

# Treatment Landscape and Prognosis After Treatment with Trastuzumab Emtansine

## Behandlungslandschaft und Prognose nach der Therapie mit Trastuzumab Emtansin



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advanced breast cancer, metastatic, chemotherapy, anti-hormone therapy, HER2 c-erbB2, HER2/neu, trastuzumab, pertuzumab, T-DM1, lapatinib

### Schlüsselwörter

fortgeschrittener Brustkrebs, metastatisch, Chemotherapie, Antihormontherapie, HER2 c-erbB2, HER2/neu, Trastuzumab, Pertuzumab, T-DM1, Lapatinib

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## ABSTRACT

**Purpose** Pertuzumab and T-DM1 are two efficient anti-HER2 treatments for patients with HER2-positive advanced breast cancer. While pertuzumab is usually given in first-line treatment and T-DM1 in second-line treatment, standard therapy options seem to be exhausted up to now after the treatment of patients with these two therapy options. Therefore, it is important to have data that describes the therapy situation and prognosis after T-DM1 treatment.

**Methods** The PRAEGNANT metastatic breast cancer registry (NCT02338167) is a prospective registry for breast cancer patients with a focus on molecular biomarkers. Patients of all therapy lines with any kind of treatment are eligible. Collected data comprises therapies, adverse events, quality of life and other patient reported outcomes. Here we report on the patient characteristics and descriptive prognostic data for HER2-positive patients who have completed a treatment with T-DM1. Therapy patterns after T-DM1 and progression-free survival are reported as well as overall survival.

**Results** A total of 85 patients were identified for the study who were prospectively observed during therapy after the termination of T-DM1. The main reason for T-DM1 termination was progress. Following T-DM1, lapatinib, trastuzumab and chemotherapy were the main therapy choices. Median progression-free survival was 4.8 months (95% CI: 3.2–6.3) and median overall survival was 18.4 months (95% CI: 15.5–21.3).

**Conclusions** Therapy options after T-DM1 in a real-world setting seem to exhibit a relevant clinical efficacy, supporting the concept of continuous anti-HER2 treatments in the advanced therapy setting for breast cancer patients. Novel therapies are needed to improve the rather short median progression-free survival.

## ZUSAMMENFASSUNG

**Ziel** Pertuzumab und T-DM1 sind 2 wirksame Anti-HER2-Therapien, die zur Behandlung von Patientinnen mit fortgeschrittenem HER2-positiven Brustkrebs eingesetzt werden. Die Primärtherapie besteht meist aus Pertuzumab und die Second-Line-Therapie aus T-DM1. Bisher waren die Standard-Behandlungsoptionen erschöpft, nachdem Patientinnen eine Behandlung mit diesen beiden Therapieoptionen erhalten hatten. Das Sammeln von Daten über die Therapielandschaft und zur Prognose nach Abschluss einer T-DM1-Behandlung ist daher wichtig.

**Methoden** Das PRAEGNANT-Brustkrebsregister von Frauen mit metastasiertem Mammakarzinom (NCT02338167) ist ein prospektives Register mit einem Schwerpunkt im Bereich molekularer Biomarker. Daten von Patientinnen über alle Therapielinien hinweg sowie nach allen Behandlungsoptionen werden ins Register aufgenommen. Die gesammelten Daten umfassen eingesetzte Therapien, unerwünschte Ereignisse, Lebensqualität sowie weitere Patient reported Outcomes. Wir berichten hier über Patientinnenmerkmale und deskriptive prognostische Daten von HER2-positiven Patientinnen nach Abschluss einer Therapie mit T-DM1. Therapieschemata nach T-DM1, progressionsfreies Überleben sowie Gesamtüberleben wurden untersucht.

**Ergebnisse** Es wurden insgesamt 85 Patientinnen für diese Studie ermittelt, die während der Therapie nach Beendigung der T-DM1-Behandlung prospektiv observiert wurden. Der Hauptgrund für die Beendigung der Therapie mit T-DM1 war das Fortschreiten der Erkrankung. Nach T-DM1 waren Lapatinib, Trastuzumab und Chemotherapie die wichtigsten Therapieoptionen. Das mittlere progressionsfreie Überleben war 4,8 Monate (95%-K: 3,2–6,3), und die durchschnittliche Gesamtüberlebenszeit betrug 18,4 Monate (95%-KI 15,5–21,3).

**Schlussfolgerungen** Die Behandlungsoptionen nach T-DM1 in der realen Welt zeigten eine klinisch relevante Effizienz und stützten damit das Konzept einer fortlaufenden Anti-HER2-Behandlung als fortgeschrittene Therapie zur Behandlung von Brustkrebspatientinnen mit progredienter Erkrankung. Neuartige Therapien werden benötigt, um die eher kurze durchschnittliche progressionsfreie Überlebenszeit zu verlängern.

## Introduction

Over the last few decades, the treatment of patients with HER2-positive breast cancer (BC) has been highly dynamic. Since the discovery that HER2-gene amplifications were associated with a

clearly unfavorable prognosis in patients with metastatic breast cancer [1, 2], the anti-HER2 antibody, trastuzumab, has not only been introduced for the treatment of metastatic BC [3] but, because of its efficacy, has also been used in the adjuvant [4, 5] and neoadjuvant [6, 7] treatment of BC patients. Subsequent improve-

ments of anti-HER2 therapies, like the pertuzumab antibody, were also first shown to be efficient in patients with metastatic breast cancer [8] and were then quickly introduced to the neoadjuvant [9–12] and adjuvant setting [13]. Recently, trastuzumab emtansine (T-DM1), which has shown an improved disease-free and overall survival rate in patients with metastatic BC [14], has also been shown to improve invasive disease-free survival in patients who did not respond with a pathological complete response (pCR) after a standard neoadjuvant treatment with trastuzumab and chemotherapy [15]. However, the rapid sequence of these studies in the metastatic and adjuvant setting presents some challenges concerning the planning of therapies. Up to now, the most frequently used therapy sequence in the metastatic setting is the combination of pertuzumab and trastuzumab in first-line treatment and, subsequently, T-DM1 therapy in second-line treatment [16]. While this was reflected in the design of the CLEOPATRA and EMILIA studies, patients taking part in EMILIA received T-DM1 without prior treatment with pertuzumab [14]. However, there is some evidence that patients in this therapy sequence still gain reasonable clinical benefits from T-DM1 treatment after pertuzumab [17–19].

With novel developments and increasing use of pertuzumab and T-DM1 in the curative setting, these scenarios will be changing again. Therefore, it is becoming increasingly important to learn about therapy patterns after the most recently approved therapy regimens and to assess their efficacy and safety. Two novel substances (tucatinib and trastuzumab-deruxtecan) have also shown very promising activity in patients with heavily pretreated HER2-positive advanced BC [20,21] and have been approved in the U.S. All the patients had been previously treated with T-DM1.

This analysis will focus on the patient population after treatment with T-DM1 in the metastatic setting before tucatinib and trastuzumab-deruxtecan became available and will present data from a real-world registry. There is very limited data on this patient population. In a case study of 20 metastatic BC patients who stopped T-DM1 treatment without previous pertuzumab treatment, 15 received a subsequent therapy, which was either trastuzumab/lapatinib-based or without anti-HER2 treatment [22]. The authors conclude that a continued anti-HER2 treatment is beneficial for patients in this therapy situation, supporting the concept that a HER2 blockade regimen should be continued beyond progression [23].

The aim of this study is to describe the therapy patterns after a treatment with T-DM1 in a real-world registry of advanced BC patients to give an insight into the prognosis of this patient population.

## Patients and Methods

### The PRAEGNANT research network

The PRAEGNANT study (Prospective Academic Translational Research Network for the Optimization of the Oncological Health Care Quality in the Adjuvant and Advanced/Metastatic Setting, NCT02338167 [24]) is an ongoing, prospective BC registry with documentation similar to a clinical trial. The aims of PRAEGNANT are to assess treatment patterns and the quality of life and to identify patients who might be eligible for clinical trials or specific

targeted treatments [24–27]. Patients can be included at any time point during the course of their disease. All patients provide informed consent, and the studies are approved by the respective ethics committees.

### Patients

A total of 2932 patients with advanced or metastatic BC were registered on the PRAEGNANT study between July 2014 and January 2019 at 52 study sites. Patients were excluded in the following hierarchical order: patients with an unknown or negative HER2 status ( $n = 2232$ ), patients with an unknown first-metastasis date, those with an unknown date of birth, male patients and patients with no documented therapies ( $n = 46$ ). This left 654 patients with confirmed HER2-positive advanced BC. Of those, 221 were documented to have been treated with T-DM1, of which 158 patients had an end of therapy documented. The next therapy line was documented in 123 patients. For prospective evaluation, 85 patients were available. Prospective in this context implies that the first therapy after T-DM1 must not have started later than 90 days before study inclusion and some follow-up information needed to be available. The patient flow chart is shown in ► Fig. 1.

### Data collection

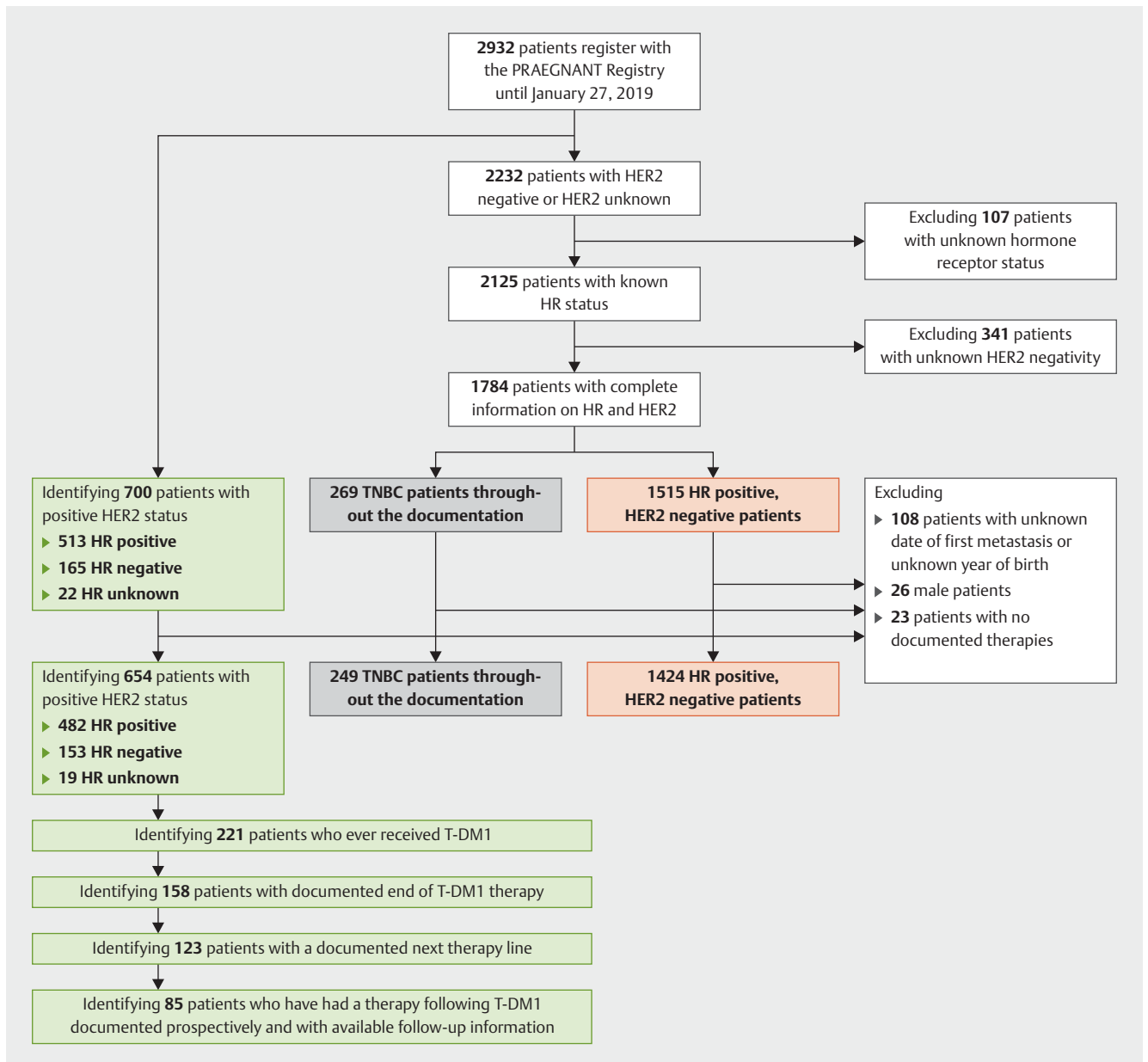
The data was collected by trained staff and documents were transferred into an electronic case report form [24]. Data was monitored using automated plausibility checks and on-site monitoring. Data not usually documented as part of routine clinical work was collected prospectively using structured paper questionnaires. This data was comprised of epidemiological data, such as family history, cancer risk factors, quality of life, nutrition and lifestyle and psychological health. Supplementary Table S1 provides an overview of the collected data.

### Definition of hormone receptor, HER2 status, and grading

The definition of the status and grading of the HER2 hormone receptors has been described before [25]. Briefly, data about the estrogen receptor (ER) status, progesterone receptor (PR) status and HER2 status and grading was requested for the documentation of each tumor that had been biopsied. Therefore, there could be several sources of data – right breast, left breast, local recurrence or metastatic site. The biomarker status for ER, PR and HER2 was determined as follows. If a biomarker assessment of the metastatic site was available, this receptor status was taken for this analysis. If there was no information from metastases, the latest biomarker results from the primary tumor were taken. Additionally, all patients who had ever been treated with an ET were assumed to be HR positive and all patients who had ever been treated with an anti-HER2 therapy were assumed to be HER2 positive. There was no central review of biomarkers. The study protocol recommended that the ER and PR status be assessed as positive if  $\geq 1\%$  of them were stained. A positive HER2 status required an IHC score of 3+ or a positive FISH/CISH.

### Statistical analysis

The primary aim was to describe the patient cohort that started a treatment after T-DM1. Patient and tumor characteristics as well



► Fig. 1 Patient flow chart and patient selection.

as previous and subsequent therapies were described with adequate descriptive methods.

In an exploratory analysis, progression-free survival (PFS) was assessed in relation to commonly known prognostic factors. PFS was defined as the period from the start of the treatment to the earliest disease progression (distant metastasis, local recurrence or death from any cause) or the last progression-free time point. Median survival times and survival rates were estimated for the total cohort as well as for subgroups using the Kaplan–Meier product limit method.

Similar analyses were performed for overall survival.

Calculations were performed using IBM SPSS software, version 24 (Armonk, New York, USA).

## Results

### Patient and disease characteristics

A total of 85 patients who had had at least one documented therapy after a T-DM1 therapy were identified for this analysis (► Fig. 1). Patients were, on average, 57 years old and the time from the first diagnosis to the occurrence of metastases was, on average, 35 months. 40% of the patients ( $n = 34$ ) had metastases at the time of diagnosis. A total of 33 patients (38.8%) had brain metastases and 45.9% ( $n = 39$ ) had visceral metastases. Complete patient and disease characteristics are shown in ► Table 1.

► **Table 1** Patient characteristics.

Characteristic	n or mean	% or SD
Age at study entry (years)	56.9	12.8
BMI (kg/m <sup>2</sup> )	25.7	4.9
Time from diagnosis to metastases (months)	34.9	46.5
Grading		
▪ 1 or 2	34	42.5
▪ 3	46	57.5
▪ Unknown	5	
HR status		
▪ Negative	25	30.9
▪ Positive	56	69.1
▪ Unknown	4	
ECOG		
▪ 0	39	48.8
▪ 1	34	42.5
▪ 2	5	6.3
▪ 3	1	1.3
▪ 4	1	1.3
▪ Unknown	5	
Metastasis site at study entry		
▪ Brain*	33	38.8
▪ Visceral**	39	45.9
▪ Bone only	4	4.7
▪ Other***	9	10.6
Metastasized at time of diagnosis		
▪ No	51	60.0
▪ Yes	34	40.0

\* Patients in the "brain" category were allowed to have metastases at any other site.

\*\* Patients were allowed to have metastases at any other site except the brain.

\*\*\* Patients were not allowed any brain, visceral or bone metastases.

The majority of the patients had received T-DM1 in therapy lines two and three with 40% of the patients (n = 34) treated in the second line and 27.1% (n = 23) treated in the third line. The vast majority of patients had received a previous anti-HER2 treatment in the metastatic setting (n = 74, 87.1%), with the patients who had received first-line T-DM1 (n = 9) forming the majority of those who had not received any previous anti-HER2 treatment. The median duration of T-DM1 treatment was 7.8 months and disease progression was the main reason for treatment termination in 84.5% (n = 72) of cases. The treatment characteristics are summarized in ► **Table 2**.

The treatments documented after T-DM1 termination showed broad variability. In the first line of therapy after T-DM1, most patients were treated with lapatinib and chemotherapy (n = 21, 24.7%). However, trastuzumab and chemotherapy and chemotherapy without an anti-HER2 treatment were seen in 20.0%

► **Table 2** Treatment characteristics of T-DM1 treatment.

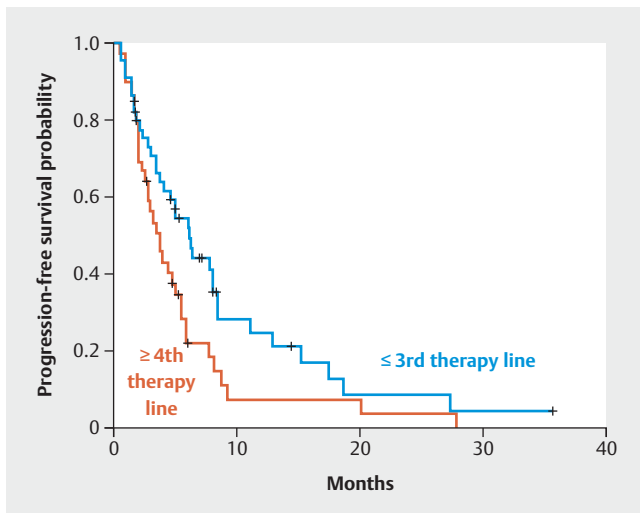
Characteristic	n or median	% or IQR
Duration of T-DM1 treatment (years and Interquartile range)	7.8	5.4–10.3
Therapy line T-DM1 given		
▪ 1	9	10.6
▪ 2	34	40.0
▪ 3	23	27.1
▪ 4 or higher	19	22.4
Previous HER2-treatment before T-DM1*		
▪ PTZ/TZM	48	56.5
▪ TZM	29	34.1
▪ Lapatinib	9	10.6
▪ Lapatinib/TZM	5	5.9
▪ Any HER2	74	87.1
Reason for T-DM1 termination		
▪ Planned cycles completed	3	3.5
▪ Toxicity	4	4.7
▪ Patient's wish	3	3.5
▪ Progress	72	84.7
▪ Unknown	3	3.5

\* Multiple choices possible.

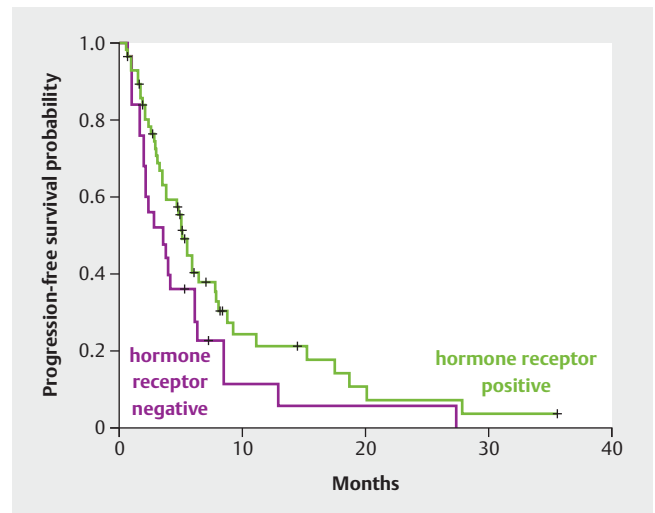
► **Table 3** Treatments reported for the therapy line directly after termination of T-DM1. This information was reported for all 85 patients.

Therapy	Frequency	%
LAP/Chemo	21	24.7
TZM/Chemo	17	20.0
Chemo	10	11.8
PTZ/TZM/Chemo	10	11.8
LAP/TZM	6	7.1
TZM	4	4.7
Clinical trial	4	4.7
AH	3	3.5
Unknown	3	3.5
LAP/AH	1	1.2
LAP/TZM/Chemo	1	1.2
PTZ/TZM	1	1.2
TDM1/PTZ	1	1.2
TDM1/PTZ/Chemo	1	1.2
TDM1/PTZ/TZM/Chemo	1	1.2
TZM/AH	1	1.2

LAP: lapatinib; TZM: trastuzumab; PTZ: pertuzumab; AH: anti-hormone therapy



► **Fig. 2** Progression-free survival according to therapy line after T-DM1 treatment. Median progression-free survival time for patients up to the 3rd therapy line is 6.1 months (95% CI: 4.5–7.8) and for patients treated in the 4th or subsequent therapy lines was 3.7 months (95% CI: 2.5–4.9).



► **Fig. 3** Progression-free survival according to hormone receptor status. Median progression-free survival time for hormone receptor positive patients is 5.1 months (95% CI: 4.1–6.0) and for hormone receptor negative patients 3.5 months (95% CI: 1.2–5.8).

(n = 17) and 11.8% (n = 10) of cases, respectively. The dual blockade with pertuzumab, trastuzumab and chemotherapy was also seen in 10 cases (11.8%). All documented therapies in the first line after T-DM1 are shown in ► **Table 3**. In both the second and third line after T-DM1, chemotherapies without anti-HER2 treatments were the most frequently given therapy (► **Tables 4 and 5**). However, a broad variability of anti-HER2 treatments were given as well. Only four, six and two patients from the first, second and

third line, respectively, were treated with some kind of anti-endocrine treatment after T-DM1. Interestingly, in some cases, a combination therapy with CDK4/6 inhibitors was performed.

The median PFS for the total cohort was 4.8 months (95% CI: 3.2–6.3) (Supplementary Fig. S1). Kaplan–Meier curves for PFS according to the therapy line and hormone receptor status are shown in ► **Figs. 2 and 3**.

► **Table 4** Treatments reported for the therapy line two lines after termination of T-DM1. This information was reported for 50 patients.

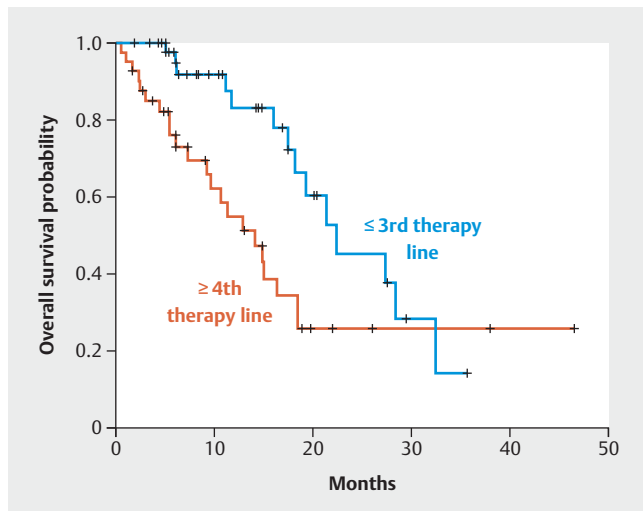
Therapy	Frequency	%
Chemo	17	34.0
LAP/Chemo	7	14.0
PTZ/TZM/Chemo	5	10.0
TZM/Chemo	4	8.0
AH	3	6.0
AH and CDK4/6i	3	6.0
LAP	2	4.0
LAP/TZM	2	4.0
LAP/TZM/Chemo	2	4.0
Clinical Trial	2	4.0
BEV/Chemo	1	2.0
TZM	1	2.0
TZM/AH	1	2.0

LAP: lapatibib; TZM: trastuzumab; PTZ: pertuzumab; AH: anti-hormone therapy

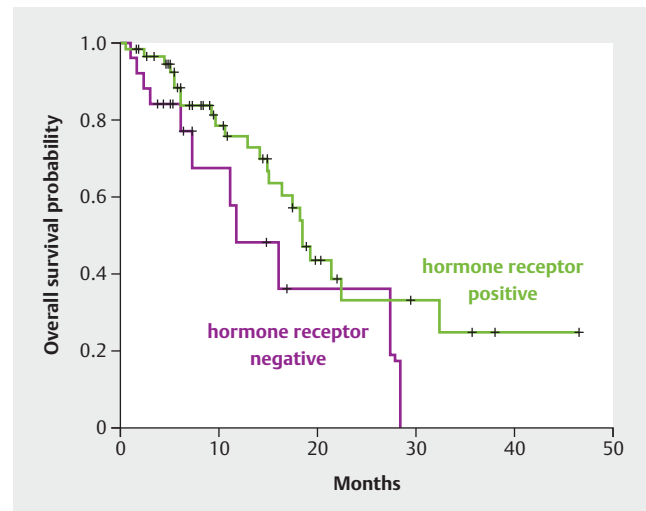
► **Table 5** Treatments reported for the therapy line three lines after termination of T-DM1. This information was reported for 15 patients.

Therapy	Frequency	%
Chemo	6	40.0
TZM/Chemo	3	20.0
AH	1	6.7
LAP	1	6.7
LAP/TZM/AH	1	6.7
PTZ	1	6.7
T-DM1	1	6.7
TZM/AH	1	6.7

LAP: lapatibib; TZM: trastuzumab; PTZ: pertuzumab; AH: anti-hormone therapy



► **Fig. 4** Progression-free survival according to therapy line after T-DM1 treatment. Median overall survival time for patients up to the 3rd therapy line is 22.3 months (95% CI: 13.7–31.0) and for patients treated in the 4th or subsequent therapy lines was 14.1 months (95% CI: 9.1–19.1).



► **Fig. 5** Overall survival according to hormone receptor status. Median overall survival time for hormone receptor positive patients is 18.4 months (95% CI: 16.1–20.6) and for hormone receptor negative patients 11.7 months (95% CI: 5.3–18.1).

Median overall survival time was 18.4 months (95% CI: 15.5–21.3) (Supplementary Fig. S2). The Kaplan–Meier curves according to the therapy line and hormone receptor status are shown in ► **Figs. 4 and 5**.

## Discussion

We have shown that most patients received a subsequent anti-HER2 therapy after a T-DM1 therapy. The median PFS of patients treated after a previous treatment with T-DM1 was about five months and overall survival was about 18 months. The chosen treatments varied from lapatinib-based therapies to chemotherapies without anti-HER2 treatment. Anti-hormone therapies did not seem to play a major role in the heavily pre-treated HER2-positive advanced BC patients.

There is limited evidence from similar studies. A case study with 15 patients who were treated with T-DM1 before pertuzumab was available reported a reasonable therapy efficacy with a median therapy duration of 5.5 to 6.4 months [22]. This is similar to our study, although the patients in this analysis were treated with pertuzumab and trastuzumab before T-DM1 in more than 50% of cases. In the previously published study, the authors concluded from the partial response rate of 33% (five out of 15 patients) and the duration of the therapy, that a previous treatment with T-DM1 did not exhaust the potential of subsequent anti-HER2 therapies [22]. The concept of a continuous anti-HER2 treatment regardless of therapy progression has already been previously addressed without novel therapies. The “treatment-beyond-progression” trial compared the continuation of a treatment with trastuzumab and one with a changed chemotherapy combination partner. This early study has proven the concept that anti-HER2 therapies should be continued after progression [23].

With novel anti-HER2 therapies that at least in part address several resistance mechanisms, there is an even greater chance that the continuation of an anti-HER2 treatment after progression results in a clinically relevant therapy efficacy. For example, Neratinib, another tyrosine kinase inhibitor, has been approved for the adjuvant treatment of patients with HER2-positive early BC for an extended adjuvant therapy and has also been approved in the U. S. for metastatic BC [28, 29]. Afatinib, however, did not show any improvement in the outcomes for patients with metastatic BC compared to trastuzumab [30]. Margetuximab has now made a third novel HER2 antibody available that appears to enhance antibody-dependent cellular toxicity (ADCC) while at the same time being well tolerated [31]. Its efficacy and safety are currently being investigated in the phase III SOPHIA trial in patients with HER2-positive metastatic BC who have previously been treated with trastuzumab, pertuzumab, and T-DM1 [32]. The HER2CLIMB and DESTINY-B01 studies have investigated the specific patient population of HER2-positive advanced BC patients who had previously been treated with T-DM1 [20, 21]. In a large early phase study, trastuzumab deruxtecan demonstrated a PFS of 16.4 months (95% CI, 12.7–not reached) [21]. Tucatinib, in combination with trastuzumab and capecitabine, achieved an improvement in PFS (+ 2.2 months) and overall survival (+ 4.5 months) compared to trastuzumab and capecitabine alone [20]. This effect was also seen in patients with brain metastases [33].

Interestingly, in our study, only a minority of patients had been treated with a combination of hormone therapies and anti-HER2 treatments. However, there is data from several studies that the combination of aromatase inhibitors with trastuzumab, for example, represents an efficient combination therapy for patients with HER2-positive hormone receptor positive BC [34, 35]. According to national and international guidelines, the combination of anti-hormone therapy and anti-HER2 agents is also considered reason-



able after the exhaustion of all standard treatments [36,37]. Therefore, the low utilization of these efficient therapies with a favorable toxicity profile cannot be explained and treating physicians should be aware of these therapy options for patients who have already been treated with trastuzumab, pertuzumab and T-DM1.

With only 85 patients, this study has clear limitations; however, to our knowledge, no larger cohort of patients in this therapy situation has yet been described. Furthermore, the 85 patients selected for observation from the beginning of therapy restricted the study population further, but this emphasizes the value of extended prospective observation times. The patient population was identified from a real-world registry, which might mean that this population is different to the ones in clinical trials. The data might therefore not be directly comparable with previously published data from clinical trials.

In conclusion, our study adds to the evidence that the continuation of anti-HER2 treatments even after T-DM1 in a population that has also been pretreated to a high degree with pertuzumab is associated with a reasonable clinical efficacy. PFS in this population is low with a median of five months. Recent clinical trials that address specific resistance mechanisms have shown successful prognostic improvements, suggesting the need for further trials to be conducted in this population with patients who have a high likelihood of benefitting from further anti-HER2 treatments.

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## Conflict of Interest

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## References

- [1] Slamon DJ, Clark GM, Wong SG et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987; 235: 177–182
- [2] Slamon DJ, Godolphin W, Jones LA et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 1989; 244: 707–712
- [3] Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; 344: 783–792
- [4] Slamon D, Eiermann W, Robert N et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011; 365: 1273–1283
- [5] Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005; 353: 1659–1672
- [6] Untch M, Fasching PA, Konecny GE 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* 2011; 29: 3351–3357
- [7] Untch M, Rezaei M, Loibl S et al. Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: results from the GeparQuattro study. *J Clin Oncol* 2010; 28: 2024–2031
- [8] Baselga J, Cortes J, Kim SB et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012; 366: 109–119
- [9] Fasching PA, Hartkopf AD, Gass P et al. Efficacy of neoadjuvant pertuzumab in addition to chemotherapy and trastuzumab in routine clinical treatment of patients with primary breast cancer: a multicentric analysis. *Breast Cancer Res Treat* 2019; 173: 319–328
- [10] Gianni L, Pienkowski T, Im YH 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* 2012; 13: 25–32
- [11] Gianni L, Pienkowski T, Im YH et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol* 2016; 17: 791–800



- [12] Schneeweiss A, Chia S, Hickish T 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* 2013; 24: 2278–2284
- [13] von Minckwitz G, Procter M, de Azambuja E et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *N Engl J Med* 2017; 377: 122–131
- [14] Verma S, Miles D, Gianni L et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012; 367: 1783–1791
- [15] von Minckwitz G, Huang C-S, Mano MS et al.; KATHERINE Investigators. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. *N Engl J Med* 2019; 380: 617–628
- [16] Lux MP, Nabieva N, Hartkopf AD et al. Therapy Landscape in Patients with Metastatic HER2-Positive Breast Cancer: Data from the PRAEGNANT Real-World Breast Cancer Registry. *Cancers (Basel)* 2018; 11: 10
- [17] Dzimitrowicz H, Berger M, Vargo C et al. T-DM1 Activity in Metastatic Human Epidermal Growth Factor Receptor 2-Positive Breast Cancers That Received Prior Therapy With Trastuzumab and Pertuzumab. *J Clin Oncol* 2016; 34: 3511–3517
- [18] Huober J, Weder P, Veyret C et al. PERNETTA – A non comparative randomized open label phase II trial of pertuzumab (P) + trastuzumab (T) with or without chemotherapy both followed by T-DM1 in case of progression, in patients with HER2 positive metastatic breast cancer (SAKK 22/10/UNICANCER UC-0140/1207). *Ann Oncol* 2018; 29: mdy272.280
- [19] Vici P, Pizzuti L, Michelotti A et al. A retrospective multicentric observational study of trastuzumab emtansine in HER2 positive metastatic breast cancer: a real-world experience. *Oncotarget* 2017; 8: 56921–56931
- [20] Murthy RK, Loi S, Okines A et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. *N Engl J Med* 2020; 382: 597–609
- [21] Modi S, Saura C, Yamashita T et al.; DESTINY-Breast01 Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. *N Engl J Med* 2020; 382: 610–621
- [22] Olson EM, Lin NU, DiPiro PJ et al. Responses to subsequent anti-HER2 therapy after treatment with trastuzumab-DM1 in women with HER2-positive metastatic breast cancer. *Ann Oncol* 2012; 23: 93–97
- [23] von Minckwitz G, du Bois A, Schmidt M et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. *J Clin Oncol* 2009; 27: 1999–2006
- [24] Fasching PA, Brucker SY, Fehm TN et al. Biomarkers in Patients with Metastatic Breast Cancer and the PRAEGNANT Study Network. *Geburtshilfe Frauenheilkd* 2015; 75: 41–50
- [25] Hartkopf AD, Huober J, Volz B et al. Treatment landscape of advanced breast cancer patients with hormone receptor positive HER2 negative tumors – Data from the German PRAEGNANT breast cancer registry. *Breast* 2018; 37: 42–51
- [26] Muller V, Nabieva N, Haberle L et al. Impact of disease progression on health-related quality of life in patients with metastatic breast cancer in the PRAEGNANT breast cancer registry. *Breast* 2018; 37: 154–160
- [27] Hein A, Gass P, Walter CB et al. Computerized patient identification for the EMBRACA clinical trial using real-time data from the PRAEGNANT network for metastatic breast cancer patients. *Breast Cancer Res Treat* 2016; 158: 59–65
- [28] Deeks ED. Neratinib: First Global Approval. *Drugs* 2017; 77: 1695–1704
- [29] Saura C, Oliveira M, Feng YH et al. Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With  $\geq 2$  HER2-Directed Regimens: Phase III NALA Trial. *J Clin Oncol* 2020; 38: 3138–3149
- [30] Harbeck N, Huang CS, Hurvitz S et al. Afatinib plus vinorelbine versus trastuzumab plus vinorelbine in patients with HER2-overexpressing metastatic breast cancer who had progressed on one previous trastuzumab treatment (LUX-Breast 1): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2016; 17: 357–366
- [31] Bang YJ, Giaccone G, Im SA et al. First-in-human phase 1 study of margetuximab (MGAH22), an Fc-modified chimeric monoclonal antibody, in patients with HER2-positive advanced solid tumors. *Ann Oncol* 2017; 28: 855–861
- [32] Loibl S, Gianni L. HER2-positive breast cancer. *Lancet* 2017; 389: 2415–2429
- [33] Lin NU, Murthy RK, Anders CK et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with previously treated HER2+ metastatic breast cancer with brain metastases (HER2CLIMB). *J Clin Oncol* 2020; 38: 1005–1005
- [34] Kaufman B, Mackey JR, Clemens MR et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. *J Clin Oncol* 2009; 27: 5529–5537
- [35] Huober J, Fasching PA, Barsoum M et al. Higher efficacy of letrozole in combination with trastuzumab compared to letrozole monotherapy as first-line treatment in patients with HER2-positive, hormone-receptor-positive metastatic breast cancer – results of the eLECTRA trial. *Breast* 2012; 21: 27–33
- [36] Wockel A, Festl J, Stuber T et al. Interdisciplinary Screening, Diagnosis, Therapy and Follow-up of Breast Cancer. Guideline of the DGGG and the DKG (S3-Level, AWMF Registry Number 032/045OL, December 2017) – Part 1 with Recommendations for the Screening, Diagnosis and Therapy of Breast Cancer. *Geburtshilfe Frauenheilkd* 2018; 78: 927–948
- [37] Wockel A, Festl J, Stuber T et al. Interdisciplinary Screening, Diagnosis, Therapy and Follow-up of Breast Cancer. Guideline of the DGGG and the DKG (S3-Level, AWMF Registry Number 032/045OL, December 2017) – Part 2 with Recommendations for the Therapy of Primary, Recurrent and Advanced Breast Cancer. *Geburtshilfe Frauenheilkd* 2018; 78: 1056–1088