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Trastuzumab Emtansine in Patients with HER2-Positive Metastatic Breast Cancer: a Multicenter Japanese Retrospective Study

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Abstract

Introduction: Trastuzumab emtansine (T-DM1) is currently approved for the treatment of patients with HER2-positive metastatic breast cancer after failure of prior anti-HER2 therapies. However, the efficacy of T-DM1 in patients who received pertuzumab, and in those patients with brain metastases, is currently unclear.

Methods: A total of 63 women with HER2-positive metastatic breast cancer were treated with T-DM1 between April 2014 and April 2016. The efficacy and safety of T-DM1 therapy was investigated.

Results: There were 43 (67%) patients with visceral metastases and 14 (22%) patients with brain metastases. As adjuvant or neoadjuvant therapy in 45 patients with recurrent breast cancer, 19 (30%) patients had received trastuzumab. In the metastatic setting, all but two patients (97%) had undergone trastuzumab, 41 (65%) patients had received pertuzumab and 21 (33%) patients had received lapatinib prior to T-DM1. Patients had received a median of three regimens prior to T-DM1 for metastatic breast cancer. The response rate of patients on T-DM1 was 35%, the clinical benefit rate was 49%, and median time to treatment failure (TTF) was 4.0 months. In 41 patients pretreated with pertuzumab, the response rate was 29%, the clinical benefit rate was 46%, and median TTF was 5.0 months. In 14 patients with brain metastases, median TTF was 6.0 months, although none achieved CR or PR for brain tumors. The most commonly reported grade 3 or 4 adverse event was thrombocytopenia, which was experienced by 13 (21%) patients, although this was not associated with severe bleeding. Treatment termination was necessary in 5 (8%) patients because of side effects.

Conclusions: T-DM1 is an effective and well-tolerated treatment for patients with HER2-positive metastatic breast cancer that had progressed after previous anti-HER2 therapies. T-DM1 could be used for patients who have experienced progression following prior treatment with pertuzumab.

Keywords

Trastuzumab emtansine, Pertuzumab, Metastatic breast cancer, HER2-positive, Clinical experience

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Abbreviations

T-DM1: Trastuzumab emtansine; HER2: Human epidermal growth factor receptor type 2; ER: Estrogen receptor; PgR: Progesterone receptor; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; TTF: Time to treatment failure; HR: Hazard ratio

Introduction

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate incorporating the HER2-targeting antitumor properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent, DM1 [1,2]. Trastuzumab and DM1 are conjugated via a stable linker. T-DM1is the most recently approved (2014) anti-HER2 agent in Japan, and has been used for the treatment of HER2-positive metastatic breast cancer after failure of prior anti-HER2 therapies.

Results from phase III studies have confirmed the efficacy and safety of T-DM1 in patients with HER2-positive metastatic breast cancer [3,4]. The pivotal "EMILIA" study was a phase III randomized international trial that evaluated the efficacy and safety of T-DM1 compared to the combination of lapatinib plus capecitabine in patients with metastatic or locally advanced HER2-positive breast cancer, these patients had been previously treated with trastuzumab and taxanes [3]. A total of 991 patients participated, and median progression-free survival (PFS) was 9.6 months with T-DM1 vs. 6.4 months with lapatinib plus capecitabine (hazard ratio (HR) = 0.65, 95% confidence interval (CI), 0.55 to 0.77; P < 0.001). Overall survival (OS) was also significantly longer in patients treated with T-DM1 (median OS was 30.9 months with T-DM1 vs. 25.1 months with lapatinib plus capecitabine, HR = 0.68; 95% CI, 0.55 to 0.85; P < 0.001). Another randomized phase III trial, the TH3RESA trial, has compared T-DM1 with a treatment of the physician's choice in patients with progressive disease after two or more HER2-directed regimens for metastatic breast cancer [4]. PFS was significantly improved with T-DM1 compared with physician's choice (median 6.2 months [95% CI 5.59–6.87] vs. 3.3 months [2.89-4.14]; stratified HR 0.528 [95% CI 0.422-0.661]; P < 0.0001). Interim overall survival analysis showed a trend favoring T-DM1 (stratified HR 0.552 [95% CI 0.369-0.826]; P = 0.0034), but the stopping boundary was not crossed. T-DM1 had a lower incidence of grade 3 or worse adverse events (32%) when compared to the treatment of the physician's choice (43%), and was also associated with a favorable toxicity profile. Furthermore, a single arm phase II study (JO22997) in Japanese patients who had been intensively pretreated for locally advanced or metastatic breast cancer has been conducted [5]. In 73 patients treated with 3.6 mg/kg T-DM1 every 3 weeks, the objective response rate was 38.4% and median PFS was 5.6 months.

Although controlled clinical trials provide the highest levels of evidence, they do not always reflect clinical reality. For patients with HER2-positive metastatic breast cancer who have progressed during or after first-line HER2-targeted therapy with the combination of trastuzumab, pertuzumab, and a taxane, T-DM1 therapy is now a standard second-line treatment [6]. However, neither the EMILIA nor other T-DM1 trials included patients who had received pertuzumab and there is no published clinical trial that addresses this issue. Moreover, few data are currently available regarding the efficacy and safety of T-DM1 in patients with brain metastases, since most clinical trials have excluded patients with these complications, or have only included highly selected patients.

A retrospective exploratory analysis in the Emilia trial suggested that T-DM1 may confer a survival advantage over lapatinib-capecitabinein patients with treated, asymptomatic central nervous system (CNS) metastases and previously treated HER2-positive metastatic breast cancer, without increasing the risk for CNS progression [7]. The estimated median OS with CNS metastases at baseline was 26.8 months versus 12.9 months in the T-DM1 and lapatinib-capecitabine arms, respectively. This finding was consistent with the OS result among all randomized patients in the EMILIA trial, with a median OS of 30.9 months in the T-DM1 arm and 25.1 months in the lapatinib-capecitabine arm (HR = 0.68; P < 0.001).

Table 1: Characteristics of patients.

	Number of patients (%)
Total	63
Median age, years (range)	64 (40-80)
Hormone receptor status	
ER-positive and/or PgR-positive	35 (56%)
ER-negative and PgR-negative	28 (44%)
HER2 status	
IHC 3+	56 (89%)
IHC 2+ and ISH positive	7 (11%)
Stage IV	18 (29%)
Recurrence	45 (71%)
Median disease free interval, months (range)	29 (2-104)
< 2 years	19 (42%)
2–5 years	19 (42%)
≥ 5 years	7 (16%)
Site of disease involvement	
Visceral	43 (67%)
Nonvisceral	21 (33%)
Metastatic site	
Lung	28 (44%)
Liver	21 (33%)
Bone	25 (40%)
Brain	14 (22%)
Lymph node	31 (49%)
Other	30 (48%)

IHC: immunohistochemistry; ISH: in situ hybridization.

Table 2: Prior treatments.

	Number of patients (%)
Adjuvant or neoadjuvant therapies	
Anthracycline	26 (41%)
Taxane	22 (35%)
Trastuzumab	19 (30%)
Endocrine therapy	21 (33%)
Previous anti-HER2 therapies for metastatic breast cancer	
Trastuzumab	61 (97%)
Pertuzumab	41 (65%)
Lapatinib	21 (33%)
Number of previous regimens for metastatic breast cancer	
0 (first line)	0 (0%)
1 (second line)	17 (27%)
2 (third line)	8 (13%)
3 (forth line)	12 (19%)
≥ 4	26 (41%)
Median time since first-line treatment of metastatic breast cancer, months (range)	29 (6-217)

In the present study, we report our experience with T-DM1 in patients with HER2-positive metastatic breast cancer that had progressed after previous anti-HER2 therapies. Of 63 patients in our cohort, 41 patients (65%) had received pertuzumab prior to T-DM1 therapy. The effectiveness and safety of T-DM1 treatment were retrospectively investigated.

Patients and Methods

Patients and treatment

A retrospective review was carried out on a total of 63 women with HER2-positive metastatic breast cancer who were treated with T-DM between April 2014 and April 2016 in 13 hospitals (Table 1). Most patients were heavily pretreated prior to T-DM1 therapy (Table 2). Patients were given T-DM1 at a dose of 3.6 mg/kg intravenously every 21 days. If a patient needed a dose reduction, the dose was reduced first from 3.6 mg/kg to 3.0 mg/kg and then from 3.0 mg/kg to 2.4 mg/kg. Echocardiography was performed prior to T-DM1 therapy

and during anti-HER2 therapies (including T-DM1) approximately every three months.

Clinical responses were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). CT, MRI, ultrasonography, and/or bone scintigraphy were used to evaluate the response to T-DM1 for patients without measurable lesions or for patients with bone metastasis only and the results were included in this study. The evaluation of brain metastases was performed using contrast-enhanced MRI or CT. Radiologists in each hospital assessed the existence of metastases and tumor response to T-DM1 therapy. Clinical benefit rate was defined as the sum of all patients experiencing complete response (CR), partial response (PR) or stable disease (SD) lasting 6 months or more. Time to treatment failure (TTF) and safety were also retrospectively analyzed. TTF was defined as the time from the date of T-DM1 treatment commencement to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death. Adverse events were evaluated using the National Cancer Institute Common Toxicity Criteria, version 4.0. This study was done in accordance with the guidelines of the 1996 Declaration of Helsinki.

Statistical analysis

Estimation of survival was performed using the Kaplan-Meier method. Patients who were still receiving T-DM1, ended T-DM1 therapy because of side effects, or died for other reasons at the time of analysis were included as censored cases. Univariate analysis with Cox proportional hazards regression models was used to identify factors predicting TTF during T-DM1 treatment. P values < 0.05 were considered to be significant.

Results

Patients' characteristics

Of 63 patients, 45 (71%) had recurrent breast cancer and 18 (29%) had stage IV disease (Table 1). Median age at the time of the start of T-DM1 therapy was 64 years (range, 40-80 years). There were 35 (56%) patients with ER or progesterone receptor (PgR)-positive and HER2-positive tumors, and 28 (44%) patients with tumors that were ER-and PgR-negative and HER2-positive. Regarding the estimation of HER2 status, 56 (89%) patients were evaluated as 2+ by immunohistochemistry (IHC), and 7 (11%) patients were evaluated as 2+ by IHC and positive by in situ hybridization. Forty-three (67%) patients had visceral metastases. There were 28 (44%) patients with lung metastases, 21 (33%) patients with liver metastases, 25 (40%) patients with bone metastases and 14 (22%) patients with brain metastases.

Prior treatments before T-DM1 therapy

The previous treatments, in the adjuvant and metastatic setting, and the numbers of previous regimens for metastatic breast cancer prior to treatment with T-DM1 are listed in Table 2. As adjuvant or neoadjuvant therapy in 45 patients with recurrent breast cancer, 26 (41%) patients had received anthracyclines, 22 (35%) patients had received taxanes, and 19 (30%) patients had received trastuzumab. In the metastatic setting, all but two patients (97%) had undergone trastuzumab therapy, 41 (65%) patients had received pertuzumab and 21 (33%) patients had received lapatinib prior to T-DM1 therapy. Various chemotherapeutic drugs were combined with anti-HER2 agents prior to T-DM1, these included docetaxel, paclitaxel, vinorelbine, eribulin, gemcitabine, and capecitabine. Patients had received a median of three regimens prior to T-DM1 for metastatic breast cancer. Seventeen (27%) patients received T-DM1 as the second-line therapy, 8 (13%) patients as the third-line, 12 (19%) patients as the forth-line, and 26 (41%) patients as the fifth line or more. The median time since first-line treatment of metastatic breast cancer was 29 months (range, 6–217 months).

Response to T-DM1 therapy and survival

There were 3 (5%) patients with complete response (CR), 19 (30%) patients with partial response (PR), 9 (14%) patients with long stable disease (SD) (≥ 6 months), 9 (14%) patients with SD (< 6 months), and 21 (33%) patients with progressive disease (PD) with T-DM1 therapy, so that the objective response rate was 35%, and the clinical benefit rate was 49% (Table 3). The median TTF of patients who received T-DM1 therapy was 4.0 months (range, 0.7-26 months, Figure 1). In 41 patients pretreated with pertuzumab, the response rate was 29%, the clinical benefit rate was 46%, and median TTF was 5.0 months (Table 4). In 14 patients with brain metastases, median TTF was 6.0 months, although none achieved CR or PR for brain tumors (Table 5). There were 5 patients with SD and 5 patients with PD for brain metastases.

Table 3: Response to T-DM1.

Response	Number of patients (%)
Complete response	3 (5%)
Partial response	19 (30%)
Long stable disease (≥ 6 months)	9 (14%)
Stable disease (< 6 months)	9 (14%)
Progressive disease	21 (33%)
Not evaluable	2 (3%)
Response rate	35%
Clinical benefit rate	49%
Median time to treatment failure, months (range)	4.0 (0.7-26.0)

Table 4: Details in patients pre-treated with pertuzumab.

		Number of patients (%)
Total		41
Number of previous regimens for metastatic breast cancer		
	0	0
	1	11 (27%)
	2	5 (12%)
	3	6 (15%)
	≥ 4	19 (46%)
Response to T-DM1		
	Complete response	2 (5%)
	Partial response	10 (24%)
	Long stable disease (≥ 6 months)	7 (17%)
	Stable disease (< 6 months)	6 (15%)
	Progressive disease	14 (34%)
	Not evaluable	2 (5%)
Response rate		29%
Clinical benefit rate		46%
Median time to treatment failure, months (range)		5.0 (0.7-21.0)
Adverse events (Grade 3/4)		
	Thrombocytopenia	9 (22%)
	Increased ALT and/or AST	3 (7%)
	Rash	0
	Neutropenia	1 (2%)

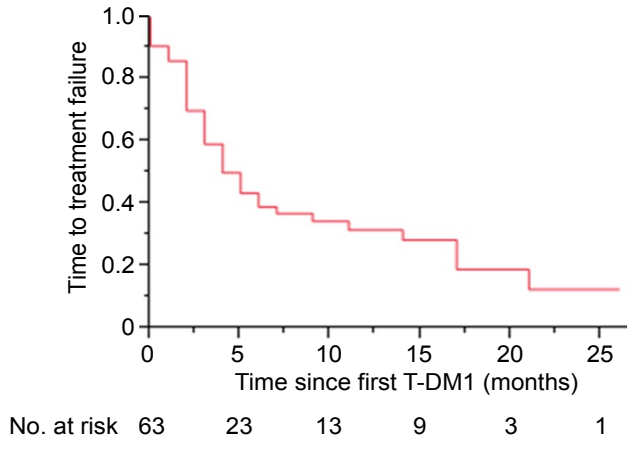

Figure 1: Time to treatment failure (TTF) Kaplan-Meier curve in 63 patients treated with T-DM1 therapy. The median TTF was 4.0 months (range, 0.7-26 months).

Table 5: Details in patients with brain metastases.

		Number of patients (%)
Total		14
Number of previous regimens for metastatic breast cancer		
	0	0
	1	4 (29%)
	2	2 (14%)
	3	4 (29%)
	≥ 4	4 (29%)
Loco-regional treatment for brain metastases		
	None	1 (7%)
	Surgery	0
	Radiation therapy	12 (86%)
	Surgery + radiation therapy	1 (7%)
Response to T-DM1 for brain metastases		
	Complete response	0
	Partial response	0
	Stable disease	5 (36%)
	Progressive disease	5 (36%)
	Not evaluable	4 (29%)
Median time to treatment failure, months (range)		6.0 (0.8-21.0)
Adverse events (Grade 3/4)		
	Thrombocytopenia	3 (21%)
	Increased ALT and/or AST	0
	Rash	0
	Neutropenia	0

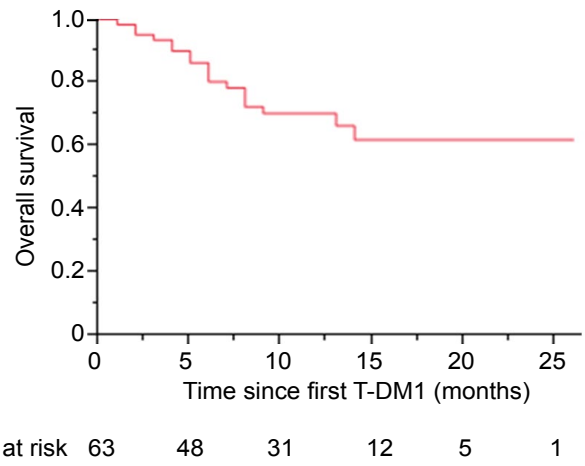

Figure 2: Overall survival Kaplan-Meier curve in 63 patients treated with T-DM1 therapy (range, 1.0-26 months).

At the time of the analysis, 21 (33%) patients were still receiving T-DM1. As anti-HER2 therapies and chemotherapies after T-DM1 treatment, 15 patients received trastuzumab with chemotherapeutic agents such as vinorelbine, eribulin and gemcitabine, 8 patients received both trastuzumab and pertuzumab with chemotherapeutic agents such as vinorelbine, paclitaxel and eribulin, and 9 patients received lapatinib plus capecitabine. The range of overall survival spanned 1.0-26 months (Figure 2).

We analyzed factors predicting TTF during T-DM1 treatment with Cox proportional hazards regression models. Univariate analysis did not show any factor that was correlated with TTF (Table 6).

Adverse events

The most commonly reported adverse events were thrombocytopenia (n = 48, 76%) and increased ALT and/or AST (n = 42, 67%) (Table 7). Grade 3 thrombocytopenia was seen in 11 (18%) patients, and grade 4 thrombocytopenia was observed in 2 (3%) patients. Of these patients with thrombocytopenia, hemorrhage (nasal, gingival, or subcutaneous bleeding) was seen in 9 (14%) patients (grade 1 in 8 patients and grade 2 in 1 patient). None of the patients required a platelet transfusion. Increased ALT and/or AST of grade 3 were seen in 3 (5%) patients. Other serious adverse events were observed in one patient with rash (grade 3) and in one patient with neutropenia (grade 3). Fatigue (grade 1 and 2) was seen in 24 (38%) patients. No case of febrile neutropenia was documented. There were 5 (8%) patients with dose delays, and 11 (17%) patients with dose reductions because of side effects. Treatment termination was necessary in 5 (8%) patients because of side effects. None of the patients experienced cardiac toxicity during or after T-DM1 treatment.

Table 6: Univariate analysis of factors predicting time to progression during T-DM1 treatment.

	HR	95%CI	p-value
Age	1.02	0.98-1.04	0.35
ER/PgR status	1.09	0.59-2.01	0.77
HER2 status	0.85	0.36-2.03	0.71
Stage IV/Recurrence	0.99	0.84-1.18	0.96
Disease-free interval	1.01	0.99-1.02	0.24
Metastatic sites			
Number of metastatic organs (single/multiple)	1.27	0.60-2.68	0.54
Visceral involvement	1.12	0.53-2.36	0.77
Presence of liver metastases	0.73	0.37-1.42	0.36
Presence of brain metastases	1.82	0.37-1.68	0.58
Number of previous regimens for metastatic breast cancer	1.03	0.91-1.17	0.6
Previous anti-HER2 therapies for metastatic breast cancer			
Pertuzumab	1.23	0.65-2.34	0.53
Lapatinib	1.13	0.58-2.15	0.72
Time since diagnosis of metastatic breast cancer	1	0.99-1.01	0.66

HR: hazard ratio; CI: confidence interval.

Table 7: Adverse events.

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3/4 (%)
Thrombocytopenia	24	11	11	2	21%
Increased ALT and/or AST	28	11	3	0	5%
Hemorrhage	8	1	0	0	0
Fatigue	17	7	0	0	0
Rash	3	0	1	0	2%
Peripheral sensory neuropathy	3	2	0	0	0
Neutropenia	0	0	1	0	2%
Nausea	6	4	0	0	0
Patients with dose delays because of side effects, N (%)				5 (8%)	
Patients with dose reductions because of side effects, N (%)				11 (17%)	
Ended therapy because of side effects, N (%)				5 (8%)	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; N: number of patients.

Discussion

Here we report our clinical experience with T-DM1 in patients with HER2-positive metastatic breast cancer pretreated with anti-HER2 therapies and chemotherapies. The response rate in our study was 35%, which was similar to that of previous phase II trials [1,2] including the Japanese phase II JO22997 study (38.4%) [5], although central radiology review was not done in this study. Most patients in our study were heavily treated prior to T-DM1 therapy. Moreover, 41 (65%) patients had received pertuzumab prior to T-DM1 treatment. The combination of trastuzumab, pertuzumab, and a taxane is the standard of care in first-line treatment for patients with advanced HER2-positive breast cancer and T-DM1 is recommended as the second-line treatment in this setting [6]. However, clinical trials available with T-DM1 didn't accrued patients treated with pertuzumab because the drug was not approved when the EMILIA and Th3RESA trials were designated.

Dzimitrowicz and colleagues recently reported a retrospective study on the efficacy of T-DM1 in routine contemporary clinical practice in patients that had received pertuzumab any time before T-DM1 treatment [8]. Among the 78 patients who received T-DM1 as a predominantly second-line or later treatment regimen, one third received therapy with T-DM1 for ≥ 6 months, although tumor

response rates were 17.9%. This study also reported that the median duration of therapy was 4.0 months, which is the same as the median TTF in our analysis. However, our median TTF is poorer than those of PFS reported in the EMILIA (9.6 months), TH3RESA (6.2 months), and JO22997 (5.6 months) trials [3-5]. Because all of the patients in Dzimitrowicz's study and 65% of patients in this study received pertuzumab prior to T-DM1 treatment, we infer that prior pertuzumab therapy might modulate the efficacy of shorter duration T-DM1 therapy. However, we could not find predictive factors including neither prior pertuzumab treatment nor other factors that were significantly predictive of the response to T-DM1 therapy.

The EMILIA study investigated whether tumor biomarkers, such as HER2, EGFR, and HER3 mRNA expression, PTEN protein expression and PIK3CA mutations could predict the efficacy of T-DM1 [9]. None of the factors were predictive, and T-DM1 appeared to be effective in both PIK3CA-mutated and wild-type tumors, although other standard HER2-directed therapies are less effective in tumors with PIK3CA-mutations. On the other hand, the ZEPHIR trial found that pretreatment HER2 imaging using HER2-positron emission tomography/computed tomography with ^{89}Zr-trastuzumab showed intra-/interpatient heterogeneity in HER2 mapping of metastatic disease, and that this may be a useful predictor of the T-DM1 response [10]. Although the equipment for HER2 imaging is limited, we may suggest that imaging biomarkers will be an increasingly important tool for predicting HER2-targeting therapies.

Our study showed that the most commonly reported grade 3 or 4 adverse event was thrombocytopenia. We observed this in 21% of patients experienced, which is consistent the JO22997 study (22%), but more frequent than observed in the EMILIA (12.9%), TH3RESA (4%) and previously reported trials (8-9%) [5]. Also similar to the JO22997 study in Japanese patients, we found that grade 3/4 thrombocytopenia was not associated with severe bleeding, and none of patients received a platelet transfusion. An integrated safety analysis of 884 patients treated with T-DM1 in six studies demonstrated that decreases in platelet count were more common in Asian than non-Asian patients irrespective of platelet count values at baseline [11]. According to the ethnic sensitivity assessment of T-DM1 in Japanese patients and the global population, pharmacokinetics was comparable across ethnic groups [12]. T-DM1 is used at a dose of 3.6 mg/kg every 21 days in Japan and other countries. A Japanese phase II trial also reported that the pharmacokinetic profile of T-DM1 3.6 mg/kg every 21 days in Japanese patients showed no relevant differences from the predictable and well-characterized profile consistently demonstrated in phase II studies in non-Japanese populations [5]. Modeling of T-DM1-associated thrombocytopenia suggests that this side effect is caused by partial depletion of the platelet pool [13] and is typically transient [14]. This may explain why grade 3/4 thrombocytopenia has not been associated with clinically serious symptoms in Japanese patients receiving T-DM1.

Fourteen (22%) patients had brain metastases in our study, and none of them responded to T-DM1 treatment. On the other hand, the presence of brain metastases did not affect TTF. A direct correlation between quantitative HER2 expression and the risk for advanced breast cancer patients to develop brain metastases has been reported [15]. Jacot and colleagues recently reported a retrospective study on the efficacy and safety of T-DM1 in patients with brain metastases [16]. Of 39 patients, clinical benefit was 59%, and median PFS was 6.1 months. Their study indicated that treatment was well tolerated and free of unexpected toxicities, treatment delay, or dose reduction. Recently, expansion hematoma in delayed cerebral radiation necrosis was observed in two individuals who were treated with T-DM1 [17]. A potential enhancement of radiation necrosis in the brain appears to be one of the most significant adverse events associated with T-DM1 in patients that have received stereotactic radiosurgery for brain metastases.

In conclusion, our study demonstrates that T-DM1 is an effective and well-tolerated treatment for patients with HER2-positive metastatic breast cancer that had progressed after previous anti-HER2 therapies including pertuzumab and trastuzumab therapies.T-DM1 could be used for patients who have experienced progression following prior pertuzumab treatment.

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