)	4 (14.7)
Hormone receptor status	Negative	18 (56.3)	14 (43.8)
	Positive	90 (76.3)	28 (23.7)
Grade	1	2 (100)	0 (0)
	2	45 (78.9)	12 (21.1)
	3	50 (64.1)	28 (35.9)
Primarily metastatic	No	68 (73.9)	24 (26.1)
	Yes	40 (69.0)	42 (28.0)

DISCUSSION

This analysis of a cohort from a real-world breast cancer registry presents how frequently anti-HER2 therapies are used. While most patients received trastuzumab, the percentage of patients who received pertuzumab and trastuzumab, lapatinib, or T-DM1 was clearly lower. Most of the trastuzumab and pertuzumab therapies were administered in the first-line setting, but TDM-1 was administered in most cases between the second and fourth lines and lapatinib more often in the third- and fourth-line setting. The sequence of TDM-1 after pertuzumab was administered in up to 40% of patients with four therapy lines while the sequence T-DM1 followed by pertuzumab was only administered in about 5% of the patients.

The analysis shows that HER2-positive metastatic breast cancer is a subgroup with a clinically relevant frequency. The frequency of HER2-positive patients in the present cohort of metastatic breast cancer patients was with 23.3%, a rate very similar to the initially described frequencies of 25-30% in primary breast cancer before the introduction of anti-HER2 therapies [2]. The frequency of triple-negative breast cancer was much lower in this cohort, at 9.1% of all cases.

Pertuzumab and T-DM1 were approved in Germany in 2013. These therapies were thus inevitably not prevalent in the cohort before that time. Few patients were treated in clinical trials before that, and it can be clearly seen that the use of pertuzumab and trastuzumab during the first four therapy lines increased from 27–36% around 2013 to 63–71% after 2013. Most of these treatments were administered as first-line therapy, which is in accordance with the current national therapy guidelines [9]. T-DM1, which is administered after tumor progression in the metastatic setting, was already used in 23–58% of patients around 2013 and continued to be administered in 33–53% of patients after 2013. This therapy pattern also matched the current national therapy guidelines [9].

With regard to possible predictive factors that may have influenced physicians in deciding to treat patients with the pertuzumab/ trastuzumab sequence, it appears that patients with more advanced disease or a more unfavorable prognosis were more likely to be treated with the PTZ → T-DM1 therapy sequence. Parameters that were associated with a higher frequency of PTZ → T-DM1 use were poorer ECOG scores, brain and visceral metastases, negative hormone receptor status, and higher grading. To the best of our knowledge, no comparable data concerning this health-care research question have previously been published. Hormone receptor status in particular appears to be of special interest, since a desire to avoid chemotherapy in this patient group is a possible reason why specific treatment regimens are not administered in this group.

CONCLUSION

The utilization of trastuzumab appears to be sufficiently high in this cohort of patients with metastatic breast cancer. The utilization of the PTZ → T-DM1 sequence appeared to be rather low, and the reasons for this should be analyzed in future studies.

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