T-DM1 Activity in Metastatic Human Epidermal Growth Factor Receptor 2–Positive Breast Cancers That Received Prior Therapy With Trastuzumab and Pertuzumab

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ABSTRACT

Purpose

Ado-trastuzumab emtansine (T-DM1) is currently approved for treatment in patients with human epidermal growth factor receptor 2 (HER2)–positive, metastatic breast cancer (MBC) who previously received trastuzumab and a taxane. However, there are no data on the activity of T-DM1 in patients who received prior pertuzumab, which is now included as standard first-line therapy. The goal of this study was to assess the efficacy of T-DM1 in routine clinical practice in a contemporary patient population that received both prior trastuzumab and pertuzumab.

Patients and Methods

We identified all patients with HER2-positive MBC who received T-DM1 after trastuzumab and pertuzumab between March 1, 2013, and July 15, 2015, via electronic pharmacy records and departmental databases at three institutions: MD Anderson Cancer Center, Smilow Cancer Hospital at Yale, and The James Cancer Hospital at the Ohio State University. We reviewed medical records of each case to confirm treatment sequencing and outcome.

Results

Of patients, 82 were identified and 78 were available for outcome analysis; 32% received T-DM1 as first- and second-line therapy, and 48% received it as fourth-line treatment or later. Rate of prolonged duration on therapy, defined as duration on therapy $\geq$ 6 months, was 30.8% (95% CI, 20.6% to 41.1%), and tumor response rate was 17.9% (95% CI, 9.4% to 26.4%). Median duration on therapy was 4.0 months (95% CI, 2.7 to 5.1; range, 0 to 22.5 months). T-DM1 was discontinued for disease progression in 84% of patients and for toxicity in 10%.

Conclusion

Tumor response rates were lower than in prior reports of trastuzumab-resistant, HER2-positive MBC, but one third of patients received therapy with T-DM1 for $\geq$ 6 months, which suggests a clinically relevant benefit in patients who received prior pertuzumab.

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INTRODUCTION

Despite the success of trastuzumab (Herceptin; Genentech, South San Francisco, CA) in treatment of human epidermal growth factor receptor 2 (HER2)–positive breast cancer, almost all patients with metastatic breast cancer (MBC) will eventually progress on trastuzumab^{1,2} and some patients with early-stage, HER2-positive breast cancer continue to experience relapse after trastuzumab-containing adjuvant therapy.^{3,4} These clinical observations motivated the development of

several other HER2-directed therapies, including lapatinib, pertuzumab, and ado-trastuzumab emtansine (T-DM1).

T-DM1 is an antibody–drug conjugate composed of the cytotoxic agent DM1 attached to trastuzumab via a stable thioether linker.⁵ T-DM1 was approved by the US Food and Drug Administration on February 23, 2013 as second-line therapy for patients with HER2-positive MBC who previously received trastuzumab and a taxane. Approval was based on results of the phase III EMILIA trial that demonstrated increased progression-free

survival (PFS) and overall survival in the T-DM1 arm compared with capecitabine and lapatinib in patients who experienced progression on one prior line of trastuzumab-containing therapy for metastatic cancer.^{6,7} The nearly simultaneous clinical development of pertuzumab and its approval as first-line therapy for HER2-positive MBC in June 2012, and subsequently as neoadjuvant therapy in September 2013, resulted in the unusual circumstance that the patient population enrolled in the pivotal registration trial for T-DM1 no longer exists. The standard first-line therapy for HER2-positive MBC has changed from trastuzumab and a taxane—the prior treatment received by the EMILIA patient population—to trastuzumab and a taxane plus pertuzumab.^{8,9} Many patients with early-stage HER2-positive breast cancer now also receive pertuzumab and trastuzumab as part of neoadjuvant chemotherapy.^{10,11} Neither the EMILIA trial nor other T-DM1 trials included patients who had received pertuzumab.⁷ Currently, there is no published clinical trial or observational data on the activity of T-DM1 in patients previously exposed to pertuzumab.

The goal of this study was to assess the efficacy of T-DM1 in routine clinical practice in a contemporary patient population that included patients who received prior therapy with pertuzumab. In clinical trials, objective response rate and PFS are measured by using the RECIST criteria, which include strict definitions for tumor measurements and assignment of response categories.¹² In routine practice, the same tumor response terminology, that is, partial response, stable disease, progression, etc, is often used to describe the outcome of therapy but rarely reflects the same rigorous tumor evaluation called for by RECIST. Therefore, in this article, we use an alternative terminology to describe clinical benefit in routine practice to avoid confusion with RECIST terms used in clinical trials. In routine care, medical oncologists usually continue treatment with a given drug until disease progression or until intolerable adverse effects develop, and, therefore, duration on therapy is a practical combined measure of clinical benefit and tolerability. Disease progression is usually indicated by new or enlarging lesions on tumor imaging on the basis of radiologist assessment or by symptomatic deterioration. Tumor response usually signifies a radiologic report that states tumor response—with or without actual tumor measurements—and/or symptomatic improvement. To easily convey information about clinical benefit in the routine care setting and to alert readers that these metrics do not directly correspond to RECIST terms, we introduce a new terminology. We created four categories as efficacy measures that correspond to clinical practice: tumor response (TR) indicates physician-reported clinical or imaging response—we abbreviate this as TR to avoid confusion with RECIST objective response terms (objective response, partial response, complete response); prolonged duration on therapy (PDT) indicates T-DM1 therapy $\geq$ 6 months; minimal benefit (MB) indicates physician-reported stable disease as the initial response to T-DM1 but discontinuation of T-DM1 before 6 months; and progressive disease indicates symptomatic deterioration or progression on routine radiologic assessment.

PATIENTS AND METHODS

Patient Population

Electronic pharmacy records (at Ohio State University [OSU] and Yale University) and a prospectively maintained departmental database

(MD Anderson Cancer Center [MDACC]) were used to identify patients who received T-DM1 after previous therapy with pertuzumab for the diagnosis of metastatic HER2-positive breast cancer between March 1, 2013 (T-DM1 was approved by the US Food and Drug Administration in the United States on February 23, 2013), and July 15, 2015, at three institutions: Smilow Cancer Hospital Yale Cancer Center, MDACC, and James Cancer Hospital at OSU. Patients received HER2 targeted therapy as routine clinical care in these respective institutions. This study was approved by the institutional review boards of each participating institution, and waivers for obtaining informed consent were granted.

Table 1. Demographic and Disease Characteristics of Study Population (N = 82)

Characteristic	No. (%)
Age, years	
Median (range)	54 (29-97)
Treatment location	
Yale	21 (25.6)
OSU	23 (28.0)
MDACC	38 (46.3)
Hormone receptor status	
ER- and/or PR-positive	51 (62.2)
ER- and PR-negative	31 (37.8)
Neoadjuvant or adjuvant therapy	
Chemotherapy + trastuzumab + pertuzumab	2 (2.4)
Chemotherapy + trastuzumab	23 (28.0)
Chemotherapy alone	7 (8.5)
Trastuzumab + pertuzumab without chemotherapy	1 (1.2)
Trastuzumab without chemotherapy	1 (1.2)
Endocrine therapy	15 (18.3)
Unknown	1 (1.2)
Adjuvant trastuzumab for 1 year	
Yes, completed	22 (26.8)
Yes, did not complete	5 (6.1)
No	53 (64.6)
Unknown	2 (2.4)
Prior lines of therapy for metastatic disease before T-DM1	
0	2 (2.4)
1	24 (29.3)
2	17 (20.7)
3	19 (23.1)
4	13 (15.9)
$\geq$ 5	7 (8.5)
No. of distinct sites of metastases	
1	23 (28.0)
2	22 (26.8)
3	22 (26.8)
4	11 (13.4)
5	4 (4.9)
Site of metastasis at time of starting T-DM1	
Bone	53 (64.6)
Lung	38 (46.3)
Liver	33 (40.2)
Soft Tissue	49 (59.8)
Brain	23 (28.0)
Disease-free interval	
De novo stage IV disease	36 (43.9)
Metastatic recurrence $\leq$ 1 year after diagnosis	14 (17.1)
Metastatic recurrence $>$ 1 year after diagnosis	32 (39.0)

Abbreviations: ER, estrogen receptor; MDACC, MD Anderson Cancer Center; OSU, Ohio State University; PR, progesterone receptor; T-DM1, ado-trastuzumab emtansine.

Data Collection

The electronic medical record of each patient who received both T-DM1 and pertuzumab was reviewed manually by local study investigators, and each site completed an identical data acquisition form. A final combined database was created that merged data from all three sites for analysis. The following data items were collected: patient demographics, including date of birth and race; tumor characteristics, including date of diagnosis of primary breast cancer; estrogen receptor (ER) and progesterone receptor (PR) status of the primary tumor, and metastatic lesion if receptor status was reassessed; HER2 status, including immunohistochemistry result and fluorescent in situ hybridization result if both were available; date of metastatic recurrence; and sites of metastases at the time of starting T-DM1 therapy, including bone, visceral, brain, or soft tissue (ie skin, lymph node, or breast). Estrogen and HER2 receptor status were assigned according to 2010 and 2013 ASCO/College of American Pathologists guidelines, respectively, on the basis of local pathology results.^{13,14} Treatment history was also collected, including prior neoadjuvant or adjuvant chemotherapy regimens, adjuvant endocrine therapy, and number and type of chemotherapies for metastatic breast cancer. The first treatment administered for metastatic recurrence—or the overall first treatment in case of de novo stage IV disease—was counted as first-line therapy for metastatic cancer. The next new treatment at the time of progression during or after first-line therapy was called second-line therapy, and numbering of the lines of treatment continued in this manner. Dates of first and last courses of pertuzumab, and dates of first and last courses of T-DM1 were also recorded. Tumor response was determined by the treating physician in the context of routine care. Radiology reports and results of clinical assessments during T-DM1 therapy were reviewed as documented in the medical records to assign tumor response. Reasons for T-DM1 discontinuation were also extracted from medical records as well as the date of death, if applicable.

Statistical Analysis

Duration on T-DM1 therapy was measured from the date of a patient's first T-DM1 treatment to the date of the last T-DM1 treatment. TR is defined as physician-reported response on the basis of imaging and clinical assessment. PDT is defined as ≥ 6 months of T-DM1 therapy, with or without documented TR.

MB indicates physician-reported stable disease as the initial response to T-DM1 but discontinuation of T-DM1 before 6 months. Progressive

disease was defined as progression of cancer as best response at the time of first evaluation. Descriptive statistics are reported with point estimates and 95% CIs. These metrics were calculated for all patients and also separately for the following predefined subsets: ER-positive and/or PR-positive tumors, ER-negative and PR-negative tumors, T-DM1 as second-line therapy or earlier for metastatic disease, T-DM1 beyond second-line therapy for metastatic disease, de novo metastatic disease, metastatic recurrence < 1 year after initial diagnosis, metastatic recurrence > 1 year after initial diagnosis, and prior lapatinib. Kaplan-Meier method was used to estimate a survival curve from the time of first T-DM1 treatment.

RESULTS

Database searches identified a total of 82 patients across the three institutions who had received single-agent T-DM1 between March 1, 2013, and July 15, 2015, for metastatic HER2-positive

Table 3. Investigator Reported Rates of TR, PDT, and AB, Defined as TR and/or PDT

Characteristic	No. of Patients (%)	95% CI
All patients	78	
PDT	24 (30.8)	20.6 to 41.1
TR	14 (17.9)	9.4 to 26.4
AB	29 (37.2)	26.5 to 47.9
Hormone receptor status		
ER- and/or PR-positive	49	
PDT	16 (32.7)	19.6 to 45.8
TR	10 (20.4)	9.1 to 31.7
AB	21 (42.9)	29.0 to 56.8
ER- and PR-negative	29	
PDT	8 (27.6)	11.3 to 43.9
TR	4 (13.8)	1.3 to 26.4
AB	8 (27.6)	11.3 to 43.9
T-DM1 as second-line therapy or earlier	26	
PDT	9 (34.6)	16.3 to 52.9
TR	6 (23.1)	6.9 to 39.3
AB	11 (42.3)	23.3 to 61.3
T-DM1 as later than second-line therapy	52	
PDT	15 (28.8)	16.5 to 41.1
TR	8 (15.4)	5.6 to 25.2
AB	18 (34.6)	21.7 to 47.5
Prior lapatinib	18	
PDT	5 (27.8)	7.1 to 48.5
TR	2 (11.1)	0 to 25.6
AB	5 (27.8)	7.1 to 48.5
Recurrence-free interval		
De novo metastatic disease	33	
PDT	10 (30.3)	14.6 to 46.0
TR	7 (21.2)	7.3 to 35.2
AB	13 (39.4)	22.7 to 56.1
Metastatic recurrence	14	
< 1 year after diagnosis		
PDT	5 (35.7)	10.6 to 60.8
TR	3 (21.4)	0 to 42.9
AB	6 (42.9)	17.0 to 68.8
Metastatic recurrence	31	
> 1 year after diagnosis		
PDT	9 (29.0)	13.0 to 45.0
TR	4 (12.9)	1.1 to 24.7
AB	10 (32.3)	15.8 to 48.8

Abbreviations: AB, any benefit; ER, estrogen receptor; PDT, prolonged duration on therapy; PR, progesterone receptor; T-DM1, ado-trastuzumab emtansine; TR, tumor response.

Table 2. Type of Prior Therapies for Metastatic Disease Before T-DM1

Prior Drugs in the Metastatic Setting	No. of Patients (%)
Trastuzumab	79 (96.3)
Pertuzumab	79 (96.3)
Taxane	72 (87.8)
Hormonal therapy	34 (41.5)
Lapatinib	19 (23.2)
Capecitabine	13 (15.9)
Vinorelbine	10 (12.2)
Carboplatin	9 (11.0)
Gemcitabine	5 (6.1)
Doxorubicin	4 (4.9)
Eribulin	3 (3.7)
Bevacizumab	3 (3.7)
Cyclophosphamide	2 (2.4)
Her2 vaccine trial	2 (2.4)
Ixabepilone	2 (2.4)
IGF-1R/IR inhibitor	1 (1.2)
HDAC inhibitor	1 (1.2)

Abbreviations: HDAC, histone deacetylase; Her2, human epidermal growth factor receptor 2; IGF, insulin-like growth factor; T-DM1, ado-trastuzumab emtansine.

breast cancer and who also received pertuzumab any time before T-DM1 treatment began. [Table 1](#) gives patient characteristics. Of patients, 96% received both prior trastuzumab and pertuzumab, 88% received a taxane, and 23% also received lapatinib as treatment of metastatic cancer before receiving T-DM1 ([Table 2](#)). Of patients, 32% received T-DM1 as first- or second-line therapy, and 48% received it as fourth-line therapy or later.

Of patients, 78 were available for efficacy outcome analysis. TR rate was 17.9% (n = 14; 95% CI, 9.4% to 26.4%), and rate of PDT was 30.8% (n = 24; 95% CI, 20.6% to 41.1%), including six patients who received therapy for ≥ 1 year, and nine patients who also achieved a TR. Either TR or PDT was observed in 37.2% of patients (95% CI, 26.5% to 47.9%; [Table 3](#)). MB rate was 12.8% (n = 10; 95%), and 39 patients (50%) had progressive disease as their best response ([Fig 1](#)). Overall median duration

Fig 1. Duration of ado-trastuzumab emtansine (T-DM1) therapy (in months) and best response by investigator assessment. Each bar represents the duration of therapy for the corresponding patient, beginning at day zero (administration of first dose of T-DM1). Three patients received only one dose of T-DM1 (duration, 0). Patients with estrogen receptor (ER)- and/or progesterone receptor (PR)-positive disease are represented in blue; patients with ER- and PR-negative disease are represented in red. Best response for each patient is indicated in the left column. (*)Nine patients with PDT had a tumor response. MB, minimal benefit; PD, progressive disease; PDT, prolonged duration on therapy; TR, tumor response.

on therapy was 4.0 months (95% CI, 2.7 to 5.1; range, 0 to 22.5 months; Fig 1). Median duration on therapy for patients who received T-DM1 as either first- or second-line therapy (n = 26) was also 4.0 months (95% CI, 2.4 to 6.8). Of patients, 8 continued on T-DM1 at the time of data collection. Overall survival was estimated from the time of first dose of T-DM1 (Fig 2).

Progression of disease was the reason for discontinuation of T-DM1 in 84.3% of patients (59 of 70). One patient discontinued therapy after continued fatigue and falls that resulted in transition to hospice care. One patient refused further therapy as a result of disbelief in her diagnosis despite a partial response to T-DM1. Another patient elected to discontinue medical care despite a complete response to T-DM1. One patient discontinued T-DM1 after continued stable disease. Only seven patients (10%) discontinued T-DM1 as a result of toxicity or poor tolerance. Two patients discontinued T-DM1 because of thrombocytopenia. Each of the remaining five patients discontinued T-DM1 as a result of a different toxicity. These included arthralgia, fatigue, and anorexia; a serum sickness–like presentation, including fever and joint pain; neuropathic foot pain; reduced cardiac ejection fraction; and elevated hepatic aminotransferases.

DISCUSSION

This is the first report, to our knowledge, to demonstrate the efficacy of T-DM1 in a contemporary patient population that has received pertuzumab. Clinical trials of T-DM1 accrued patients with variable prior therapies but none who received prior pertuzumab. In our study, we examined T-DM1 activity in routine contemporary clinical practice as predominantly second-line or

later treatment. Rate of PDT was 30.8% (95% CI, 20.6% to 41.1%), TR rate was 17.9% (95% CI, 9.4% to 26.4%), and median duration on therapy was 4.0 months (95% CI, 2.7 to 5.1), with a range of 0 to 22.5 months. These results are less favorable than the objective tumor response rates and PFS reported in clinical trials of T-DM1 (Table 4). They are most comparable to results obtained in the TH3RESA and M4347g trials that enrolled heavily pretreated patients (Table 4).^{7,15-19}

Of importance, 31% of patients in our study remained on treatment for ≥ 6 months, which demonstrates a meaningful tumor control rate and overall benefit in patients who received prior pertuzumab and multiple other lines of therapy. T-DM1 was well tolerated; treatment was discontinued for disease progression in 84% of patients and for toxicity in only 10%, which is consistent with safety data from clinical trials. Our study also shows that in contemporary clinical practice, T-DM1 is often used after many previous lines of therapy for metastatic disease; 68% of patients received T-DM1 as third-line therapy or later. This practice is supported by results from several phase II and III trials. In current practice, many patients were diagnosed with metastatic disease before approval of either pertuzumab or T-DM1, which results in a population that has received multiple prior lines of therapy before it receives these newer HER2-targeted therapies.

Our study is a retrospective evaluation of patient outcomes treated in routine clinical practice, which limits comparison with trial results. In clinical trials, patient eligibility is strictly defined and accrual is often limited by the number of prior therapies, and, therefore, the study population is more homogeneous than patient cohorts included in routine clinical databases. In routine practice, radiologists provide their best overall estimate of disease status rather than report response by RECIST criteria, and some patients are assessed less frequently than others, which adds potential variability to duration on therapy and response metrics. In this study, we used duration on therapy as an approximation of PFS or time to treatment failure. Progression of disease, rather than toxicity, resulted in discontinuation of T-DM1 in 84% of cases in our study, which supports the use of duration on treatment as a reasonable surrogate for PFS or time to treatment failure. Although duration on therapy in the context of routine care is not a standardized metric, it reflects the clinical utility of a drug because oncologists usually continue treatment until disease progression or until intolerable adverse effects develop.

We also note that in our study population 44% of patients (36 of 82) presented with de novo stage IV metastatic disease, which was confirmed by review of their medical records and also independently observed in MDACC and combined Yale and OSU patient cohorts. Large, population-based data sets indicate that, overall, only 5% to 10% of breast cancers present as de novo stage IV disease.²⁰ In a prior retrospective analysis at MDACC that focused on patients with HER2-positive breast cancer who received first-line trastuzumab-based therapy for metastatic disease, it was observed that 31% of patients (160 of 513) presented with de novo stage IV HER2-positive breast cancer.²¹ Over-representation of stage IV disease in our study may reflect referral patterns to tertiary academic centers or may be a result of a genuine change in the HER2-positive metastatic patient population. Highly effective trastuzumab- and pertuzumab-containing adjuvant

Fig 2. Overall survival. Kaplan-Meier estimates of overall survival from time of first dose of ado-trastuzumab emtansine (T-DM1) for all patients who received at least one dose of T-DM1 (82 patients).

Table 4. Phase II and III Trials of T-DM1 to Date

Trial	Study Design	Prior Therapies for Metastatic Disease	Treatment Arm	T-DM1 Result
MARIANNE ¹⁵	Randomized phase III	No prior therapy for MBC	T-DM1 + pertuzumab (n = 363); T-DM1 (n = 367); trastuzumab + taxane (n = 365)	ORR: T-DM1, 59.7%; T-DM1 + pertuzumab, 64.2%; PFS: T-DM1, 14.1 months; T-DM1 + pertuzumab, 15.2 months
TDM4450g ¹⁶	Randomized phase II	No prior therapy for MBC	T-DM1 (n = 67); trastuzumab + docetaxel (n = 70)	ORR, 64.2%; PFS, 14.2 months
EMILIA ⁷	Randomized phase III	Trastuzumab and a taxane; no prior lapatinib or capecitabine; previous regimens for MBC: 0 or 1, 61%; > 1, 39%	T-DM1 (n = 495); lapatinib + capecitabine (n = 496)	ORR, 43.6%; complete response, 1.0%; partial response, 42.6%; PFS, 9.6 months
TH3RESA ¹⁷	Randomized phase III	≥ 2 previous HER2-targeted agents (trastuzumab and lapatinib); previous regimens for MBC: ≤ 3, 39%; 4-5, 33%; > 5, 28%	T-DM1 (n = 404); physician choice (n = 198)	ORR, 31%; PFS, 6.2 months
TDM4258g ¹⁸	Single-arm phase II	At least one prior HER2-targeted therapy and chemotherapy; median prior anticancer agents for MBC, 5.0	T-DM1 (n = 112)	ORR, 25.9%; complete response, 0%; partial response, 25.9%; PFS, 4.6 months
TDM4374g ¹⁹	Single-arm phase II	Trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine; median prior anticancer agents for MBC, 7.0	T-DM1 (n = 110)	ORR, 34.5%; complete response, 0%; partial response, 34.5%; CBR, 48.2%; PFS, 6.9 months

Abbreviations: CBR, clinical benefit rate; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; ORR, objective response rate; PFS, progression-free survival; T-DM1, ado-trastuzumab emtansine.

chemotherapies significantly reduced recurrence rates of stage I to III HER2-positive breast cancer, which could lead to a shift in the proportion of recurrent versus de novo metastatic cases. Registry data also suggest that de novo HER2-positive MBC approaches 50% of newly diagnosed cases, even in community practices.²² This unusual patient composition might have influenced our results and could limit extrapolation to different patient populations. In one previous observational cohort study of patients with HER2-positive MBC (N = 1,023), patients with de novo MBC had a 28% and 23% lower hazard of progression and death, respectively, compared with patients with recurrent MBC.²³ In addition, other retrospective studies have reported similar observations that disease recurrence after use of adjuvant trastuzumab is associated with worse clinical outcomes and shorter duration of trastuzumab use in the metastatic setting.^{21,24} However, in another retrospective analysis of 331 patients with HER-positive MBC, response rates and PFS to first-line trastuzumab-based therapy did not differ significantly between de novo and recurring stage IV disease.²⁵ In our study, we also did not observe a difference in PDT and TR rates in patients with de novo metastatic disease compared with metastatic recurrence > 1 year after initial diagnosis (Table 3). These results suggest that the high percentage of de novo metastatic cases in our study is unlikely to alter the generalizability of the data.

There is one ongoing prospective study that will examine the efficacy of T-DM1 specifically in patients who have received prior pertuzumab (ClinicalTrials.gov identifier: NCT01835236). This study is recruiting patients with previously untreated HER2-positive MBC and will randomly assign patients to either pertuzumab plus trastuzumab plus chemotherapy or pertuzumab plus trastuzumab,

both followed by T-DM1 in the case of progression. This study will provide prospective clinical trial data on the efficacy of T-DM1 in a pertuzumab-pretreated population. A company-sponsored nationwide registry study (SystHERs Registry, NCT01615068) is also underway to collect information on treatment patterns and treatment sequencing for HER2-positive MBC. Until results from these studies are reported, our results provide support for clinically meaningful activity of T-DM1 in patients with metastatic HER2-positive breast cancer who have experienced progression on prior pertuzumab- and trastuzumab-containing therapies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

T-DM1 Activity in Metastatic Human Epidermal Growth Factor Receptor 2–Positive Breast Cancers That Received Prior Therapy With Trastuzumab and Pertuzumab

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