ORIGINAL RESEARCH

Clinical efficacy and safety of T-DMI for patients with HER2-positive breast cancer

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http://dx.doi.org/10.2147/OTT.S100499

Purpose: The aim of this study was to evaluate the therapeutic efficacy and safety of trastuzumab emtansine (T-DM1) for the treatment of patients with human epidermal growth factor receptor 2-positive breast cancer.

Methods: We performed a systemic review and meta-analysis of the relevant published clinical studies. A computerized search was performed for controlled clinical trials of T-DM1 in targeted treatment. Overall survival, progression-free survival, objective response rate, symptom progression free, and adverse events (AEs) were evaluated.

Results: Eight eligible trials with a total of 2,016 patients with breast cancer were included in the present meta-analysis. The treatment of patients with breast cancer with T-DM1 was associated with significantly increased overall and progression-free survival when compared with controls (P < 0.0001). An analysis of the objective response rate and symptom progression free also demonstrated favorable results for T-DM1 treatment ($P \le 0.0001$). There was no significant difference between the T-DM1 and control groups with respect to nonhematologic or hematologic AEs (P=0.99 and P=0.30, respectively).

Conclusion: Overall, T-DM1 is efficacious in the treatment of patients with human epidermal growth factor receptor 2-positive breast cancer and low rates of AEs compared with controls. Keywords: breast cancer, meta-analysis, HER2, T-DM1, efficacy

Introduction

Breast cancer accounts for ~28% of all new cancers in women. It is a major health problem and the second leading cause of cancer death in the USA.^{1,2} Breast cancer is now known to be a heterogeneous disease, which is characterized by a variety of biological drivers and related clinical results.³ Human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor family of transmembrane receptors.⁴⁻⁶ The other three family members are HER1 (also known as epidermal growth factor receptor), HER3 (ErbB3), and HER4 (ErbB4). Protein overexpression and/or gene amplification of HER2 (also known as ErbB2, p185^{HER2}, and neu) is present in ~15%-25% of new patients with breast cancer.^{4,7,8} HER2 overexpression results in an aggressive form of breast cancer that is associated with poor clinical outcomes and greater therapeutic resistance compared with HER2-normal patients.^{9,10} The clinical outcomes of these patients with breast cancer have greatly improved with the development of HER2-targeted therapies, but therapeutic resistance is still common, and the management of toxicity remains a challenge.¹¹ Therefore, new treatments are needed for patients with breast cancer who demonstrate disease progression following HER2-targeted therapies.

HER2-targeted therapies include trastuzumab, the first humanized monoclonal antibody, and newer drugs such as lapatinib, ertumaxomab, and pertuzumab. Trastuzumab

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(Herceptin; Genentech, Inc., South San Francisco, CA, USA) combined with others is the standard treatment for HER2-positive patients with early or metastatic breast cancer.¹² The molecular mechanisms behind trastuzumab include mitogenactivated protein kinases and phosphoinositide 3 kinase (PI3K)/AKT signaling inhibition, antibody-dependent cellmediated cytotoxicity, induction of apoptosis, and prevention of HER2 ectodomain cleavage.^{13,14} DM1, an antimicrotubule agent, is derived from maitansine. Trastuzumab emtansine (T-DM1, Kadcyla), which has been developed by Genentech, Inc. and ImmunoGen, Inc. (Waltham, USA), combines trastuzumab and DM1, allowing preferential intracellular drug delivery to HER2-positive tumor cells.^{2,15,16}

T-DM1, an antibody–drug conjugate, was granted marketing approval by the US Food and Drug Administration in 2013. Because the toxicity associated with chemotherapy is a large source of distress for patients, the antibody–drug conjugate is considered to be a promising treatment.^{7,17} T-DM1 combines the antitumor effects of trastuzumab with a cytotoxic antimicrotubule agent (DM1) that is released within HER-positive tumor cells. In August 2015, we identified 48 registered Phase I, II, or III clinical trials on the treatment of breast cancer with T-DM1 on <u>ClinicalTrials.gov</u> website, using the keywords "T-DM1" and "breast cancer". Ten of those clinical trials have been completed.

In the current study, we performed a systematic review and meta-analysis of clinical trials to assess the efficacy and safety of T-DM1 in the treatment of patients with breast cancer. The aim was to evaluate the clinical response to T-DM1 by assessing overall survival (OS), progression-free survival (PFS), the objective response rate (ORR), and symptom progression free (SPF), in addition to adverse events (AEs).

Materials and methods Search strategy, study design, and eligibility criteria

PubMed, ScienceDirect, the Cochrane Central Register of Controlled Trials, the China Science and Technology Journal Database, the Wanfang Database, and China Journal Net were searched for relevant studies published from 1980 until August 5, 2015. The search strategy included the keywords ("trastuzumab emtansine" or "T-DM1" or "trastuzumab-DM1") and "HER2" and ("breast cancer" or "metastatic breast cancer") and clinical trial, without language or time limitations. We also searched the <u>ClinicalTrials.gov</u> website for information on ongoing trials, using the keywords ("trastuzumab emtansine" or "T-DM1" or "trastuzumab-DM1") and "breast cancer". Publication citations displayed at the bottom of the "Full Text View" tab of a study record under the "More Information" heading. In addition, relevant review papers, postgraduate articles, and previously published trials were examined to identify further relevant trials. We carefully searched the latest reports of the European Cancer Conference and the American Society of Clinical Oncology Annual Meeting and the Word Conference on Breast Cancer. Studies were eligible for inclusion if they 1) were English or Chinese studies on T-DM1 treatment of patients with breast cancer; 2) included an appropriate control arm; and 3) enrolled ten or more patients. Reviews and Phase I studies were excluded. In addition, studies on cell lines and animals, case reports, studies investigating multiple types of cancer, and those lacking patients' details were excluded.

Data selection criteria and quality assessment

Data extraction and study selection were independently conducted by two reviewers (Qianqian Ma and Hongqiang Wang) using a standardized approach. Any differences were adjudicated by a third reviewer (Bo Ma), based on the original publication. Study features extracted included the first author's name, country and year of publication, clinical trial phase, tumor characteristics, number of patients, sample size per arm, mean patient age, previous treatments, T-DM1 dose and route of administration, and number of estrogen receptor-, and/or progesterone receptor-positive patients. Any data that could not be directly obtained from the articles were calculated from the graphed data using Adobe Photoshop and Illustrator.

Definition of outcome measures

OS was defined as the time from study treatment initiation to death from any cause. PFS was defined as the interval from study treatment initiation to the first occurrence of progressive disease. ORR was defined as a complete or partial response on two consecutive tumor assessments not <4 weeks apart. SPF was defined as the time from study treatment initiation to symptom progression. The primary endpoints were OS and PFS. Secondary outcomes were ORR, SPF, and safety. AEs and toxicities were graded according to the National Cancer Institute Common Toxicity Criteria.

Statistical analysis

Data on OS, PFS, ORR, SPF, and AEs were extracted from the identified trials. In this analysis, we compared the T-DM1 treatment groups form the trials with their respective control

groups. The meta-analysis was performed using Review Manager Version 5.0 (Nordic Cochrane Centre) and Stata Version 12.0 (StataCorp LP, College Station, TX, USA). The effects of T-DM1 treatment were reflected by odds ratios (ORs). Fixed- and random-effects models were used to estimate the effects of T-DM1 treatment. Heterogeneity among the trials was assessed to determine which model should be used. We used the χ^2 -based Q-test to examine heterogeneity among the studies, and the significance level was fixed at P < 0.10. The quantity I^2 was also calculated to evaluate heterogeneity, and $I^2 > 50\%$ was considered to indicate a high level of heterogeneity. A random-effects model was used when statistical heterogeneity was confirmed; otherwise, a fixed-effects model was employed. $P \le 0.05$ was considered to be statistically significant, and all reported P-values resulted from two-sided version tests of the respective tests.¹⁸ To assess the possibility of publication bias, Egger's test and Begg's test were used.

Results

Trial selection

The data search yielded 119 references, 75 of whom were excluded for various reasons (Figure 1). A further 36 studies were excluded because they were published in other languages, did not provide detailed enough clinical data, or did not have an appropriate control arm. Finally, eight articles reporting clinical trials of T-DM1-based therapy for breast cancer were selected for this meta-analysis (Figure 1).^{19–26}

Baseline patient characteristics

The baseline characteristics of the patients in the eight selected publications that described six clinical trials are listed in Table 1. The trials involved a total of 2,016 patients with locally advanced or metastatic breast cancer. All the eight papers were fully published and described four Phase II trials^{19,21,22,24,25} and two Phase III trials.^{20,23,26} The patients enrolled were between 24 years and 84 years of age, with a median age of >52 years. Patients with breast cancer had received previous treatments, including trastuzumab, anthracyclines, taxanes, capecitabine, carboplatin, lapatinib, endocrine therapy, and radiotherapy. In all the trials, patients assigned to T-DM1 were given a dose of 3.6 mg/kg intravenously every 3 weeks, while patients assigned to the control arms received trastuzumab, docetaxel, lapatinib, capecitabine, or hormonal therapy. A total of 1,065 patients (53%) were estrogen receptor and/or progesterone receptor positive.

Overall survival

Two-month, 4-month, and 6-month OS

Information on the 2-month, 4-month, and 6-month OS rates was available from two trials.^{20,26} These two trials contained a total of 1,593 patients, of whom 899 patients received T-DM1, and 694 controls did not receive T-DM1

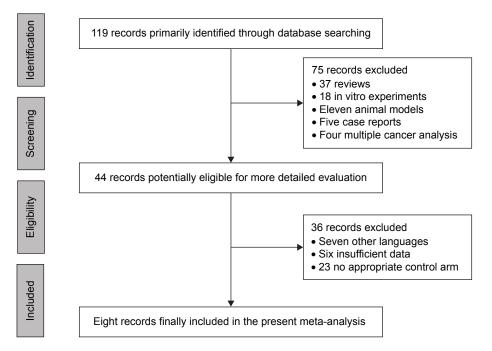


Figure I Flow diagram of the study identification, screening, and inclusion process.

References	Country	Clinical trial phase	Trial identifier	Tumor characteristic	Number of patients (control)	Age, years (median)	ER and/or PR positive (control)	Previous treatment	Control arm	T-DMI arm	T-DMI doses and the route of administration
Krop et al ²⁶	USA	=	NCT01419197	≥⊥	404 (198)	53 (54)	103 (208)	Trastuzumab, lapatinib	CT, HT, trastuzumab,	T-DMI	3.6 mg/kg per 21 days; IV
Perez et al ²⁴ and Hurvitz et al ²²	USA	=	NCT00679341	≥ ⊣	67 (70)	55 (52)	33 (38)	Trastuzumab, anthracycline,	Trastuzumab + docetaxel	T-DMI	3.6 mg/kg per 21 days; IV
Verma et al ²⁰ and Welslau et al ²³	Germany	≡	NCT00829166	≥ H	495 (496)	53 (53)	282 (263)	taxane, Trastuzumab, lapatinib,	Lapatinib + capecitabine	T-DMI	3.6 mg/kg per 21 days; IV
Miller et al ²⁵	NSA	=	NCT00875979		64	54	30	antmacycline, E I Trastuzumab, lapatinib, capecitabine, taxane,	N	T-DMI	3.6 mg/kg per 21 days; IV
Krop et al ²¹	USA	=	NCT00679211	Ē	011	52.5	55	anthracycline, Trastuzumab, lapatinib, capecitabine, taxane, anthracycline, RT,	ž	T-DMI	3.6 mg/kg per 21 days; IV
Burris et al ¹⁹	USA	=	NCT00509769	N ⊢	112	54.5	23	HT Trastuzumab, lapatinib, capecitabine, anthracycline, taxane, carboplatin	ž	T-DMI	3.6 mg/kg per 21 days; IV

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or were HER2 negative. The 2-month OS rate was 96% (866/899) for patients receiving T-DM1 compared with 92% (640/694) for controls. The meta-analysis showed a significantly higher 2-month OS rate for patients receiving T-DM1 compared with the control group (OR, 2.73; 95% confidence interval [CI], 1.73-4.31; P<0.0001). Cochran's Q-test yielded a P-value of 0.84, and the corresponding I^2 was 0%, indicating that the degree of variability between the two trials was consistent with what would be expected by chance alone (Figure 2A). The 4-month OS rate for the 899 patients in the T-DM1 group was 88% compared with 83% for controls. Pooled analysis showed that T-DM1 significantly increased the 4-month OS rate compared with the control group (OR, 2.11; 95% CI, 1.55-2.87; P < 0.0001). Cochran's Q-test yielded a P-value of 0.95, and the corresponding I^2 was 0% (Figure 2A). A significant difference was also demonstrated in the 6-month OS rate (OR, 1.60; 95% CI, 1.23-2.10; P=0.0006). Cochran's Q-test yielded a P-value of 0.76, and the corresponding I^2 was 0% (Figure 2A).

Eight-month, 10-month, and 12-month OS

Information on the 8-month, 10-month, and 12-month OS rates was available from two trials,^{20,26} including a total of 1,593 patients (899 of whom received T-DM1; Figure 2B). T-DM1 treatment was associated with 8-month, 10-month, and 12-month OS rates of 63%, 54%, and 42% (566/899, 483/899, and 379/899 patients), respectively. Both the trials showed a longer OS for patients who received T-DM1 in comparison with controls or HER2-negative patients at 8 months, 10 months, and 12 months. The estimated pooled OR showed significantly improved 8-month and 12-month OS rates for patients with breast cancer receiving T-DM1 (OR, 1.56; 95% CI, 1.15–2.12; P=0.005 and OR, 1.61; 95% CI, 1.25–2.07; *P*=0.0002, respectively), but the 10-month OS rate was not significantly improved (OR, 1.46; 95% CI, 0.84-2.54; P=0.17). The overall Cochran's O-test had a *P*-value of 0.39, and the corresponding I^2 was 5%.

Fourteen-month and 16-month OS

Information on the 14-month and 16-month OS rates was available from two trials,^{20,26} which contained a total of 1,593 patients (899 of whom received T-DM1; Figure 2C). T-DM1 was associated with 14-month and 16-month OS rates of 33% and 27% (300/899 and 242/899 patients), respectively. Both the trials showed a longer OS for patients receiving T-DM1 in comparison with controls or HER2-negative patients at 14 months. The estimated

pooled OR showed a highly improved 14-month and 16-month OS rate for patients who received T-DM1 (OR, 1.53; 95% CI, 1.20–1.96; P=0.0007 and OR, 1.37; 95% CI, 1.07–1.76; P=0.01, respectively). The overall Cochran's Q-test yielded a P-value of 0.75, and the corresponding I^2 was 0%.

Progression-free survival

Two-month, 4-month, and 6-month PFS

Information on the 2-month, 4-month, and 6-month PFS rates was available from six trials.^{19-22,25,26} These six trials included a total of 1,984 patients, 1,141 of whom received T-DM1 and 843 controls who did not receive T-DM1 treatment or who were HER2 negative. The 2-month PFS rate was 83% (952/1,141) for patients receiving T-DM1 and 76% (641/843) for controls. The meta-analysis showed a significantly higher 2-month PFS rate for patients receiving T-DM1 compared with controls (OR, 1.93; 95% CI, 1.07-3.45; P=0.03; Figure 3A). Cochran's Q-test yielded a P-value of 0.001, and the corresponding l^2 was 75%. The 4-month PFS rate for the 1,141 patients in the T-DM1 group was 65% compared with 56% for 843 controls. The pooled analysis showed that T-DM1 treatment did not significantly increase the 4-month PFS rate compared with controls (OR, 1.89; 95% CI, 0.97-3.68; P=0.06; Figure 3A). Cochran's Q-test yielded P < 0.00001, and the corresponding I^2 was 85%. The 6-month PFS rate for the 1,141 patients in the T-DM1 group was 42% compared with 33% for 843 controls. A significant difference was also demonstrated in the 6-month PFS rate (OR, 1.90; 95% CI, 1.13-3.19; P=0.02). Cochran's Q-test yielded a *P*-value of 0.01, and the corresponding l^2 was 67% (Figure 3A).

Eight-month, 10-month, and 12-month PFS

Information on the 8-month, 10-month, and 12-month PFS rates was available from six trials,^{19–22,25,26} which included a total of 1,984 patients (1,141 of whom received T-DM1; Figure 3B). T-DM1 treatment was associated with 8-month, 10-month, and 12-month PFS rates of 31%, 21%, and 14% (355/1,141, 240/1,141, and 165/1,141 patients), respectively, compared with only 24%, 14%, and 9% (199/843, 116/843, and 75/843 patients), respectively, in the control group. The results showed a longer PFS for patients who received T-DM1 in comparison with controls or HER2-negative patients at 8 months, 10 months, and 12 months. The estimated pooled OR showed a significantly improved 8-month,10-month, and 12-month PFS rates for patients with breast cancer receiving T-DM1 (OR, 2.00; 95% CI, 1.69-2.37; P < 0.00001).

		T-DM1 events	Total	Control events	Total	Weight (%)	Odds ratio M–H, fixed, 95% Cl	Odds ratio M–H, fixed, 95% Cl
Kro Vei	rma et al ²⁰		404 495	169 471	198 496	7.9 5.8	2.84 (1.60, 5.06) 2.57 (1.22, 5.42)	
Tot		, 866	899	640	694	13.7	2.73 (1.73, 4.31)	•
	terogeneity: st for overall		· ·	,,	0%			
os	6 4 months							
Vei		316 474 CI)	404 495 899	125 453	198 496 694	22.3 11.7 34.0	2.10 (1.44, 3.05) 2.14 (1.25, 3.67) 2.11 (1.55, 2.87)	<u>+</u> ★
Tot He	•	, 790 χ²=0.00,	df=1 (P	,,				
os	6 months							
Vei	op et al ²⁶ rma et al ²⁰ Ibtotal (95%)		404 495 899	80 435	198 496 694	31.9 20.4 52.3	1.55 (1.10, 2.19) 1.69 (1.10, 2.58) 1.60 (1.23, 2.10)	<u>+</u>
Tot He	•	, 664 χ²=0.09,	df=1 (P	, .		02.0	1.00 (1.20, 2.10)	•
	tal (95% CI) tal events	2.320	2,697	1.733	2,082	100	1.93 (1.61, 2.32)	•
He Tes	terogeneity: st for overall st for subgrou	$\chi^2 = 4.59$, effect: Z=	6.99 (P	=0.47); <i>I</i> ² = <0.00001)				0.01 0.1 1 10 10 T-DM1 Control

Study or subgroup	T-DM1 events	Total	Control events	Total	Weight (%)	Odds ratio M–H, random, 95% Cl	Odds ratio M–H, random, 95%	CI
OS 8 month	\$							
Krop et al ²⁶	127	404	51	198	15.4	1.32 (0.90, 1.94)	-	
Verma et al ²⁰		495	403	496	17.4	1.81 (1.26, 2.59)		
Subtotal (95	% CI)	899		694	32.8	1.56 (1.15, 2.12)	•	
Total events	566		454					
Heterogeneit	y: τ²=0.01;	$\chi^2 = 1.38$	8 df=1 (P=0).24); /²:	=28%			
Test for overa	all effect: Z	=2.82 (<i>I</i>	P=0.005)	,				
OS 10 mont	าร							
Krop et al ²⁶	65	404	30	198	10.3	1.07 (0.67, 1.72)	+	
Verma et al ²⁰	418	495	368	496	22.1	1.89 (1.38, 2.59)	-	
Subtotal (95	% CI)	899		694	32.4	1.46 (0.84, 2.54)	•	
Total events	483		398					
Heterogeneit	y: τ²=0.12;	χ ² =3.81	, <i>df</i> =1 (<i>P</i> =	0.05); <i>I</i> ²	=74%			
Test for overa	all effect: Z	=1.36 (<i>I</i>	P=0.17)					
OS 12 mont	ıs							
Krop et al ²⁶	30	404	9	198	4.0	1.68 (0.78, 3.62)	+	
Verma et al ²⁰	349	495	297	496	30.8	1.60 (1.23, 2.09)	-	
Subtotal (95	% CI)	899		694	34.8	1.61 (1.25, 2.07)	•	
Total events	379		306					
Heterogeneit	y: τ ² =0.00;	χ ² =0.01	, df=1 (P=	0.90); <i>I</i> ²	=0%			
Test for overa	all effect: Z	=3.74 (<i>I</i>	P=0.0002)					
Total (95% C	1)	2,697		2,082	100	1.58 (1.36, 1.85)	•	
Total events	1,428		1,158					
Heterogeneit	y: τ ² =0.00;	$\chi^2 = 5.24$, df=5 (P=	0.39); <i>I</i> 2	=5%			
Test for overa	all effect: Z	=5.88 (<i>I</i>	><0.00001)			0.01 0.1 1 10	
				-			T-DM1 Cont	rol

Figure 2 (Continued)

subgroup	•		Control events	Total	Weight (%)	Odds ratio M–H, fixed, 95% C		dds ratio –H, fixed, 95% Cl	
OS 14 month	s								
	7	404	3	198	1.9	1.15 (0.29, 4.48)			
•	293	495	240	496	47.5	1.55 (1.20, 1.99)		-	
Subtotal (95%	% CI)	899		694	49.4	1.53 (1.20, 1.96)			
		•	, ·						
OS 16 month	s								
Krop et al ²⁶	0	404	0	198		Not estimable			
Verma et al ²⁰	242	495	204	496	50.6	1.37 (1.07, 1.76)			
Subtotal (95%	6 CI)	899		694	50.6	1.37 (1.07, 1.76)		•	
Heterogeneity	r: not app		204 <i>P</i> =0.01)						
			0.01)						
Total (95% C)	1,798		1,388	100	1.45 (1.22, 1.73)		♦	
Heterogeneity	$\chi^2 = 0.57$ Il effect: Z	2=4.13 (P<0.0001)			0.01 0. T-D		100
	Krop et al ²⁶ Verma et al ²⁰ Subtotal (95% Total events Heterogeneity Test for overa OS 16 month Krop et al ²⁶ Verma et al ²⁰ Subtotal (95% Total events Heterogeneity Test for overa Total (95% CI Total events Heterogeneity	Verma et al ²⁰ 293 Subtotal (95% CI) Total events 300 Heterogeneity: $\chi^2=0.18$ Test for overall effect: 2 OS 16 months Krop et al ²⁶ 0 Verma et al ²⁰ 242 Subtotal (95% CI) Total events 242 Heterogeneity: not appl Test for overall effect: 2 Total (95% CI) Total events 542 Heterogeneity: $\chi^2=0.57$	Krop et al ²⁶ 7 404 Verma et al ²⁰ 293 495 Subtotal (95% CI) 899 Total events 300 Heterogeneity: χ^2 =0.18, df=1 (Test for overall effect: Z=3.38 (OS 16 months Krop et al ²⁶ 0 Verma et al ²⁰ 242 Subtotal (95% CI) 899 Total events 242 Heterogeneity: not applicable Test for overall effect: Z=2.45 (Total (95% CI) 1,798 Total events 542 Heterogeneity: χ^2 =0.57, df=2 (Krop et al ²⁶ 7 404 3 Verma et al ²⁰ 293 495 240 Subtotal (95% CI) 899 Total events 300 243 Heterogeneity: χ^2 =0.18, df =1 (P =0.67); I Test for overall effect: Z =3.38 (P =0.0007) OS 16 months Krop et al ²⁶ 0 404 0 Verma et al ²⁰ 242 495 204 Subtotal (95% CI) 899 104 0 Verma et al ²⁰ 242 495 204 Subtotal (95% CI) 899 104 104 Total events 242 204 204 Heterogeneity: not applicable 105 105 Test for overall effect: Z =2.45 (P =0.01) 105 Total (95% CI) 1,798 Total events 542 447 Heterogeneity: χ^2 =0.57, df =2 (P =0.75); I	Krop et al2674043198Verma et al20293495240496Subtotal (95% CI)899694Total events300243Heterogeneity: χ^2 =0.18, df =1 (P =0.67); l^2 =0%Test for overall effect: Z =3.38 (P =0.0007)OS 16 monthsKrop et al2604040Verma et al20242495204Subtotal (95% CI)899694Total events242204Heterogeneity: not applicableTest for overall effect: Z =2.45 (P =0.01)Total (95% CI)1,7981,388	Krop et al26740431981.9Verma et al2029349524049647.5Subtotal (95% CI)89969449.4Total events300243Heterogeneity: χ^2 =0.18, df =1 (P =0.67); l^2 =0%Test for overall effect: Z =3.38 (P =0.0007)OS 16 monthsKrop et al2604040Yerma et al2024249520449650.6Subtotal (95% CI)89969450.6Total events242204Heterogeneity: not applicableTest for overall effect: Z =2.45 (P =0.01)Total (95% CI)1,7981,388100Total events542447Heterogeneity: χ^2 =0.57, df =2 (P =0.75); l^2 =0%	Krop et al26740431981.91.15 (0.29, 4.48)Verma et al2029349524049647.51.55 (1.20, 1.99)Subtotal (95% Cl)89969449.41.53 (1.20, 1.99)Total events300243Heterogeneity: χ^2 =0.18, df=1 (P=0.67); I²=0%7Test for overall effect: Z=3.38 (P=0.0007)Not estimableOS 16 monthsNot estimableKrop et al2604040Verma et al20242495204Verma et al20242495204Verma et al20242495204Verma et al20242204Heterogeneity: not applicable1.37 (1.07, 1.76)Total events242204Heterogeneity: not applicable1.3881001.45 (1.22, 1.73)Total events542447Heterogeneity: χ^2 =0.57, df=2 (P=0.75); I²=0%1.45 (1.22, 1.73)	Krop et al26740431981.91.15 (0.29, 4.48)Verma et al2029349524049647.51.55 (1.20, 1.99)Subtotal (95% CI)89969449.41.53 (1.20, 1.96)Total events300243Heterogeneity: χ^2 =0.18, df=1 (P=0.67); l²=0%Test for overall effect: Z=3.38 (P=0.0007)OS 16 monthsKrop et al2604040198Not estimableVerma et al2024249520449650.61.37 (1.07, 1.76)Subtotal (95% CI)89969450.61.37 (1.07, 1.76)Total events242204447Heterogeneity: χ^2 =0.57, df=2 (P=0.75); l²=0% Test for overall effect: Z=4.13 (P<0.0001)0.010.01	Krop et al ²⁸ 7 404 3 198 1.9 1.15 (0.29, 4.48) Verma et al ²⁰ 293 495 240 496 47.5 1.55 (1.20, 1.99) Subtotal (95% CI) 899 694 49.4 1.53 (1.20, 1.96) Total events 300 243 Heterogeneity: $\chi^2=0.18$, $df=1$ ($P=0.67$); $I^2=0\%$ Test for overall effect: $Z=3.38$ ($P=0.0007$) OS 16 months Krop et al ²⁸ 0 404 0 198 Verma et al ²⁰ 242 495 204 496 50.6 1.37 (1.07, 1.76) Subtotal (95% CI) 899 694 50.6 1.37 (1.07, 1.76) • Total events 242 204 204 1.45 (1.22, 1.73) • Total events 242 204 204 1.45 (1.22, 1.73) • Total events 542 447 447 447 447 447 447 447 0.01 0.1 1 10

Figure 2 Forest plots of OS rates between patients undergoing T-DMI therapy and controls at (A) 2 months, 4 months, and 6 months, (B) 8 months, 10 months, and 12 months, and (C) 14 months and 16 months.

Notes: Fixed- and random-effects models (M–H method) were used. Each trial is represented by a square, the center of which gives the odds ratio for that trial. The size of the square is proportional to the information in that trial. The ends of the horizontal bars denote 95% Cls. Black diamonds give the overall odds ratios for the combined results of all trials. Abbreviations: Cls, confidence intervals; *df*, degrees of freedom; M–H, Mantel–Haenszel; OS, overall survival; T-DM1, trastuzumab emtansine.

The overall Cochran's *Q*-test had a *P*-value of 0.37, and the corresponding I^2 was 7%.

Fourteen-month, 16-month, and 18-month PFS

Information on the 14-month PFS rate was available from six trials,^{19–22,25,26} which included a total of 1,984 patients (1,141 of whom received T-DM1; Figure 3C). T-DM1 treatment was associated with a 14-month PFS rate of 9% (107/1,141 patients) compared with 6% (47/843 patients) in the control group. The estimated pooled OR showed a significantly improved 14-month PFS rate for patients who received T-DM1 (OR, 2.52; 95% CI, 1.73-3.65; P<0.0001). Cochran's Q-test yielded a P-value of 0.60, and the corresponding P was 0%. Information on the 16-month and 18-month PFS rates was available from four trials,^{20-22,25} which included a total of 1,287 patients (663 of whom received T-DM1). T-DM1 treatment was associated with 16-month and 18-month PFS rates of 11% and 8% (70/663 and 50/663 patients, respectively, compared with 5% and 3% (33/624 and 20/624 patients), respectively, in the control group. The results showed a higher PFS rate for patients with breast cancer receiving T-DM1 in comparison with controls at 16 months and 18 months. The estimated pooled OR showed a highly improved 16-month and 18-month PFS rates for patients who received T-DM1 treatment (OR, 2.20; 95% CI, 1.42-3.41; P=0.0004 and

OR, 2.59; 95% CI, 1.52–4.41; P=0.0005, respectively). The overall Cochran's Q-test yielded a P-value of 0.66, and the corresponding P was 0%.

Objective response rate

Information on the ORR was available from five trials,^{19–21,24,25} which included a total of 1,155 patients (627 of whom received T-DM1; Figure 4). The ORR was 44% (278/627) for patients receiving T-DM1 compared with 33% (175/528) in the control group. Pooled analysis indicated that T-DM1 treatment was associated with a favorable result with respect to ORR (OR, 1.82; 95% CI, 1.41–2.34; P<0.00001). Cochran's *Q*-test had a *P*-value of 0.24, the corresponding *I*² was 28% (<50%), and a fixed-effects model was used (Figure 4).

Symptom progression free

Two-month, 4-month, and 6-month SPF

Information on the 2-month, 4-month, and 6-month SPF rates was available from two trials,^{20,22} which included a total of 1,027 patients (515 of whom received T-DM1; Figure 5A). T-DM1 treatment was associated with 2-month, 4-month, and 6-month SPF rates of 77%, 57%, and 37% (395/515, 296/515, and 193/515 patients), respectively, compared with only 67%, 45%, and 37% (341/512, 231/512, and

Odds ratio M-H, random, 95% Cl	┝ ┝ ┝	┝ ┝ ┝	<u></u>	0.01 0.1 1 10 100 T-DM1 Control
Odds ratio M–H, random, 95% Cl	3.05 (1.11, 8.40) 0.52 (0.14, 1.86) 4.95 (1.55, 15.79) 3.10 (2.11, 4.55) 1.29 (0.35, 4.72) 1.26 (0.90, 1.75) 1.33 (1.07, 3.45)	5.28 (1.62, 17.21) 0.35 (0.14, 0.93) 6.00 (1.57, 22.96) 3.24 (2.26, 4.65) 1.31 (0.44, 3.91) 1.33 (1.02, 1.73) 1.89 (0.97, 3.68)	14.42 (1.84, 113.22) 0.70 (0.33, 1.49) 11.45 (1.44, 91.32) 2.39 (1.51, 3.76) 1.53 (0.54, 4.36) 1.66 (1.28, 2.14) 1.90 (1.13, 3.19)	1.90 (1.41, 2.56)
Weight (%)	4.7 3.6 3.5 3.5 3.5 3.5	ر بر بر بر بر بر بر بر بر بر بر بر بر بر	6 6 7 7 7 2 2 7 7 7 7 7 7 7 7 7 7 7 7 7	100 75%
Total	21 70 198 843 843	 I); I²=75% 21 21 70 15 198 43 436 843 301); I²=8 	21 70 15 198 43 496 843	2,529 0001); <i>I</i> ² =
Control events	66 66 7 7 7 20 404	641 6 (<i>P</i> =0.001 63 63 62 62 62 310 468 3(<i>P</i> <0.000	1 53 1 1 176 176 277 (<i>P</i> =0.01)	1,386 7 (<i>P</i> <0.00 1)
Total	74 67 80 404 1 ,141	9.97, df=5 (P=0.03) 74 67 80 404 21 495 1,141 2.94, df=5	(P=0.06) 74 67 80 404 21 495 1,141 5.07, <i>df</i> =5 (P=0.02)	3,423 3.02, <i>df</i> =1 (<i>P</i> <0.000
T-DM1 events	57 60 65 334 17 419	952 0.33; $\chi^2=15$ ct: $Z=2.20$ 51 41 51 48 241 14 341 341 341 0.50; $\chi^2=35$	ct: Z=1.87 31 36 36 36 114 11 236 474 236 236 236 ct: Z=2.41	2,162 0.23; $\chi^2=68$ ct: Z=4.20
Study or subgroup	PFS 2 months Burris et $a1^{19}$ Hurvitz et $a1^{22}$ Krop et $a1^{26}$ Krop et $a1^{26}$ Willer et $a1^{25}$ Verma et $a1^{20}$ Subtotal (95% CI)	Total events 952 641 Heterogeneity: τ^2 =0.33; χ^2 =19.97, df =5 (P=0.001); /²=75% Test for overall effect: Z =2.20 (P=0.03) PFS 4 months 41 74 4 21 3. Burris et al ¹⁹ 41 74 4 21 3. Krop et al ²⁰ 51 67 63 70 5. Krop et al ²⁰ 241 404 62 198 8. Miller et al ²⁰ 341 495 310 496 9. Subtotal (95% CI) 1,141 843 3. Total events 736 468 9.	Test for overall effect: Z=1.87 ($P=0.06$) PFS 6 months Burris et al ¹⁹ 31 74 1 21 Hurvitz et al ²⁰ 31 74 1 21 Krop et al ²¹ 36 80 1 15 Krop et al ²⁶ 114 404 28 198 Miller et al ²⁵ 11 21 18 43 Verma et al ²⁰ 236 495 176 496 Subtotal (95% CI) 474 277 277 43 Total events $r^2=0.22$; $\chi^2=15.07$, $df=5$ ($P=0.01$); $l^2=67\%$ Test for overall effect: Z=2.41 ($P=0.02$)	Total (95% CI)3,4232,52910Total events2,1621,386Heterogeneity: $r^2=0.23$; $\chi^2=68.02$, $df=17$ (P<0.00001); $l^2=75\%$ Test for overall effect: Z=4.20 (P<0.0001)

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	↑ ↑	t t	L Ť.	T €
Odds ratio M–H, random, 95% Cl	│ │ ╷ │ ⊦ ↓ ▲	 ↓ ◆	+ ◆	• 10 Control
Odds ratio M–H, rando				0.1 1.0 1
Odds ratio M–H, random, 95% Cl	23.49 (1.37, 403.56) 1.05 (0.53, 2.10) 17.76 (1.02, 307.69) 1.57 (1.49, 5.17) 1.55 (0.53, 4.55) 1.67 (1.27, 2.19) 1.93 (1.19, 3.14)	15.11 (0.87, 261.43) 1.74 (0.88, 3.44) 10.50 (0.60, 183.48) 2.29 (0.93, 5.65) 2.48 (0.81, 7.56) 2.06 (1.50, 2.84) 2.12 (1.62, 2.76)	75.42) 5.28) 149.99) 6.6.71) 6.6.71) (3.07) (3.07)	
Odds ratio M–H, rando	23.49 (1.37, 403 1.05 (0.53, 2.10) 17.76 (1.02, 307 2.78 (1.49, 5.17) 1.55 (0.53, 4.55) 1.67 (1.27, 2.19) 1.93 (1.19, 3.14)	15.11 (0.87, 261, 1.74 (0.88, 3.44) 10.50 (0.60, 183 2.29 (0.93, 5.65) 2.48 (0.81, 7.56) 2.06 (1.50, 2.84) 2.12 (1.62, 2.76)	4.08 (0.22, 75.42) 2.36 (1.06, 5.28) 8.54 (0.49, 149.99) 6.03 (0.78, 46.71) 1.89 (0.59, 46.71) 2.14 (1.50, 3.07) 2.26 (1.66, 3.07)	2.00 (1.69, 2.37)
Weight (%)	2 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	0.3 5.8 3.4 2.10 33.0	25.1 25.1 25.1 25.1 25.1 25.1 25.1 25.1	8
Total	21 70 15 498 843 8 43	21 70 15 43 8 43 ≈ 843	21 70 15 438 843 843 843	z,523 ; <i>I</i> ² =7%
Control events	0 0 13 13 129 129 199 199 199 199	0 27 27 10 73 73 73 73 73 73 70 001); <i>P</i>	0 12 12 53 53 53 53 53); / ⁵	390 =17 (P=0.37) 0001)
s Total	74 67 67 80 404 1,141 1,141 1,141		74 67 67 80 404 21 1,141 1,141 1,141 1,141 1,141	3,423 ² =18.24, <i>d</i> f [:] 8.07 (P<0.00
T-DM1 events	<pre>\$ 26 26 42 42 42 29 66 9 183 355</pre>	15 15 19 20 20 20 21 22 20 22 20 22 22 20 22 22 20 22 22	s 6 22 17 12 10 10 10 165 <i>x</i> 101 165 <i>x</i>) 760 : τ²=0.01; χ l effect: Z=8
Study or subgroup	PFS months 74 0 21 Burris et al ¹⁹ 26 74 0 21 Burris et al ¹⁹ 26 74 0 21 Hurvitz et al ²² 42 67 43 70 Krop et al ²¹ 29 80 0 15 Krop et al ²⁶ 66 404 13 198 Miller et al ²⁶ 9 21 14 43 Verma et al ²⁶ 183 495 129 496 Subtotal (95% Cl) 1,141 845 199 Total events 355 10.51, <i>df</i> =5 (<i>P</i> =0.06); / ² =52% Total events 73.66 (<i>D</i> =0.06); / ² =52%	PFS 10 months 74 0 2 Burris et al ¹⁹ 19 74 0 2 Hurvitz et al ²² 35 67 27 7 Krop et al ²⁴ 20 80 0 1 Krop et al ²⁶ 27 404 6 1 Krop et al ²⁶ 9 21 10 4 Willer et al ²⁶ 9 21 10 4 Verma et al ²⁶ 130 495 73 4 Zubtotal (95% Cl) 1,141 8 8 6 Total events 240 1,141 8 8 Total events 240 16 16 4 Total events 240 16 6 16 Total events 240 16 6 16 Test for overall effect: $Z=5.55$ ($P<0.00001$) 16 73 8	PFS 12 months Burris et al ¹⁹ 6 74 0 2 Hurvitz et al ²² 22 67 12 72 Krop et al ²⁴ 17 80 0 11 Wrop et al ²⁶ 7 21 404 1 1 11 Miller et al ²⁶ 7 21 9 4 4 Verma et al ²⁰ 101 495 53 4 4 Subtotal (95% CI) 1,141 9 75 Total events 165 7 75 Heterogeneity: r^2 =0.00; χ^2 =2.11, df =5 (P =0.83); l^2 =0% Test for overall effect: Z=5.18 (P <0.00001)	Total (95% CI) $3,423$ $2,5.$ Total events 760 390 390 Heterogeneity: $\tau^2=0.01$; $\chi^2=18.24$, $df=17$ ($P=0.37$); $l^2=7\%$ Test for overall effect: $Z=8.07$ ($P<0.00001$)
ш				

Figure 3 (Continued)

M–H, fixed, 95% CI					+	•						+	+ -	•					+	ł	•		•	1 10 Control
M-H,												1						I						0.01 0.1 T-DM1
M-H, fixed, 95% CI	Not estimable	4.76 (1.49, 15.20) 6.20 (0.35, 110.02)	0.20 (0.33, 110.02) Not estimable	2.19 (0.67, 7.18)	2.24 (1.47, 3.43)	2.52 (1.73, 3.65)				3.34 (0.65, 17.19)	3.63 (0.20, 66.35)	0.65 (0.12, 3.53)	2.31 (1.41, 3.77)	2.20 (1.42, 3.41)			1.59 (0.26, 9.85)	1.40 (0.07, 28.49)	0.20 (0.01, 3.97)	3.36 (1.82, 6.21) 7 59 (1 52 / 4 41)			2.43 (1.89, 3.12)	
(%)		3.6	0.0	4.2	35.7	44.3				2.1	0.9	4.3	26.6	33.8			2.2	1.0	3.5	15.2 21 9	2		100	
Total	21	70	001	43.0	496	843				20	15	43	496	624			70	15	43	496 624	j		2,091	
events	0	4 0		ω	35		47); /²=0% 001)		7	0	9	25		33); /²=0% 04)		7	0	4	14	20); /²=24% 05)		100 3); /²=0% 001) licable
Total	74	67	404	21.	495	1,141		f=3 (P=0.60 .86 (P<0.00		67	80	21	495	663	f=3 (P=0.49 .51 (P=0.00		67	80	21	495 663	8	f=3 (P=0.27 .50 (P=0.00	2,467	<i>f</i> =11 (<i>P</i> =0.6 .93 (<i>P</i> <0.00 ces: not app
events		15 5	2 0	~	72	CI)	107	χ^2 =1.87, <i>d</i> effect: Z=4	S	9	8	2	54	CI)	70 χ^{2} =2.40, <i>d</i> effect: Z=3	S	ი	ю	0	44 CI)	50	χ^2 =3.93, <i>d</i> effect: Z=3		$\chi^{2=8.53, d}$ effect: Z=6 up difference
study or subgroup	PFS 14 months Burris et al ¹⁹	Hurvitz et al ²²	Kron et al ²⁶	Miller et al ²⁵	Verma et al ²⁰	Subtotal (95% CI	Total events	Heterogeneity: χ^2 =1.87, <i>df</i> =3 (<i>P</i> =0.60); <i>I</i> ² =0% Test for overall effect: <i>Z</i> =4.86 (<i>P</i> <0.00001)	PFS 16 months	Hurvitz et al ²²	Krop et al ²¹	Miller et al ²⁵	Verma et al ²⁰	Subtotal (95% CI)	Total events 70 33 Heterogeneity: χ^2 =2.40, <i>df</i> =3 (<i>P</i> =0.49); <i>I</i> ² =0% Test for overall effect: Z=3.51 (<i>P</i> =0.0004)	PFS 18 months	Hurvitz et al ²²	Krop et al ²¹	Miller et al ²⁵	Verma et al ²⁰ Subtotal (95% CI)	Total events	Heterogeneity: χ^2 =3.93, <i>df</i> =3 (<i>P</i> =0.27); <i>I</i> ² =24% Test for overall effect: Z=3.50 (<i>P</i> =0.0005)	Total (95% CI)	Total events 227 100 Heterogeneity: χ^2 =8.53, <i>df</i> =11 (<i>P</i> =0.66); <i>l</i> ² =0% Test for overall effect: Z=6.93 (<i>P</i> <0.00001) Test for subgroup differences: not applicable

18 months. Figure 3 Forest plots of PFS rates between patients underguing ו- ער וו שוישיאן שייב בבייבר אין אין שייב אין שייבר אין שיי Abbreviations: Cl, confidence interval: df, degrees of freedom; M–H, Mantel–Haenszel; PFS, progression-free survival; T-DMI, trastuzumab emtansine.

Study or subgroup	T-DM1 events	Total	Control events	Total	Weight (%)	Odds ratio M–H, fixed, 95% Cl	Odds ratio M–H, fixed, 95% Cl
Burris et al19	25	74	1	21	1.2	10.20 (1.29, 80.49)	·
Krop et al ²¹	33	80	3	15	3.3	2.81 (0.73, 10.74)	
Miller et al ²⁵	12	21	14	43	4.4	2.76 (0.94, 8.09)	
Perez et al ²⁴	35	55	37	60	14.4	1.09 (0.51, 2.32)	_ _ _
Verma et al ²⁰	173	397	120	389	76.7	1.73 (1.29, 2.32)	
Total (95% C	I)	627		528	100	1.82 (1.41, 2.34)	•
Total events	278		175				
Heterogeneity	/: χ²=5.54,	df=4 (P=	0.24); / ² =28	%		, F	
Test for overa	II effect: Z	=4.60 (P<	(0.00001)			0.0	
							T-DM1 Control

Figure 4 Comparison of the ORRs between patients undergoing T-DMI therapy and controls.

Note: The fixed-effects model (M-H method) was used.

Abbreviations: CI, confidence interval; df, degrees of freedom; M–H, Mantel–Haenszel; ORRs, objective response rates; T-DMI, trastuzumab emtansine.

140/512 patients) in the control group. Both the trials showed a higher SPF rate for patients who received T-DM1 in comparison with controls at 2 months, 4 months, and 6 months. The estimated pooled OR showed significantly improved 2-month, 4-month, and 6-month SPF rates for patients with breast cancer receiving T-DM1 (OR, 2.01; 95% CI, 0.96–4.17; *P*=0.06; OR, 1.64; 95% CI, 1.28–2.10; *P*<0.0001; and OR, 1.60; 95% CI, 1.23–2.08; *P*=0.0005, respectively; Figure 5A). The overall Cochran's *Q*-test had a *P*-value of 0.68, and the corresponding I^2 was 0%.

Eight-month, 10-month, and 12-month SPF

Information on the 8-month, 10-month, and 12-month SPF rates was available from two trials,^{20,22} which included a total of 1,027 patients (515 of whom received T-DM1; Figure 5B). The 8-month, 10-month, and 12-month SPF rates in the T-DM1 arm were 29%, 20%, and 15% (151/515, 104/515, and 76/515 patients), respectively, compared with 19%, 12%, and 10% (98/512, 63/512, and 49/512 patients), respectively, in the control group. The results showed that the SPF rate was significantly higher in the T-DM1 arm

	idy or ogroup	T-DM1 events	Total	Control events	Total	Weight (%)	Odds ratio M–H, random, 95% 0	Odds rat CI M–H, ran	io dom, 95% Cl
SPF	F 2 months								
	vitz et al ²²	55	65	42	67	3.3	3.27 (1.42, 7.55)		
	ma et al ²⁰	340	450	299	445	26.7	1.51 (1.13, 2.02)		+
	btotal (95%		515		512	29.9	2.01 (0.96, 4.17)		•
	al events	395		341					-
	erogeneity:		$\gamma^{2}=2.94$	• • •) () () · /2=	=66%			
	t for overall			•	,, .				
0.01	F 4 months			,					
	r 4 montns vitz et al ²²	37	65	31	67	4.8	1 52 (0 77 2 05)		
		37 259	65 450	200	67 445	4.0 32.6	1.53 (0.77, 3.05) 1.66 (1.28, 2.16)		TT-
	btotal (95%		430 515	200	512	32.0 37.4	1.64 (1.28, 2.10)		
	•		515	004	512	57.4	1.04 (1.20, 2.10)		
	al events	296	2-0.04	231	001. 12-	-00/			
	erogeneity: t for overall				J.83); I ² =	=0%			
ies		enect. Z-	·3.95 (P	<0.000T)					
	F 6 months								
	vitz et al ²²	29	65	21	67	4.5	1.76 (0.87, 3.59)		
Ver	ma et al ²⁰	164	450	119	445	28.1	1.57 (1.18, 2.09)		+
Sub	btotal (95%	CI)	515		512	32.6	1.60 (1.23, 2.08)		•
Tota	al events	193		140					
Het	erogeneity:	$\tau^2 = 0.00;$	χ ² =0.09,	df=1 (P=0).77); /²=	=0%			
Tes	t for overall	effect: Z=	3.47 (P	=0.0005)					
Tota	al (95% CI)		1,545		1,536	100	1.63 (1.40, 1.89)		•
Tota	al events	884		712					
Het	erogeneity:	$\tau^2 = 0.00$:	$\gamma^2 = 3.10.$	df=5 (P=0).68): /²=	=0%		H	
	t for overall			•	,.			0.01 0.1	1 10
			(-	,				T-DM1	Control

Figure 5 (Continued)

Study or subgroup	T-DM1 events	Total	Control events	Total	Weight (%)	Odds ratio M–H, random, 95% Cl	Odds ratio M–H, random, 95% Cl
SPF 8 month Hurvitz et al ²² Verma et al ²⁰ Subtotal (95	23 128	65 450 515	14 84	67 445 512	6.1 37.4 43.5	2.07 (0.95, 4.51) 1.71 (1.25, 2.34) 1.76 (1.31, 2.35)	*
Total events Heterogeneit Test for overa); /²=0%			
SPF 10 mon	ths						
Hurvitz et al ²² Verma et al ²⁰ Subtotal (95	85	65 450 515	6 57	67 445 512	3.7 27.7 31.4	4.20 (1.55, 11.35) 1.59 (1.10, 2.28) 2.30 (0.91, 5.83)	 +
Total events Heterogeneit Test for overa		,	•); /²=69%			
SPF 12 mon	ths						
Hurvitz et al22	9	65	4	67	2.4	2.53 (0.74, 8.67)	+
Verma et al ²⁰ Subtotal (95		450 515	45	445 512	22.7 25.1	1.55 (1.04, 2.33) 1.63 (1.11, 2.39)	•
Total events Heterogeneit Test for overa		,	``); /²=0%			
Total (95% C	:1)	1,545		1,536	100	1.73 (1.43, 2.10)	•
Total events	331		210				
Heterogeneit Test for overa); /2=0%		0.	.01 0.1 1 10 T-DM1 Control

С	Study or subgroup	T-DM1 events	Total	Control events	Total	Weight (%)	Odds ratio M–H, fixed, 95% Cl	Odds rat M–H, fix	tio ed, 95% Cl
	SPF 14 months	8							
	Hurvitz et al22	7	65	1	67	1.3	7.97 (0.95, 66.68)		<u> </u>
	Verma et al ²⁰	53	450	33	445	42.0	1.67 (1.06, 2.63)		
	Subtotal (95%	CI)	515		512	43.3	1.85 (1.19, 2.87)		•
	Total events	60		34					
	Heterogeneity: Test for overall								
	SPF 16 months			,					
	Hurvitz et al ²²	2	65	1	67	1.4	2.10 (0.19, 23.68)		
	Verma et al ²⁰	40	450	22	445	28.9	1.88 (1.10, 3.21)		
	Subtotal (95%	CI)	515		512	30.3	1.89 (1.12, 3.19)		•
	Total events	42		23					
	Heterogeneity: Test for overall		•						
	SPF 18 months	5							
	Hurvitz et al22	0	65	1	67	2.1	0.34 (0.01, 8.46)	· · · ·	<u> </u>
	Verma et al ²⁰	29	450	18	445	24.3	1.63 (0.89, 2.99)		+ - -
	Subtotal (95%	CI)	515		512	26.4	1.53 (0.85, 2.75)		•
	Total events	29		19					
	Heterogeneity: Test for overall		· ·	,.					
			(,					
	Total (95% CI)		1,545		1,536	100	1.78 (1.33, 2.38)		•
	Total events	131		76					
	Heterogeneity:	$\chi^2 = 3.14, df$	=5 (P=0.6	58); /²=0%				0.01 0.1	
	Test for overall		``	,					1 10 100
	Test for subgrou	up difference	es: not a	pplicable				T-DM1	Control

Figure 5 Forest plots of SPF between patients undergoing T-DM1 therapy and controls at (A) 2 months, 4 months, and 6 months, (B) 8 months, 10 months, and 12 months, and (C) 14 months, 16 months, and 18 months.

Note: Fixed- and random-effects meta-analysis models (M–H method) were used. Abbreviations: CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel; SPF, symptom progression free; T-DMI, trastuzumab emtansine.

in comparison with controls at 8 months, 10 months, and 12 months. The meta-analysis showed a significant improvement in the 8-month, 10-month, and 12-month SPF rates in patients who received T-DM1 compared with controls (OR, 1.76; 95% CI, 1.31–2.35; P=0.0001; OR, 2.30; 95% CI, 0.91–5.83; P=0.08; and OR, 1.63; 95% CI, 1.11–2.39; P=0.01, respectively; Figure 5B). The overall Cochran's Q-test had a P-value of 0.53. The corresponding P^2 was 0%, indicating that the degree of variability between the trials was consistent with what would be expected by chance alone.

Fourteen-month, 16-month, and 18-month SPF

Information on the 14-month, 16-month, and 18-month SPF rates was available from two trials.^{20,22} These trials included a total of 1,027 patients (515 of whom received T-DM1 treatment and 512 who acted as controls; Figure 5C). The 14-month, 16-month, and 18-month SPF rates were 12%, 8%, and 6% (60/515, 42/515, and 29/515 patients), respectively, for patients receiving T-DM1 compared with 7%, 4%, and 4% (34/512, 23/512, and 19/512 patients), respectively, for controls. The estimated pooled OR for the two trials showed significantly increased 14-month and 16-month SPF rates for patients who received T-DM1 compared with controls (OR, 1.85; 95% CI, 1.19-2.87; P=0.006 and OR, 1.89; 95% CI, 1.12–3.19; P=0.02, respectively). However, the 18-month SPF rate was not significantly improved (OR, 1.53; 95% CI, 0.85–2.75; P=0.15). The overall Cochran's O-test yielded a *P*-value of 0.68, and the corresponding I^2 quantity was 0%.

Toxicity and adverse reactions

The clinical trials included in this meta-analysis reported several AEs, including headache,¹⁹ pyrexia,^{19,21} epistaxis,^{19,21} constipation,^{19,21} cough,^{19,21} hypokalemia,^{19,21} pain in extremity,^{19,21} arthralgia,¹⁹ mucosal inflammation,²⁵ dry mouth,²¹ alopecia,²² pneumonia,²¹ etc. Because some AEs occurred less frequently than others, we analyzed only the common AEs in this meta-analysis.

Nonhematologic AEs

Information on diarrhea, fatigue, and increased aspartate aminotransferase (AST) levels was available from three trials.^{20,22,26} These three trials included a total of 1,700 patients (962 of whom received T-DM1 and 738 controls; Figure 6A). Compared with controls, fewer patients treated with T-DM1 experienced diarrhea (62% versus 17% of patients), but more patients experienced fatigue (33% versus 29%) and increased AST levels (8% versus 18%). Pooled analysis showed that diarrhea (OR, 0.19; 95% CI, 0.06–0.61; P=0.005), fatigue

(OR, 1.29; 95% CI, 1.04-1.59; P=0.02), and AST increases (OR, 3.33; 95% CI, 1.43–7.76; P=0.005) were significantly different between T-DM1-treated patients and controls (Figure 6A). Information on nausea, vomiting, and alanine aminotransferase (ALT) increases was available from two trials.^{20,22} These two trials included a total of 1,113 patients (559 of whom received T-DM1 treatment and 554 controls). Compared with control patients, nausea (45% versus 40%) and vomiting (29% versus 20%) occurred less frequently with T-DM1 treatment, whereas ALT increases occurred more frequently. Pooled analysis showed that vomiting (OR, 0.64; 95% CI, 0.42-0.98; P=0.04) and ALT increases (OR, 2.90; 95% CI, 1.20-7.01; P=0.02) were significantly different between the two groups, but nausea was not (OR, 0.89; 95% CI, 0.61-1.28; P=0.51; Figure 6A). Information on dyspnea was available from two trials,^{20,26} which included a total of 722 patients (472 of whom received T-DM1). There was no significant difference in dyspnea between the T-DM1 and control groups (OR, 0.74; 95% CI, 0.32-1.73; P=0.49; Figure 6A). Because there was a significant heterogeneity, a random-effects model was used.

Hematologic AEs

Information on neutropenia, anemia, and thrombocytopenia was available from three trials.^{20,22,26} These three trials included a total of 1,700 patients (962 of whom received T-DM1 and 738 controls). Compared with controls, T-DM1 treatment was associated with less neutropenia (17% versus 6% of patients) but more thrombocytopenia (23% versus 3%). Pooled analysis showed that the incidences of neutropenia (OR, 0.25; 95% CI, 0.09-0.73; P=0.01) and thrombocytopenia (OR, 8.50; 95% CI, 3.96-18.24; P<0.00001) were significantly different between the two groups, but anemia was not (OR, 0.85; 95% CI, 0.45–1.61; P=0.62; Figure 6B). Information on febrile neutropenia and leukopenia was available from two trials,^{22,26} which included a total of 722 patients (472 of whom received T-DM1). Compared with controls, febrile neutropenia (6% versus 0%) and leukopenia (11% versus 2%) occurred less frequently with T-DM1 treatment. The pooled analysis showed that the incidences of febrile neutropenia (OR, 0.06; 95% CI, 0.01-0.30; P=0.0008) and leukopenia (OR, 0.22; 95% CI, 0.08–0.57; P=0.002) were significantly different between patients treated with T-DM1 and controls (Figure 6B).

Publication bias

There was no evidence of publication bias for all outcomes through both Egger's test and Begg's test (P > 0.05).

subgroup	T-DM1 events	Total	Control events	Total	Weight (%)	Odds ratio M–H, random, 95% Cl	Odds ratio M–H, random, 95% Cl
Diarrhea							
Hurvitz et al ²²	11	69	30	66	5.6	0.23 (0.10, 0.51)	
Krop et al ²⁶	40	403	40	184	6.1	0.40 (0.25, 0.64)	
Verma et al ²⁰	114	490	389	488	6.3	0.08 (0.06, 0.10)	-
Subtotal (95% CI)		962		738	18.0	0.19 (0.06, 0.61)	
Total events Heterogeneity: <i>r</i> ² =0. Test for overall effec			459 P<0.00001);	/²=94%			
Fatigue							
Hurvitz et al ²²	34	69	30	66	5.8	1.17 (0.59, 2.29)	
Krop et al ²⁶	109	403	46	184	6.2	1.11 (0.75, 1.66)	
Verma et al ²⁰	172	490	136	488	6.3	1.40 (1.07, 1.84)	
Subtotal (95% CI)	172	962	100	738	18.3	1.29 (1.04, 1.59)	▲
Total events	315		212		1010		•
Heterogeneity: $r^2=0$. Test for overall effective overall effective overall effective overall effective overall effective over a section of the section of	.00; χ ² =0.96		=0.62); / ² =0 ⁴	%			
Nausea							
Hurvitz et al ²²	34	69	29	66	5.8	1.24 (0.63, 2.44)	- +- -
Verma et al ²⁰	192	490	218	488	6.3	0.80 (0.62, 1.03)	~
Subtotal (95% CI)		559		554	12.1	0.89 (0.61, 1.28)	+
Total events Heterogeneity: <i>1</i> ²=0. Test for overall effec			247 =0.23); /²=30	0%			
Vomiting							
Hurvitz et al ²²	17	69	17	66	5.7	0.94 (0.43, 2.05)	
	93					· · · /	
Verma et al ²⁰ Subtotal (95% CI)	93	490 559	143	488 554	6.3 11.9	0.57 (0.42, 0.76) 0.64 (0.42, 0.98)	-
Heterogeneity: <i>r</i> ² =0. Test for overall effec Dyspnea	ot: Z=2.03 (F	P=0.04)					
Hurvitz et al ²²	10	69	18	66	5.5	0.45 (0.19, 1.07)	
Krop et al ²⁶	40	403	17	184	5.9	1.08 (0.60,1.97)	+
Subtotal (95% Cl)		472		250	11.4	0.74 (0.32, 1.73)	-
Total events Heterogeneity: <i>τ</i> ²=0. Test for overall effec			35 =0.10); /²=6;	3%			
AST increased							
	30	69	4	66	5.0	11.92 (3.90, 36.45)	
AST increased Hurvitz et al ²² Krop et al ²⁶	30 34	69 403	10	66 184	5.0 5.7	11.92 (3.90, 36.45) 1.60 (0.77, 3.32)	
AST increased Hurvitz et al ²² Krop et al ²⁶ Verma et al ²⁰		403 490				1.60 (0.77, 3.32) 2.78 (1.92, 4.03)	
AST increased Hurvitz et al ²² Krop et al ²⁶ Verma et al ²⁰ Subtotal (95% CI)	34 110	403	10 46	184	5.7	1.60 (0.77, 3.32)	
AST increased Hurvitz et al ²² Krop et al ²⁶ Verma et al ²⁰ Subtotal (95% CI) Total events Heterogeneity: $r^2=0$.	34 110 174 .42; χ ² =8.75	403 490 962 5, df=2 (P	10 46 60	184 488 738	5.7 6.2	1.60 (0.77, 3.32) 2.78 (1.92, 4.03)	
AST increased Hurvitz et al ²² Krop et al ²⁶ Verma et al ²⁰	34 110 174 .42; χ ² =8.75	403 490 962 5, df=2 (P	10 46 60	184 488 738	5.7 6.2	1.60 (0.77, 3.32) 2.78 (1.92, 4.03)	
AST increased Hurvitz et al ²² Krop et al ²⁶ Verma et al ²⁰ Subtotal (95% CI) Total events Heterogeneity: $r^2=0$. Test for overall effec	34 110 174 .42; χ ² =8.75	403 490 962 5, df=2 (P	10 46 60	184 488 738 7%	5.7 6.2 17.0	1.60 (0.77, 3.32) 2.78 (1.92, 4.03)	
AST increased Hurvitz et al ²² Krop et al ²⁶ Verma et al ²⁰ Subtotal (95% CI) Total events Heterogeneity: $r^2=0$. Test for overall effec ALT increased	34 110 174 .42; <i>x</i> ² =8.75 :t: Z=2.79 (F	403 490 962 5, <i>df</i> =2 (<i>P</i> = 0.005)	10 46 60 =0.01); /²=7	184 488 738	5.7 6.2	1.60 (0.77, 3.32) 2.78 (1.92, 4.03) 3.33 (1.43, 7.76)	
AST increased Hurvitz et al ²² Krop et al ²⁶ Verma et al ²⁰ Subtotal (95% CI) Total events Heterogeneity: $r^2=0$. Test for overall effec ALT increased Hurvitz et al ²²	34 110 174 42; <i>χ</i> ²=8.75 t: <i>Z</i> =2.79 (<i>F</i> 18	403 490 962 5, <i>df</i> =2 (<i>P</i> : P=0.005) 69	10 46 =0.01); /²=7 4	184 488 738 7%	5.7 6.2 17.0 5.0	1.60 (0.77, 3.32) 2.78 (1.92, 4.03) 3.33 (1.43, 7.76) 5.47 (1.74, 17.19) 2.11 (1.43, 3.12)	
AST increased Hurvitz et al ²² Krop et al ²⁶ Verma et al ²⁰ Subtotal (95% CI) Total events Heterogeneity: $r^2=0$. Test for overall effec ALT increased Hurvitz et al ²² Verma et al ²⁰	34 110 174 42; $\chi^2=8.75$ 18 83 101 26; $\chi^2=2.39$	403 490 962 5, <i>df</i> =2 (<i>P</i> : <i>P</i> =0.005) 69 490 559 0, <i>df</i> =1 (<i>P</i> :	10 46 =0.01); /2=7 4 43 47	184 488 738 7% 66 488 554	5.7 6.2 17.0 5.0 6.2	1.60 (0.77, 3.32) 2.78 (1.92, 4.03) 3.33 (1.43, 7.76) 5.47 (1.74, 17.19)	
AST increased Hurvitz et al ²² Krop et al ²⁶ Verma et al ²⁰ Subtotal (95% CI) Total events Heterogeneity: $r^2=0$. Test for overall effec ALT increased Hurvitz et al ²² Verma et al ²⁰ Subtotal (95% CI) Total events Heterogeneity: $r^2=0$. Test for overall effec	34 110 174 42; $\chi^2=8.75$ 18 83 101 26; $\chi^2=2.39$	403 490 962 5, df=2 (P: P=0.005) 69 490 559 9, df=1 (P: P=0.02)	10 46 =0.01); /2=7 4 43 47	184 488 738 7% 66 488 554 8%	5.7 6.2 17.0 5.0 6.2 11.2	1.60 (0.77, 3.32) 2.78 (1.92, 4.03) 3.33 (1.43, 7.76) 5.47 (1.74, 17.19) 2.11 (1.43, 3.12) 2.90 (1.20, 7.01)	
AST increased Hurvitz et al ²² Krop et al ²⁶ Verma et al ²⁰ Subtotal (95% CI) Total events Heterogeneity: $r^2=0$. Test for overall effec ALT increased Hurvitz et al ²² Verma et al ²⁰ Subtotal (95% CI) Total events Heterogeneity: $r^2=0$.	34 110 174 42; $\chi^2=8.75$ 18 83 101 26; $\chi^2=2.39$	403 490 962 5, <i>df</i> =2 (<i>P</i> : <i>P</i> =0.005) 69 490 559 0, <i>df</i> =1 (<i>P</i> :	10 46 =0.01); /2=7 4 43 47	184 488 738 7% 66 488 554	5.7 6.2 17.0 5.0 6.2	1.60 (0.77, 3.32) 2.78 (1.92, 4.03) 3.33 (1.43, 7.76) 5.47 (1.74, 17.19) 2.11 (1.43, 3.12)	

Figure 6 (Continued)

Study or subgroup	T-DM1 events	Total	Control events	Total	Weight (%)	Odds ratio M–H, random, 95% C	Odds ratio M–H, random, 95% Cl
Neutropenia							
Hurvitz et al ²²	11	69	43	66	8.1	0.10 (0.04, 0.23)	_ - _
Krop et al ²⁶	22	403	40	184	8.5	0.21 (0.12, 0.36)	
Verma et al20	29	490	42	488	8.5	0.67 (0.41, 1.09)	
Subtotal (95%	CI)	962		738	25.2	0.25 (0.09, 0.73)	
Total events Heterogeneity: Test for overall				0.0001);	I²=89%	• • •	
		-2.55 (F	-0.01)				
Febrile neutro	•	00	•	00	4.5	0.04 (0.00, 0.70)	
Hurvitz et al ²²	0	69	9	66	4.5	0.04 (0.00, 0.76)	
Krop et al ²⁶	1	403	7	184	5.8	0.06 (0.01, 0.52)	
Subtotal (95%	•	472		250	10.3	0.06 (0.01, 0.30)	
Total events Heterogeneity: Test for overall				.84); /²=(0%		
	encot. 2	0.00 (/	0.0000)				
	0	60	10	66	0.0	0 40 (0 40 0 07)	
Hurvitz et al ²²	9	69	18	66	8.0	0.40 (0.16, 0.97)	
Krop et al ²⁶	36	403	19	184	8.4	0.85 (0.47, 1.53)	
Verma et al ²⁰	51 CN	490	38	488	8.6	1.38 (0.89, 2.14)	-
Subtotal (95%	•	962		738	25.1	0.85 (0.45, 1.61)	-
Total events	96 -2-0.01	2_0 40	75	041.12	200/		
Heterogeneity: Test for overall				.04); /*=6	59%		
Leukopenia							
Hurvitz et al ²²	7	69	17	66	7.9	0.33 (0.13, 0.85)	
Krop et al ²⁶	3	403	11	184	7.4	0.12 (0.03, 0.43)	
Subtotal (95%		403 472		250	15.3	0.22 (0.08, 0.57)	-
Total events	10	716	28	200	10.0		
Heterogeneity:		w ² -1 54		221.12-2	250/		
Test for overall				.22), 1-=;	55%		
Thrombocytop	penia						
Hurvitz et al22	19	69	4	66	7.6	5.89 (1.88, 18.43)	——
Krop et al ²⁶	61	403	6	184	8.1	5.29 (2.24, 12.48)	
Verma et al ²⁰	137	490	12	488	8.4	15.39 (8.40, 28.22)	
Subtotal (95%		962		738	24.1	8.50 (3.96, 18.24)	
Total events	217		22				· · ·
Heterogeneity: Test for overall	τ ² =0.27;		df=2 (P=0	.09); /²=	59%		
Total (95% CI)		3,830		2,714	100	0.63 (0.26, 1.51)	•
Total events	386		266				
Heterogeneity: Test for overall			· · · · · ·	P<0.0000	01); /²=94%	%	0.01 0.1 1 10 T-DM1 Control

Figure 6 Forest plots of adverse event rates between patients undergoing T-DMI therapy and controls with respect to (A) nonhematologic and (B) hematologic adverse events.

Note: A random-effects meta-analysis model (M–H method) was used.

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; CI, confidence interval; *df*, degrees of freedom; M–H, Mantel–Haenszel; T-DMI, trastuzumab emtansine.

Discussion

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women worldwide.²⁷ HER2 overexpression is closely associated with a poor prognosis in some breast cancers.¹ The effective treatment of HER2-overexpressing breast cancer after initial HER2directed therapy continues to represent an important medical need.¹⁹ A number of clinical trials have shown that HER2positive patients with breast cancer who receive T-DM1 have a more favorable prognosis than patients who do not receive T-DM1 or HER2-negative patients. T-DM1 was the first antibody-drug conjugate to use a thioether linker, which, in preclinical testing, proved to be more stable than other drugs used as linkers.²⁸ In vitro studies showed that T-DM1-activated antibody-dependent cellular cytotoxicity inhibited HER2 receptor signaling and shedding of the HER2 extracellular domain in HER2-overexpressing cells from patients with breast cancer.²⁹ In the current study, we performed a systemic analysis of the published clinical trials in order to assess the efficacy and safety of T-DM1 treatment in patients with breast cancer with respect to OS, PFS, ORR, SPF, and AEs.

Our analysis yielded several major findings. First, the overall meta-analysis showed that T-DM1 treatment could significantly improve the 2-month to 6-month, 8-month to 12-month, and 14-month to 16-month OS rates (all P<0.0001) of patients with breast cancer compared with controls Our comprehensive results calculated 2-month, 4-month, 6-month, 8-month, 10-month, 12-month, 14-month, and 16-month OS rates of 96%, 88%, 74%, 63%, 54%, 42%, 33%, and 27%, respectively, which are slightly different to the results of independent trials; the median OS was ~10 months. Although the 10-month OS rate was not significantly improved (P=0.17), this may be explained because the number of patients included in this analysis was not large enough. Thus, the advantage of logistic regression is obvious. Our data analysis showed that T-DM1 treatment can significantly prolong OS in patients with breast cancer.

Second, the results also showed that T-DM1 treatment had a significant impact on 2-month to 6-month, 8-month to 12-month, and 14-month to 18-month PFS rates (P < 0.0001) compared with controls (Figure 3). The summarized results showed that the 2-month, 4-month, 6-month, 8-month, 10-month, 12-month, 14-month, 16-month, and 18-month PFS rates were 83%, 65%, 42%, 31%, 21%, 14%, 9%, 11%, and 8%, respectively, while the respective rates for controls were 76%, 56%, 33%, 24%, 14%, 9%, 6%, 5%, and 3%, respectively. The median PFS time of patients treated with T-DM1 was between 4 months and 6 months. A previous study reported a median PFS time of 5.3 months for patients with breast cancer treated with T-DM1 (95% CI, 3.6-8.9 months),19 while another Phase II clinical trial reported a median PFS of 5.5 months (95% CI, 4.2–7.9 months).²¹ Although there were a few differences among the trials included in this meta-analysis, the positive trend was fully confirmed. However, T-DM1 therapy was not found to significantly extend the 4-month PFS rate compared with controls (P=0.06). This may be because the number of patients included in this analysis was not large enough. Through logistic regression, however, our analysis revealed that T-DM1 therapy has a significant influence on PFS.

Furthermore, the secondary endpoints of ORR and SPF showed favorable results in the T-DM1 treatment group compared with corresponding controls ($P \le 0.0001$; Figures 4 and 5). Our pooled analysis of the collected data showed that the 2-month, 4-month, 6-month, 8-month, 10-month, 12-month, 14-month, 16-month, and 18-month SPF rates were 77%, 57%, 37%, 29%, 20%, 15%, 12%, 8%, and 6%, respectively, compared with 67%, 45%, 37%, 19%, 12%, 10%, 7%, 4%, and 4%, respectively, for controls. The 2-month, 10-month, and 18-month SPF rates were not significantly improved versus controls (P=0.06, P=0.08, and P=0.15, respectively). We should note that the SPF analysis included only two trials with a total of 1,027 patients for each endpoint; a larger number of trials are required to prove these results.

The analysis also showed that nonhematologic and hematologic AEs were not significantly different between the T-DM1 and control groups (*P*=0.99 and *P*=0.30, respectively; Figure 6). Overall, therefore, according to the present study, T-DM1 treatment may prove advantageous for HER2-positive patients with breast cancer.

There are some points that may explain these results. First, T-DM1 has shown antitumor activity against breast cancer tumors and HER2-positive cancer cell lines that do not respond or that have developed resistance to trastuzumab or lapatinib.15,28,29 Furthermore, T-DM1 was the first HER2targeted agent to demonstrate a significant clinical activity in patients with breast cancer who had progressed on both lapatinib- and trastuzumab-based regimens.13 Second, T-DM1 has been shown to inhibit PI3K in cells that are insensitive to trastuzumab.^{30,31} In addition, T-DM1 has been seen to inhibit the growth of breast cancer cells that are resistant to lapatinib and have an activated PI3K pathway.^{29,32–35} Third, the maximal cytotoxicities in antibody-dependent cell-mediated cytotoxicity assay have been reported to be 57% with T-DM1 and 48% trastuzumab.^{10,36,37} In addition, the active metabolite of T-DM1, lysine-Ne-4-(N-maleimidomethyl) cyclohexane-1-carboxylate-DM1 is released when T-DM1 is internalized. Because lysine-Ne-(N-maleimidomethyl) cyclohexane-1-carboxylate-DM1 is a zwitterion, it does not readily cross the plasma membrane of neighboring normal cells. This likely contributes to the overall safety profile of T-DM1.^{33,38,39} Finally, Yu et al²⁷ have concluded that the regimen of T-DM1 as well as pertuzumab in combination with trastuzumab and docetaxel is efficacious with fewer side effects as compared with other regimens through a network meta-analysis of six HER2-targeted treatment drugs and one naive standard treatment. Although that article only included

a clinical study of T-DM1, it has been shown that T-DM1 is a better regimen.

In short, T-DM1 therapy for patients with breast cancer associated with significantly prolonged OS and PFS improved ORR and SPF and low rates of AEs.

Limitations

The reliability of this meta-analysis might be influenced by several factors. First, not all the trials included in this systemic review were multicenter clinical trials, so the results of the present meta-analysis cannot be extended to all patients with breast cancer across the world. Second, some clinical trials with good efficacy were excluded because they lacked appropriate control arms; thus, the validity of the study results might be underestimated. Third, not all the eight clinical trials included in this study were randomized controlled trials, and only two trials were Phase III trials with large samples. Therefore, this review might contain distribution and implementation biases. Finally, we included data on patients with breast cancer from published articles, rather than drawing the first-hand data from patient records. In addition, negative trial outcomes often remain unpublished. Thus, our analysis might have resulted in an overestimation of the effects of T-DM1 treatment. Finally, the results of our study may be misleading because of the different design of clinical trials included in this meta-analysis. These factors might also introduce bias into the conclusions. However, we believe that this study is valuable in improving the design of randomized controlled multicenter clinical trials.

Future perspectives

In the near future, T-DM1 will be widely used in the treatment of HER2-positive patients with breast cancer, and the costs of the therapy will be reduced. But before that, there are still some unanswered questions about T-DM1 which need to be solved. First of all, for which kinds of patients is T-DM1 most effective? We urgently need to identify biomarkers that will help to identify those patients who are most likely to benefit from T-DM1.8,40 In addition, we still need to definitively address the mechanisms of resistance to T-DM1; such research will require tumor tissue from patients with progressive disease, and biopsies from these patients should be included in future trials of T-DM1.8,41,42 Furthermore, we also need to summarize and explore the best optimal dose and dosing method for T-DM1. Finally, with the continuous progress that is being made in biotechnology, the future treatment of patients with breast cancer will move toward individualized therapy.

Conclusion

Overall, this meta-analysis of T-DM1 in HER2-positive patients with breast cancer has yielded encouraging results with superiority in OS and PFS, improvements in ORR and SPF, and low rates of AEs. Hence, these results suggest that T-DM1 has a great potential as an efficacious clinical therapy for the treatment of HER2-positive patients with breast cancer who were previously treated with trastuzumab, lapatinib, or other standard-directed therapies.

Acknowledgment

This research work was supported by the Natural Science Foundation of Zhejiang Province (No LQ12H16002) and Science and Technology Plan Projects of Huzhou (No 2013GZ13).

Disclosure

The authors report no conflicts of interest in this work.

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