pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Trastuzumab Emtansine (Kadcyla) for Early Breast Cancer

January 22, 2020

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding trastuzumab emtansine (Kadcyla) for early breast cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature trastuzumab emtansine (Kadcyla) for early breast cancer conducted by the Breast Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review is fully reported in Sections 6. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on trastuzumab emtansine (Kadcyla) for early breast cancer, a summary of submitted Provincial Advisory Group Input on trastuzumab emtansine (Kadcyla) for early breast cancer, and a summary of submitted Registered Clinician Input on trastuzumab emtansine (Kadcyla) for early breast cancer, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of the review is to evaluate the efficacy and safety of trastuzumab emtansine, hereafter referred to as T-DM1 for the treatment of patients with HER2-positive early breast cancer, who have residual disease, after pre-operative systemic treatment.

T-DM1 has been approved by Health Canada as a single agent, is indicated for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease following neoadjuvant taxane and trastuzumab-based treatment. This is in alignment with the reimbursement request. T-DM1 is available as a 100mg single-use vial containing sterile powder for concentrate for infusion solution designed to deliver 5 mL of 20 mg/mL and 160 mg single-use vial containing sterile powder for concentrate for infusion solution designed to deliver 8 mL of 20 mg/mL. The recommended dose of T-DM1 is 3.6 mg/kg given as an intravenous infusion every 3 weeks (21-day cycle) for 14 cycles or until disease progression or unacceptable toxicity.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one randomized controlled trial (RCT), the KATHERINE trial (n=1486), and the results are summarized below.[1]

KATHERINE

KATHERINE was an international, multi-centre, open-label, phase III, RCT comparing trastuzumab emtansine (hereafter referred to as T-DM1) versus trastuzumab for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual disease after pre-operative systemic treatment. Eligible patients were randomized in a 1:1 ratio to receive 14 cycles of either T-DM1 at a dose of 3.6 mg/kg by intravenous (IV) infusion, once every 3 weeks, or trastuzumab at a dose of 6 mg/kg by IV infusion once

every 3 weeks. There were 743 patients randomized to each treatment arm, with 740 that received the assigned treatment in the T-DM1 arm compared to 720 in the trastuzumab arm.

The primary endpoint of KATHERINE was invasive disease-free survival (iDFS), and secondary outcomes included the Standardized Definitions for Efficacy End Points (STEEP) definition of iDFS that included a second primary non-breast cancer as an iDFS event, disease-free survival (DFS), overall survival (OS), and distant recurrence-free interval (DRFI).[1] iDFS, DFS, and DRFI were assessed by the investigator as per clinical assessments that included vital signs measurement, physical examination, radiologic evaluation (included a bilateral mammogram and/or magnetic resonance imaging [MRI] with at least an annual mammogram of any remaining breast tissue), and laboratory assessment.[2] An iDFS event (with the exception of death without recurrence) was to be confirmed by positive histology, cytology, aspirate, biopsy, or radiology depending on the type of recurrence. Ipsilateral and contralateral lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS) were not considered as recurrence. The STEEP iDFS definition included a second non-breast primary malignancy (other than basal or squamous cell carcinoma of the skin, carcinoma in-situ of the cervix) confirmed histologically. DFS included all events as per the iDFS outcome in addition to second primary non-breast cancer and ipsilateral or contralateral ductal carcinoma in situ. Health-related quality of life (HRQoL) was also explored and assessed using European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 (QLQ-C30) and the EORTC breast cancer module (EORTC-QLQ-BR23). Safety was monitored regularly throughout the study and included all patients who received at least 1 dose of the assigned combination treatment.[1]

The median age in both treatment arms was 49 years.[1] Almost all patients were female, with the exception of 2 male patients in the T-DM1 arm and 3 male patients in the trastuzumab arm.[2] Overall, demographic and clinical characteristics were well balanced between treatment arms with the majority of patients reporting White race/ethnicity (n=1082; 72.8%), a clinical stage at presentation of operable breast cancer (n=1111; 74.8%), ER and/or PR positive (n=1074; 72.3%), and a prior treatment regimen that involved an anthracycline (n=1143, 76.9%).[1] Most patients had a baseline Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 (n=1210; 81.4%). There were 399 (53.7%) patients that were premenopausal and 344 (46.3%) patients that were postmenopausal in the T-DM1 treatment arm compared to 413 (55.6%) and 330 (44.4%) premenopausal and postmenopausal women, respectively, in the trastuzumab arm.[2] Most patients in both treatment arms had neoadjuvant HER2-directed therapy with trastuzumab alone (n=1196; 80.5%), and a similar proportion of patients in both arms had trastuzumab plus pertuzumab (overall, n=272; 18.3%).[1]

Efficacy

The key efficacy outcomes are presented in Table 1 (based on the first interim analysis with a data cut-off date July 25th, 2018).[1-3]

iDFS: The median iDFS was not estimable in both treatment arms. A total of 91 (12.2%) iDFS events occurred in the T-DM1 arm compared to 165 (22.2%) iDFS events in the T-DM1 arm.[2] The 3-year event-free rate for iDFS was 88.3% in the T-DM1 arm compared to 77.0 % in the trastuzumab arm. There was a 50% reduction in the risk of an iDFS event with the T-DM1 treatment arm compared to the trastuzumab arm (unstratified HR: 0.50; 95% CI: 0.39, 0.64; p<0.001). Subgroup analyses of iDFS also showed a consistent benefit across stratification factors and other subgroups. Of note, the confidence interval crossed 1 (indicating no difference between treatment arms) in the ≥65 years of age subgroup; in the subgroup of patients that received preoperative therapy with trastuzumab and

additional HER2-directed agent(s); tumor stage of T4 at definitive surgery; regional lymph node stage of N3 or not evaluable; patients that reported Black or African American, or Asian, or American Indian or Alaska Native, or unknown races; primary tumor stage at initial diagnosis of cT4, cT4a, cT4B, or cT4c, or cT4d; and regional lymph node stage at initial diagnosis of cN3 or cNx.[1]

iDFS (with second non-breast primary cancer included in the definition): There were 95 (12.8%) patients in the T-DM1 arm and 167 (22.5%) patients in the trastuzumab arm that had an iDFS event with this definition. The estimated 3-year event rate for iDFS was 87.7% in the T-DM1 arm and 76.9% in the trastuzumab arm.[2] There was a 49% (unstratified HR: 0.51; 95% CI: 0.40, 0.66) reduction in the risk of an iDFS event with this definition in the T-DM1 arm compared to the trastuzumab. [1]

DFS: There were 98 (13.2%) patients with a DFS event in the T-DM1 arm and 167 (22.5%) in the trastuzumab arm. The estimated 3-year event rate for DFS was 87.4% in the T-DM1 arm and 76.9% in the trastuzumab arm. There was a 47% reduction in the risk of a DFS event in the T-DM1 arm compared to the trastuzumab arm (HR: 0.53; 95% CI: 0.41, 0.68).[1]

OS: There were 42 deaths (5.7%) in the T-DM1 treatment arm and 56 (7.5%) deaths in the trastuzumab arm. The 5-year OS rates were estimated as 92.1% in the T-DM1 arm and 86.8% in the trastuzumab arm.[2] There was no statistically significant difference in OS between treatment arms (HR: 0.70; 95% CI: 0.47, 1.05) in the IA, and OS data are immature.[1]

DRFI: A total of 78 (10.5%) distant recurrence events had occurred in the T-DM1 arm compared to 121 (16.3%) events in the trastuzumab arm. The 3-year event rate was estimated at 89.7% in the T-DM1 arm and 83.0% in the trastuzumab arm. There was a 40% reduction in distant recurrence events with T-DM1 compared to trastuzumab (HR: 0.60; 95% CI: 0.45, 0.79).[1]

Health-related Quality of Life

Overall, 640 (86%) and 612 (82%) of patients in the T-DM1 and trastuzumab arms, respectively, had a valid baseline and ≥ 1 post-baseline HrQOL assessment completed. The completion rates for the EORTC QLQ-C30 and EORTC-BR23 were consistently over 70% during treatment and follow-up period.[4] Mean changes from baseline were similar for global health status for both treatment arms, with no clinically meaningful changes at Cycle 5, 11, treatment discontinuation, or at 6 and 12 month follow-up. [redacted][2] *(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 3rd, 2020 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)*

There were a higher proportion of patients in the T-DM1 treatment arm that reported a clinically meaningful deterioration in role function (49% vs. 41% in the trastuzumab arm), appetite loss (38% vs. 28% in the trastuzumab arm), constipation (47% vs. 38% in the trastuzumab arm), fatigue (66% vs. 61% in the trastuzumab arm), nausea/vomiting (39% vs. 30% in the trastuzumab arm), and systemic therapy side effects (49% vs. 36% in the trastuzumab arm) at any point in the study. A higher proportion of patients in the

trastuzumab arm reported a clinically meaningful deterioration in diarrhea (27% vs. 22% in the T-DM1 arm) at any point in the study.[4]

Harms

The median total treatment duration in the T-DM1 arm was 10 months (range 1-12 months) and in the trastuzumab arm it was 10 months (range 1-13 months). There were more patients in the T-DM1 arm that experienced a dose reduction (n=90; 12.2%) or dose interruption (n=106; 14.3%) compared to the trastuzumab arm where no patients experienced a dose reduction and 37 (5.1%) experienced a dose interruption.[2]

AEs any-grade: There were more patients in the T-DM1 arm that experienced an any-grade adverse event ([AE]; n=731; 98.8%) compared to the trastuzumab arm (any grade AEs: n=672, 93.3%). The most commonly occurring any grade AEs in both treatment arms was fatigue (T-DM1: n=366, 49.5% vs. trastuzumab: n=243, 33.8%). In the T-DM1 arm, this was followed by nausea (41.6%), decreased platelet count (28.5%), and increased aspartate aminotransferase (28.4%). In the trastuzumab arm, fatigue was followed by radiation-related skin injury (27.6%), arthralgia (20.6%), and hot flashes (20.3%).[1]

AEs grade ≥3: There were more patients in the T-DM1 arm that experienced a grade ≥3 AE (n=190; 25.7%) compared to the trastuzumab arm (n=111, 15.4%). The most commonly occurring grade ≥3 AE was decreased platelet count, which occurred in 5.7% (n=42) of patients in the T-DM1 arm and 0.3% (n=2) of patients in the trastuzumab arm. This was followed by hypertension, which occurred in 2.0% (n=15) and 1.2% (n=9) of patients in the T-DM1 and trastuzumab arms, respectively. Radiation-related skin injury occurred in 1.4% (n=10) and 1.0% (n=7) in the T-DM1 and trastuzumab arms, respectively. Peripheral sensory neuropathy ≥ grade 3 occurred in 1.4% (n=10) of patients in the T-DM1 arm and in no patients in the trastuzumab arm.[1]

Serious adverse events (SAEs): SAEs occurred in 94 (12.7%) patients in the T-DM1 arm compared to 58 (8.1%) patients in the trastuzumab arm. The most common SAEs included mastitis and decreased platelet count. Mastitis occurred in 8 (1.1%) patients in the T-DM1 arm and 6 (0.8%) in the trastuzumab arm, and decreased platelet count occurred in 10 (1.4%) patients in the T-DM1 arm and no patients in the trastuzumab arm.[2]

Withdrawal due to AEs: There was a higher proportion of patients in the T-DM1 arm who discontinued treatment due to an AE (n=133; 18%) compared to the trastuzumab arm (n=15; 2.1%) discontinued treated due to an AE.[1]

Deaths: There was 1 (0.1%) patient who died in the T-DM1 arm due to an AE and no patients that died in the trastuzumab arm.[1] This patient had a low platelet count and fell at home and died of intracranial hemorrhage. Six additional deaths occurred outside of the 30 days following the last study treatment dose that were not considered related to study treatment, which included 4 deaths occurred in the trastuzumab arm and 2 deaths in the T-DM1 arm.[2]

Table 1: Highlights of Key Outcomes in the KATHERINE trial

	KATHERINE Trial	
	Trastuzumab Emtansine (T-DM1) Arm (N=743)	Trastuzumab Arm (N=743)
Primary Outcome		
Invasive disease-free survival		
Median months (95% CI)	NE (NE, NE)	NE (NE, NE)
3-year event-free rate	88.3 (85.8, 90.7)	77.0 (73.8, 80.3)
HR (95%CI)	0.50 (0.39, 0.64)	
p-value	<0.001	

	KATHERINE Trial	
Key Secondary Outcomes		
Invasive disease-free survival (including second primary non-breast cancer as per STEEP definition)		
3-year event-free rate	87.7 (85.2, 90.2)	76.9 (73.7, 80.1)
HR (95%CI)	0.51 (0.40, 0.66)	
p-value	<0.0001	
Disease-free survival		
3-year event-free rate	87.4 (84.9, 89.9)	76.9 (73.6, 80.1)
HR (95%CI)	0.53 (0.41, 0.68)	
p-value	<0.0001	
Overall survival		
5-year survival rate	92.1 (89.4, 94.7)	86.8 (81.0, 85.9)
HR (95%CI)	0.70 (0.47, 1.05)	
p-value	0.0848	
Distant recurrence-free survival		
3-year event-free rate	89.7 (87.4, 92.0)	83.0 (80.1, 85.9)
HR (95%CI)	0.60 (0.45, 0.79)	
p-value	0.0003	
HrQOL	**Trastuzumab Emtansine (T-DM1) Arm (N=640)†**	**Trastuzumab Arm (N=612)†**
Proportion of Patients with a Clinically Meaningful Deterioration in Global Health Status from Baseline, n (%)**		
Cycle 5	[redacted]	[redacted]
Cycle 11	[redacted]	[redacted]
Trastuzumab completion/early discontinuation	[redacted]	[redacted]
T-DM1 completion/early discontinuation	[redacted]	[redacted]
Follow-up month 6	[redacted]	[redacted]
Follow-up month 12	[redacted]	[redacted]
Harms Outcome, n (%)	**Trastuzumab Emtansine (T-DM1) Arm (N=740)**	**Trastuzumab Arm (N=720)**
AE (any grade)	731 (98.8)	672 (93.3)
AE grade ≥3	190 (25.7)	111 (15.4)
SAE	94 (12.7)	58 (8.1)
TRAE	641 (86.6)	326 (45.3)
WDAE	133 (18.0)	15 (2.1)
Deaths	1 (0.1)	0 (0.0)

AE = adverse event, CI = confidence interval, HR = hazard ratio, HRQoL = health-related quality of life, NR = not reported, SD = standard deviation, STEEP = Standardized Definitions for Efficacy End Points, TRAE = treatment-related adverse event, WDAE = withdrawal due to adverse event

† Number of patients with a valid baseline and ≥1 post-baseline questionnaire completed

*HR < 1 favours T-DM1

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Limitations

- The primary outcome of the trial, iDFS, has not been validated in the published literature, thus, the strength of the association between this surrogate outcome and OS is unknown. In addition, there are varying definitions for iDFS and DFS in the literature, which make cross-trial comparisons challenging for analysis and interpretation.

- The study design was open-label, which is susceptible to reporting and performance biases as patients and investigators were not blinded to study treatment. All outcomes were investigator-assessed, of which most were confirmed either pathologically, radiologically, or using both methods. However, reporting biases remain a concern, in favour of T-DM1, with the potential for delaying pathological or radiological confirmation of an iDFS event in the T-DM1 arm based on the open-label design. It should be noted that there were a higher proportion of protocol deviations related to investigators not holding or reducing the dose of T-DM1 as per protocol, which indicated some degree of investigator bias as well as deviation bias in the T-DM1 arm. An analysis to assess for deviation bias by excluding patients who did not have their dose held or reduced as per protocol was conducted, and the results were consistent with the primary iDFS analysis, indicated the impact of deviation bias was minimal on efficacy outcomes.
- Though deviation bias related to not holding or reducing doses as per protocol may be minimal on efficacy outcomes observed in the trial, it may not be reflective of how the drug will be administered in clinical practice.[2] In theory, if clinicians administer the drug as per protocol in clinical practice (i.e., hold or reduce doses due to toxicity), it could result in the drug being less efficacious in the "real-world" setting when administered in a much larger population.
- Despite there being more patients that did not have their doses held or reduced in the T-DM1 arm due to toxicity, there were still a higher proportion of patients in the T-DM1 arm that required a dose reduction, dose interruption, and discontinued treatment due to an AE. This is indicative of a higher proportion of toxicities in the T-DM1 arm overall, which may have been underestimated due to a higher proportion of protocol deviations related to a higher proportion of protocol deviations related to not holding or reducing doses for toxicities that occurred in this treatment arm.
- Patients who discontinued T-DM1 treatment early (i.e., due to toxicity) were able to crossover to trastuzumab. Post-hoc exploratory analyses adjusting for crossover to trastuzumab of the primary endpoint of iDFS and secondary endpoint of OS, revealed results that were consistent with the primary analysis. Thus, the potential confounding of crossover to trastuzumab in the T-DM1 arm was considered to have a minimal effect on the overall trial results, although the methodology used to adjust for crossover may have been biased.
- Double the patients in the trastuzumab arm compared to the T-DM1 arm received follow-up anticancer therapies. Discussion with the CGP revealed that subsequent therapies in the trastuzumab arm were not reflective of clinical practice (for example, limited use of T-DM1, which is an established subsequent therapy following trastuzumab in the recurrent setting), which may indicate investigator bias in prescribing patterns due to the open-label nature of the study design, and may bias the results in favour of T-DM1.
- There were more patients in the trastuzumab arm who received an aromatase inhibitor compared to the T-DM1 arm, however this was not predicted to affect outcomes, and thus the potential confounding was predicted to be limited.

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

The following patient groups provided input on trastuzumab emtansine (Kadcyla) for HER2-positive early breast cancer and their input is summarized below: Rethink Breast Cancer (RBC) and The Canadian Breast Cancer Network (CBCN).

From a patient's perspective, HER2-positive early breast cancer has a significant physical and psychological impact on the lives of patients, their caregivers and loved ones. The disease limits the ability of patients to work and engage in their daily tasks. Current treatments for HER2 breast cancer include a combination of surgery, chemotherapy, targeted therapy, and radiation. Some of the most significant side effects of current therapies reported by patients are cardiac toxicity, fever, fatigue, diarrhea, muscle and joint pain, and nausea. The CBCN also commented that there are significant financial challenges endured by patients of HER2-positive early stage breast cancer due to loss of income, drug and travel costs. RBC was able to recruit survey respondents who had previous experience with trastuzumab emtansine, the majority of whom spoke highly favourable of the drug. The majority of these patients reported that trastuzumab emtansine had significantly improved their quality of life and helped control the disease, as they found the drug very tolerable with minimal side effects. Also, no patient reported any difficulty accessing the drug. The CBCN and RBC both concluded that reduced risk of recurrence and ability to manage side effects were some of the most important patient values. Respondents from both RBC and CBCN however, also mentioned that they are willing to tolerate some minimal side-effects in exchange of a decreased risk of recurrence. CBCN commented that since the side effects of trastuzumab emtansine are tolerable and reversible, this drug is an optimal option for HER2-positive early breast cancer as it aligns very well with their values.

Please see Section 3 below for more details.

Provincial Advisory Group (PAG) Input

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:
- Clarity on eligible patient population

Economic factors:
- Additional healthcare resources for monitoring and management of adverse events

Please see Section 4 below for more details.

Registered Clinician Input

The following registered clinicians provided input on trastuzumab emtansine (Kadcyla) for early breast cancer: A total of two clinician inputs were received representing a total of 4 clinicians (three oncologists and one pharmacist) - 1 single clinician input from Ottawa and 1 joint clinician input from the Cancer Care Ontario (CCO) Breast Drug Advisory Committee (DAC) representing two oncologists and one pharmacist.

All clinicians agreed that the eligibility criteria for the KATHERINE trial were applicable to clinical practice. The clinicians from CCO Breast DAC reported that trastuzumab emtansine has a significant benefit over the standard treatment of trastuzumab alone and is considered a promising treatment that addresses an unmet need in a high-risk population. Furthermore, the CCO Breast DAC reported that the toxicity associated with trastuzumab emtansine was not excessive, and it is a treatment that should be prioritized since it can prevent several patients from relapsing. The single clinician input noted that trastuzumab emtansine may not be appropriate for patients who have concomitant contraindications to standard trastuzumab (e.g., cardiac dysfunction). All clinicians providing input agreed that the number of anti-HER2 therapies should be advised by clinical trial evidence and practice guidelines. With respect to companion diagnostic testing, the single clinician input stated that patients would have had standard HER2 testing at diagnosis using standard accepted methodologies; Clinicians from CCO Breast DAC however noted that this is not being done as part of routine practice in Ontario.

Please see Section 5 below for more details.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for trastuzumab emtansine for early breast cancer

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	Disease stage	Patients with T1a/bN0 tumors were not eligible for participation in the KATHERINE trial.	Can the results be applied to patients with T1a/bN0 tumors?	The CGP do not support the generalizability of the trial evidence into patients with T1a/bN0 tumors as further evidence would be required to determine efficacy in this population.
	ECOG PS	The KATHERINE trial included patients with ECOG PS 0-1. The majority of patients had ECOG PS 0 (trastuzumab: n= 613, 82.5%; trastuzumab emtansine: n = 597; 80.3%).	Can the results be applied to patients with ECOG PS >1?	The CGP agree that the use of T-DM1 in patients with ECOG PS ≥ 1 should be left to the discretion of the treating oncologist.
	Sex	The KATHERINE trial included 5 male patients, 3 in the trastuzumab arm and 2 in the T-DM1 arm.	Can the results be applied to male patients?	The results will apply to male patients as they were included in the trial. Similarly, they also apply to patients who received additional HER2 targeted therapy in neoadjuvant setting. This was also supported by input from registered clinicians.
	Prior therapy	The KATHERINE trial included patients with preoperative trastuzumab plus pertuzumab or an additional HER2-directed therapy. A total of 147 (19.8%) patients in the trastuzumab arm and 143 (19.2%) patients in the T-DM1 arm received trastuzumab plus an additional HER2-directed therapy in the preoperative setting. The majority in both treatment arms received pertuzumab as the additional HER2-directed therapy with 139 (18.7%) patients in the trastuzumab arm and 133 (17.9%) in the T-DM1 arm.	Can the results be applied to patients treated with trastuzumab and pertuzumab (or other HER2-targeted therapy) in the neoadjuvant setting?	The CGP support the generalizability of the trial evidence into patients treated with trastuzumab and pertuzumab (or other HER2-targeted therapy) in the neoadjuvant setting as these patients were included in the KATHERINE trial. This was also supported by input from registered clinicians.
Intervention	Adjuvant trastuzumab	Patients in the KATHERINE trial did not complete adjuvant therapy prior to starting treatment with T-DM1. However, a total of 33 patients (4.6%) in the trastuzumab arm compared to 4 (0.5%) patients in the T-DM1 arm received subsequent therapy with T-DM1.	Would patients who completed one year of adjuvant trastuzumab be eligible for T-DM1?	The CGP do not support making T-DM1 available in settings where patients have already completed adjuvant treatment with trastuzumab as this was not the target population of the KATHERINE trial.
	Initiation of adjuvant therapy	Patients were randomized within 12 weeks of surgery to adjuvant therapy with T-DM1 or trastuzumab.	Would patients be able to initiate T-DM1 if more than 12 weeks since surgery have passed? If patients initiated trastuzumab, could they be switched to T-DM1 within that 12-week period or should they remain on trastuzumab?	The CGP agreed that there is no direct data to support the initiation of T-DM1 as adjuvant therapy if more than 12 weeks have passed since their surgery.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
	Cycles of T-DM1	In the KATHERINE trial, patients who discontinued trastuzumab emtansine early because of toxic effects could complete 14 cycles of treatment with trastuzumab.	Should the 14 cycles of HER2-directed therapy be completed within a specific time frame? Should the cap of a total of 14 cycles of HER2-directed therapy be considered if T-DM1 is recommended for reimbursement?	The CGP agree that patients should complete a maximum of 14 cycles of T-DM1 treatment and if T-DM1 is to be discontinued due to toxicity, that treatment with trastuzumab can be continued to complete one year of HER2-targeted therapy.
	Subsequent therapies	Subsequent therapies in the T-DM1 arm of the KATHERINE trial included trastuzumab (n= 35; 4.7%), pertuzumab (n=11; 1.5%), T-DM1 (n=4; 0.5%), and taxanes (n=17; 2.3%).	For patients who progress during or shortly after completing trastuzumab emtansine (i.e., ≤ 6 months) adjuvant therapy, what would be the appropriate metastatic treatment (e.g. T-DM1, pertuzumab, etc.)? Would it be reasonable to treat patients with T-DM1 in the metastatic setting if they were treated with T-DM1 in the adjuvant setting?	The CGP do not support the use of T-DM1 in the first line metastatic setting after completion of adjuvant T-DM1. Standard HER2 targeted therapy (in the first line metastatic setting) would be pertuzumab plus trastuzumab, if patients fulfill other requirements for that treatment (as per the CLEOPATRA trial)
Comparator	Switch to T-DM1	Patients receiving trastuzumab were not allowed to crossover to T-DM1 in the KATHERINE trial. However, a total of 33 patients (4.6%) in the trastuzumab arm compared to 4 (0.5%) patients in the T-DM1 arm received subsequent therapy with T-DM1.	For patients currently receiving adjuvant therapy with trastuzumab, is it appropriate to switch these patients to T-DM1? If so, is there an appropriate time frame (for example, <6 months)?	The CGP acknowledge the lack of evidence on switching patients currently on trastuzumab to T-DM1. The CGP agree that decision to switch treatment and appropriate time frame should be left to the discretion of the treating oncologist.
Outcomes	Invasive disease-free survival	The primary endpoint of the KATHERINE trial was invasive disease-free survival, defined as the time from randomisation to the date of first occurrence of one of the following invasive-disease events: recurrence of ipsilateral invasive breast tumor, recurrence of locoregional invasive breast cancer, contralateral invasive breast cancer, a distant disease recurrence, or death from any cause. The standardized definition for efficacy outcomes include second primary non-breast cancer as an invasive disease event, and this larger definition was used as a secondary endpoint. The primary outcome for IDFS (HR: 0.50, 95% CI: 0.39, 0.64) and secondary outcome for IDFS including second primary cancer (HR: 0.51; 95% CI: 0.40, 0.66) were consistent.	Was the selection of the endpoints appropriate and of clinical relevance to this indication and therapeutic setting? Should the larger definition have been included as the primary endpoint?	iDFS is a composite end-point that has not been validated in breast cancer and does not follow the STEEP definition (although this may not have a large impact on results based on KATHERINE data). Information on whether improvement in iDFS leads to, or correlates with, increase in cure rates is currently lacking. Ideally, in the absence of improvement in overall survival, an improvement in iDFS should at minimum be accompanied by some improvement in quality of life for a treatment to be justified for reimbursement which is not the case based on data from KATHERINE.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Setting	Countries participating in the trial	The trial was conducted in 268 sites in 28 countries, which included 58 Canadian patients representing the provinces of Ontario, Quebec, Alberta, and British Columbia.	Are there any known differences in the practice patterns between Canada and other countries that the trial was conduced in?	Close to a quarter of patients were recruited from outside North America and Europe where the standard of care of HER2+ breast cancer may be different, potentially influencing the overall outcomes.

1.2.4 Interpretation

Burden of Illness and Need

Breast cancer is the most common malignancy affecting Canadian women.[5] About 15 to 20 per cent of breast cancers overexpress the HER2 receptor. The natural history of HER2 positive breast cancer is generally that of an aggressive tumor with relatively poor prognosis.[6] Fortunately the advent of trastuzumab has significantly improved the outcome of this disease with improvement in overall survival both in early and advanced stage diseases. However, 1 in 4 women who present with early stage HER2+ breast cancer and are treated with trastuzumab based treatments, continue to have recurrence from their breast cancer within 10 years, suggesting a need for more effective therapies.

Trastuzumab emtansine (T-DM1) is the first antibody drug conjugate approved for use in solid tumor.

T-DM1 has been approved for treatment of metastatic HER2+ breast cancer in Canada based on improvement in overall survival in patients who had previously progressed on HER2 targeted therapy for metastatic disease (EMILIA trial)[7] and in patients that had previously received at least 2 lines of HER2 targeted therapy (THERESA trial) compared to relevant comparators.[8] A trial in the first line metastatic setting has demonstrated non-inferiority (but not superiority) of T-DM1 alone or in combination with pertuzumab, compared to trastuzumab plus taxane chemotherapy in terms of progression free survival (MARIANNE trial). [9] Evidence on impact of using T-DM1 in early stage HER2+ breast cancer in long term outcomes was lacking until recently.

Patients that achieve pathologic complete response (pCR) after neoadjuvant treatment have a better overall survival compared to those who do not achieve such response[10], including those with HER2+ disease and this has been demonstrated especially for the HER2 positive subtype (particularly ER negative, HER2 positive).[11] This information offers prognostic value to a patient's care. The extent of improvement in pCR with a treatment in a randomized study (comparative trial) that is necessary to achieve a meaningful improvement in long term outcomes is still unknown. Nevertheless, a significant proportion of women with HER2+ breast cancer who undergo neoadjuvant systemic therapy with trastuzumab containing regimens do not achieve pCR (30-40%); their outcomes are likely to be poorer. These patients are at a relatively high risk of breast cancer recurrence and death from breast cancer. Since the availability of trastuzumab, there have been no new therapies that have been proven in this group of patients to improve their cancer outcomes, by better targeting what is postulated to be a high burden of residual micrometastatic disease. Therefore, development of more effective therapy leading to a decrease in cancer recurrence and improvement in cure in this patient population is required and is desired by patients.

Efficacy

The KATHERINE study compared use of T-DM1 up to 14 cycles versus continuing on trastuzumab in women with HER2+ early breast cancer that had residual disease after receiving at least 6 cycles (16 weeks) of neoadjuvant systemic therapy (with minimum of 9 weeks of trastuzumab and 9 weeks of taxanes).

The primary outcome of the trial, invasive DFS (iDFS), is a composite endpoint, defined in Section 6.3.2.1a of this report. This definition of iDFS is different from the established STEEP definition [12], by excluding second primary invasive non-breast cancers. Both definitions exclude in situ carcinomas, including DCIS and LCIS (non-invasive breast cancers), and non-melanoma skin cancers. The standard STEEP definition of iDFS is often the primary outcome of adjuvant breast cancer trials, as it takes into consideration the difficulty in distinguishing second primary invasive

cancers from breast cancer metastases, and the possibility of second malignancies related to treatment. Of note the primary outcome of the trial, iDFS, has not been validated in the published literature. This composite endpoint likely provides a more conservative estimate of treatment effect, compared to the other secondary iDFS endpoint assessed in this trial (which includes the STEEP defined iDFS).[12]

Secondary end points of the trial are invasive disease-free survival defined the same way as iDFS as per STEEP definition, disease-free survival (including noninvasive breast cancers), overall survival, distant recurrence–free interval, QoL, and safety.

The study met its primary endpoint of iDFS favoring T-DM1, with iDFS rates at 3 years of 88.3% in the T-DM1 group and 77.0% in the trastuzumab group [HR, 0.50; 95% CI, 0.39 to 0.64; P<0.001]. A total of 98 deaths were reported (42 in the T-DM1 group and 56 in the trastuzumab group) but the overall survival analysis did not cross the early reporting boundary (HR for death, 0.70; 95% CI, 0.47 to 1.05). Survival rates at analysis were 94.3% for T-DM1 arm and 92.5% for trastuzumab arm, resulting in an absolute difference in survival between the arms of 1.8%. Analysis of OS adjusting for crossover of the T-DM1 arm to trastuzumab was also conducted and the unstratified results were consistent with the primary analyses (HR: 0.69; 95% CI: 0.45, 1.05, p=0.08).

The study randomized 1486 participants (743 patients in each arm) at 268 centers in 28 countries, over a period between April 2013 and December 2015. Canadian population had a reasonable representation, with participation of 23 patients in total. Close to a quarter of patients (23.7% in T-DM1 arm and 22.9% in trastuzumab arm) were recruited from outside North America and Europe. Specifically, approximately 150 patients were recruited from low-and-middle-income countries (Argentina 4, Brazil, 29, China 13, Columbia 10, Check Republic 9, Guatemala 9, Mexico 15, Panama 7, Peru 5, Serbia 11, Taiwan 31, Turkey 7) where access to HER2 targeted therapy in early as well as advanced stages may be limited. This may marginally limit generalizability of results in Canadian population.

Interpretation and Other Considerations

Discrepancy in receipt of study drugs: Of the 743 patients randomized to each arm, 23 patients assigned to trastuzumab (versus 4 patients assigned to T-DM1) did not receive assigned therapy. Furthermore, there was a large discrepancy on treatment discontinuation due to toxicity between the arms, with 18.0% of patients on T-DM1 (who were allowed a switch to trastuzumab to complete the rest of the treatment) compared to 2.1% of patients in the trastuzumab arm discontinuing the drug due to toxicity. Both of these discrepancies in receipt of therapy are notable, and may have two implications: First, it underscores notable difference in tolerability of the drugs and implicitly on their quality of life, albeit in the short term. Second, this may have led to inflation of the observed difference in outcome between the arms because patients who discontinued on T-DM1 could still derive benefits of HER2 targeted therapy. Although the Review Team are not aware of the exact methods used, post-hoc exploratory analyses was performed by the sponsors adjusting for crossover to trastuzumab of the primary endpoint of iDFS (HR: 0.47; 95% CI: 0.36, 0.62) and secondary endpoint of OS (HR: 0.69; 95% CI: 0.45, 1.05), revealed results that were consistent with the primary analysis.[13]

Protocol deviations: More patients on T-DM1 had major protocol deviation compared to trastuzumab, of which the vast majority were on-study protocol deviation (as opposed to those related to exclusion/inclusion criteria) which occurred in 83 (11.2%) of patients in the T-DM1 arm compared to only 9 (1.2%) patients in the trastuzumab arm. In particular, the dose was not reduced or held as per the protocol despite toxicities in 78 (10.5%) patients in the T-DM1 arm compared only 4 (0.5%) patients in the trastuzumab arm. The CGP agreed that this imbalance in receipt of therapy may have direct impact on outcomes, favoring T-DM1 arm. An analysis to assess for deviation bias related to dosing was conducted by the sponsor by excluding the 10.5% (n=78)

and the 0.5% (n=4) of patients in the T-DM1 and trastuzumab arms, respectively, with a deviation of not having dose reduced or held as per protocol. The results showed a HR consistent with the primary iDFS analysis (HR: 0.50; 95% CI: 0.39, 0.66).[13]

Use of subsequent treatment: It is also important to note that of the 131 (18.2%) patients in the trastuzumab arm that received anticancer therapy at recurrence, only 48 (6.7%) were treated with pertuzumab and only 33 (4.6%) were treated with T-DM1, even though both these treatments are known to prolong overall survival in metastatic HER2+ breast cancer. Post-recurrence therapies in T-DM1 arm were lower, which is explained by fewer recurrences observed in that arm. This is noteworthy because in Canada, almost everyone without major contraindications will receive pertuzumab and trastuzumab in the first line, and T-DM1 in second (or later) line. The imbalance of subsequent therapies between treatment arms may confound the results in an unknown direction.

Discrepant rates of permanent discontinuation of treatment: More patients on trastuzumab arm were reported to have discontinued the study permanently without further follow up compared to T-DM1 (19.7% versus 14.5%).[2,14] The most common reason for permanent discontinuation was reported as "patient decision".[2,14] This may impact outcomes because of differential censoring.

Treatment of lower stage HER-2 positive cancers: KATHERINE required participants to have received at least six cycles of neoadjuvant chemotherapy. Although acknowledging the benefit of T-DM1 across all subgroups, in clinical practice, many lower stage HER-2 positive patients (node negative disease and <2cm) may optimally be treated with initial surgery, followed by adjuvant chemotherapy of less relative toxicity, compared to standard anthracycline-taxane-trastuzumab regimens. In particular, there is single-arm data to support that HER-2 positive cancers that are node negative and less than 3 cm have excellent outcomes with surgery and post-operative single-agent weekly paclitaxel and trastuzumab.[15] T2 tumours consisted of 9% of this study population. One could anticipate that an increasing number of patients may be offered neoadjuvant therapy in order to have a better sense of disease response, prognostication, and the ability to access adjuvant T-DM1 if funded, but risk of harm with such approach in lower risk population needs to be considered. Clinicians and patients alike will ideally balance these approaches, although the risk of overtreatment (particularly with longer and more toxic chemotherapy) in these earlier stage patients who already have excellent outcomes with better tolerated regimens cannot be ignored. In the afore mentioned APT trial only 4 distant recurrences out of 410 participants were noted after 7 years of follow-up - an outcome that is hard to improve on. Therefore, exposing these patients to more aggressive treatment with little room for improvement in outcomes is noteworthy. A randomized controlled trial in this setting would be difficult to design and conduct.

KATHERINE included node negative disease at presentation [476/1486 (32%)], and tumors <2cm [180/1486 (12%)]. The sub-group analysis, although considered exploratory, was aligned with the ITT results and supports benefit of adjuvant T-DM1 in those subgroups. However, in clinical practice clinicians and patients alike will ideally balance the treatment approaches for patients with lower stage HER-2 positive disease (e.g. patients may optimally be treated with initial surgery, followed by adjuvant chemotherapy of less relative toxicity, compared to standard anthracycline-taxane-trastuzumab regimens).

Impact of single Her2 targeted therapy in neo-adjuvant setting: An additional HER2 targeted therapy was used in the neoadjuvant setting in 19.5% of patients in the KATHERINE study. However, in Canada only trastuzumab is currently reimbursed in the neo-adjuvant setting. Use of more than one HER2 targeted therapy improves pathologic complete response rates by close to 2-folds (but not necessarily the long-term outcomes: a reason why this is not reimbursed in Canada).[16,17] The implication of this is that higher proportion of patients treated in Canada will have residual disease after neoadjuvant chemotherapy and be treated with T-DM1 should it be reimbursed.

Smaller difference in rates of distant recurrences: The event that is most consequential for patients with early stage breast cancer is development of distant metastatic disease. This is because distant metastasis is a necessary event to lead to death from breast cancer, as opposed to patients with locoregional recurrence or contralateral breast cancer alone, many of whom may be considered for more radical "curative intent" therapy. Difference in distant recurrence as the invasive-disease event was smaller (compared to iDFS) between the groups: three-year event free rate for distant recurrence-free interval was 83% versus 89.7% for trastuzumab and T-DM1, respectively.

Patient Reported Outcomes and Quality of Life: Patients enrolled into KATHERINE were asked to complete the EORTC QLQ-C30 and QLQ-BR23 questionnaires.[4] Both of these quality of life measures are well validated in breast cancer, compared to patients on trastuzumab arm, a higher proportion of patients in the T-DM1 arm reported a clinically meaningful deterioration at any point in the study in role functioning (41% vs 49%), appetite loss (28% vs 38%), constipation (38% vs 47%), fatigue (61% vs 66%), nausea/vomiting (30% vs 39%), and systemic therapy side effects (36% vs 49%) except for diarrhea (27% vs 22%). Collectively, these data suggest that with regards to almost all quality of life measurements, T-DM1 had a worse impact compared to trastuzumab. Indeed, patients who are treated with T-DM1 (but not trastuzumab) would also require regular bloodwork to check for platelets and liver function, leading to added inconvenience. One should note, however, that longer term QoL metrics have not been reported from this study. Short-term decreases in QoL have been seen in other adjuvant breast cancer therapies, attributable to the increased toxicities sometimes seen with novel agents, but overall benefits have so far been marginal at most with such agents. Given that most impact on QoL in adjuvant treatments are while patients are still on therapy, short term effect on QoL are paramount because large number of "cured" patients need to be treated to prevent recurrence in a minority.

Potential higher local recurrence after breast-conserving therapy with neoadjuvant treatment: KATHERINE included 75% of patients that were operable but received neoadjuvant therapy (62.8% had T1 or T2 disease). A recent meta-analysis of 10 randomized controlled trials in early breast cancer has demonstrated that tumors downsized by neoadjuvant therapy might have higher local recurrence after breast-conserving therapy than might tumors of the same dimensions in women who have not received neoadjuvant therapy.[18] In KATHERINE, approximately 40% of patients in both arms received breast conserving surgery. Given that there is likely to be a shift in practice pattern with smaller HER2+ breast cancer patients receiving neoadjuvant therapy and treated with breast conservation therapy if T-DM1 is reimbursed in this setting, this potential additional unintended harm must be considered by treating oncologists.

Patient advocacy input: Two patient advocacy groups provided input (31 patients in the first group and 55 in the second). Most patients in the first group were non-Canadians. Only 6 patients in the first group and none in the second group had any experience with T-DM1. Some of these patients had metastatic breast cancer rather than early stage disease. Although the patient input was highly valuable to understand the expectations of breast cancer patients in general, it was not fully representative of the population in question for this review. In general, the patient input demonstrates patients' desire to access treatments that are effective and extend survival.

Principle of treatment for early stage breast cancer: The primary aim of adjuvant treatment of breast cancer patients is to improve "cure rates". Although the invasive disease-free interval was significantly different favoring T-DM1, whether that translates into improving cure rates (i.e., improvement in overall survival) is yet to be seen. As stated above, T-DM1 is already approved for use in metastatic breast cancer based on significant improvement in overall survival. Although T-DM1 may maintain its efficacy in patients with metastatic disease that are exposed to this drug in adjuvant setting based on recurrence-free interval after adjuvant T-DM1, this assumption is currently not based on data.

Safety

There were more patients in the T-DM1 arm that experienced any AE (n=731; 98.8%) and grade ≥3 AEs (n=190; 25.7%) compared to the trastuzumab arm (any grade AEs: n=672, 93.3%; grade ≥3 AEs: n=111, 15.4%). The most commonly occurring any grade AEs in both treatment arms was fatigue (T-DM1: n=366, 49.5% vs. trastuzumab: n=243, 33.8%). The most commonly occurring grade ≥3 AE was decreased platelet count, which occurred in 5.7% (n=42) of patients in the T-DM1 arm and 0.3% (n=2) of patients in the trastuzumab arm. Increased aspartate aminotransferase that occurred in 28.4% of patients (compared to 5.6% in the trastuzumab arm). Serious adverse events occurred in 94 (12.7%) patients in the T-DM1 arm compared to 58 (8.1%) patients in the trastuzumab arm. The most common serious adverse event included mastitis and decreased platelet count. Mastitis occurred in 8 (1.1%) patients in the T-DM1 arm and 6 (0.8%) in the trastuzumab arm, and decreased platelet count occurred in 10 (1.4%) patients in the T-DM1 arm and no patients in the trastuzumab arm. In the T-DM1 group, the most common adverse events leading to discontinuation of the drug were laboratory abnormalities (decreased platelet count [in 4.2%], elevated blood bilirubin level [in 2.6%], elevated aspartate aminotransferase level [in 1.6%], and elevated alanine aminotransferase level [in 1.5%]), peripheral sensory neuropathy (in 1.5%), and decreased ejection fraction (in 1.2%). There was 1 (0.1%) patient who died in the T-DM1 arm due to an AE and no patients that died in the trastuzumab arm. This patient had a low platelet count and fell at home and died of intracranial hemorrhage. Cardiac side effects were not different between the groups.

While there were differences in AE rates between study groups, no new safety signals detected in the T-DM1 treatment group, and there was no difference in incidence of fatal AEs (deaths) between the treatment groups.

1.3 Conclusions

There was incomplete consensus amongst the CGP regarding the overall clinical conclusions. Two out of three CGP members agreed that T-DM1 is a meaningful option for the patient population included in the study based on the current data from KATHERINE. Lack of consensus remained on the relative impact of trial conduct/bias on the overall results (although the extent to which these factors may have impacted the overall results is uncertain), the relevance of iDFS as an important endpoint (versus early OS data), and the risk of overtreatment/unintended consequences of treating smaller, node negative tumours (as described below and in the Interpretation). Based on this, the CGP concluded that there may be a clinically meaningful net overall benefit to T-DM1 compared with trastuzumab, in adjuvant treatment of breast cancer for up to 14 cycles, in patients who do not achieve a pathologic complete response (residual invasive disease in breast and/or lymph nodes), after completing at least 6 cycles (16 weeks) of a conventional pre-operative chemotherapy regimen that consists of at least 9 weeks of trastuzumab and at least 9 weeks of a taxane. One member of the CGP noted that in the presence of an already effective treatment (i.e., trastuzumab), uncertainties exist as to whether the risk of harm (due to use of more aggressive chemotherapy in order to qualify for adjuvant T-DM1, as well as from T-DM1 itself) is justified in the context of reported benefits in all early stage HER2+ breast cancer.

Overall, the CGP agreed that adjuvant T-DM1 be considered for patients treated with neoadjuvant therapy (including a taxane and trastuzumab) who have residual invasive disease in the breast and/or lymph nodes on final surgical pathology. Given the lack of complete consensus amongst the CGP, one consideration is to limit this therapeutic option to patient with initial ≥2 cm tumours, with a mechanism for re-evaluating reimbursement recommendations once longer-term data (especially as it relates to OS and toxicity) are available. One of the CGP members suggested that oncologists should consider this approach only in patients who are usually considered for the

type and duration of chemotherapy needed to be eligible for KATHERINE study, in order to minimize harms from overtreatment.

In reaching this conclusion, the CGP considered the following:

- There was a statistically significant improvement in iDFS in a phase III randomized controlled trial showing 3-year iDFS rates of 88.3% with T-DM1 (compared to 77%) for current standard of care. Overall survival analysis did not cross the early reporting boundary, and the absolute difference in survival between the arms was 1.8% (94.3% for T-DM1 versus 92.5% for trastuzumab). This may represent a trend towards improving OS to a greater degree as trial data matures, but evidence as to whether or not improvement in iDFS leads to or correlates with increase in OS is currently lacking.
- The results will apply to male patients as they were included in the trial. Similarly, they also apply to patients who received additional HER2 targeted therapy in neoadjuvant setting.
- There were more side effects with T-DM1, and significantly higher rates of treatment discontinuation related to toxicity with T-DM1 (18.0% versus 2.1%). Also, more patients on trastuzumab did not receive the protocol assigned therapy compared to T-DM1 (23 patients versus 4 patients). Patient who discontinued T-DM1 could receive trastuzumab to complete their HER2 targeted therapy. Patients who discontinued (or did not receive) trastuzumab did not receive adjuvant T-DM1 or other HER2 targeted therapy. This may bias results in favor of the T-DM1 arm.
- Use of adjuvant T-DM1 is not associated with improvement of patient reported outcomes and quality of life. Conversely, there was noticeable deterioration in most domains of the well-validated quality of life measures used in the study in the T-DM1 arm. However, long term QoL data is often not available, and it is not known whether patient preference would be to accept the balance of toxicity and clinical benefit for this particular therapy.
- Of the 131 patients in trastuzumab arm that received further anticancer therapy, only 48 were treated with pertuzumab and only 33 were treated with T-DM1. Both of these treatments are known to improve overall survival for metastatic disease. Majority of patients with HER2+ metastatic breast cancer in Canada would be treated with these life-prolonging therapies at recurrence.
- KATHERINE clinical trial included significant proportion of patients that presented initially with surgically resectable tumors: over 30% of patients were clinically node negative, and 12% had <2 cm tumors. Reimbursement of T-DM1 in node negative tumors < 3cm (who already have excellent outcome with much less aggressive chemotherapy such as weekly paclitaxel and trastuzumab) will likely lead to a significant change in practice pattern towards more frequent use of neoadjuvant treatment in earlier stage HER2+ cancers leading to potential overtreatment in this patient population with potential use of aggressive neo-adjuvant chemotherapy unnecessarily, followed by T-DM1 in those with residual disease.
- Close to a quarter of patients were recruited from outside North America and Europe where the standard of care of HER2+ breast cancer may be different, influencing the overall outcomes.
- T-DM1 is already approved for metastatic HER2+ breast cancer and improves overall survival in that setting. It is possible that retreatment with T-DM1 in metastatic setting may still be beneficial in those with longer time to recurrence after completion of adjuvant t-DM1, although there is no data to confirm this assumption, guide acceptable duration of time to

recurrence, or if the extent of such benefit will be comparable to that observed in T-DM1 naïve population.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Breast Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Breast Cancer is a commonly diagnosed malignancy in Canadian women, with 27,200 new cases diagnosed in 2019.[5] Approximately 1 in 8 women will be diagnosed with breast cancer in their lifetime.[5] Fortunately, the majority of these cases represent early stage, are potentially curable disease. Improved diagnosis and more effective systemic therapy have contributed to improved breast cancer outcomes.

A proportion of breast cancers (15-30%) overexpress HER2/neu, an epidermal growth factor receptor.[19] Her2/neu (referred to hereafter as HER2) is a transmembrane receptor tyrosine kinase in the ERBB family. HER2 overexpression leads to excessive stimulation of this signaling pathway, leading to uncontrolled growth, reduced apoptosis, and metastasis of malignant cells.[6] HER2 overexpression has historically been associated with a more aggressive disease course, with earlier metastatic potential, and a predilection for metastasis to the central nervous system. Fortunately, the outcome of HER2 positive breast cancer has improved significantly in the last two decades due to advent of effective targeted therapies.

2.2 Accepted Clinical Practice

Several randomized controlled trials have demonstrated improvement in outcomes of patients with early stage HER2 positive breast cancer with the use of trastuzumab (Herceptin), an anti-HER2 monoclonal antibody, in combination with adjuvant chemotherapy. The 3-year disease-free survival (DFS) rate for patients receiving trastuzumab in these studies, all of whom had operable disease, was approximately 85% to 90% [6,20,21]. Chemotherapy backbone for combination with trastuzumab in this setting generally contains an anthracycline and/or a taxane containing regimens, is given for at least a total of 6 cycles, at least 9 weeks of a taxanes, and a total of 1 year of trastuzumab.

Trastuzumab binds the extracellular domain of the HER2 receptor, preventing homodimerization with other HER2 receptors, and subsequent downstream auto- phosphorylation of intracellular tyrosine domains. Trastuzumab was initially approved in 1998 for treatment of HER2 positive metastatic disease.[19] This indication was expanded by the US Food Drug Administration (FDA) for the treatment of early breast cancer (EBC) in 2004. The current standard of care therapy for HER2 positive EBC is 12 months of adjuvant trastuzumab, in combination with anthracycline and/or taxane-based chemotherapy.[6,20] While trastuzumab is generally well tolerated, it is associated with cardiac toxicity, such as cardiomyopathy, decreased ejection fraction, and in severe cases, signs/symptoms of congestive heart failure.[20] This cardiac toxicity is hypothesized to be related to impairment of normal HER2-mediated cellular repair pathways, and is often reversible with discontinuation of therapy and medical management of cardiomyopathy.[21]

Recently, pertuzumab (Perjeta), a second monoclonal antibody against HER2 receptor, was evaluated by CADTH for use in adjuvant treatment of early breast cancer patients at high risk of recurrence in combination with trastuzumab and chemotherapy. This combination received a negative reimbursement recommendation because the pCODR Expert Review Committee (pERC) was not satisfied that there is a clinically meaningful added benefit of using this strategy

compared to current standard of care in adjuvant setting (trastuzumab and chemotherapy). Previously, use of pertuzumab in combination with trastuzumab and a taxane chemotherapy for the treatment of metastatic HER2 positive breast cancer as the first-line therapy was recommended for funding across Canada because of impressive improvement in survival of these patients compared to trastuzumab and chemotherapy alone.

Trastuzumab emtansine (T-DM1) is a novel antibody-drug conjugate, composed of 3 main components: (1) trastuzumab, (2) DM1, an anti-microtubule agent derived from maytansine; and succinimidyl 4-[N-maleimidomethyl] cyclohexane-1-carboxylate (SMCC)], and (3) a thioether linker molecule used to conjugate DM1 to trastuzumab. Trastuzumab emtansine, here after referred to as T-DM1, is 400-fold more potent than paclitaxel and binds to HER2 with an affinity similar to that of unconjugated trastuzumab.

T-DM1 has been assessed previously for treatment of previously treated unresectable locally advanced or metastatic setting in two separate phase III randomized clinical trials. First of these, the EMELIA study, compared T-DM1 to lapatinib and capecitabine in patients with HER2+ metastatic breast cancer treated previously with trastuzumab and a taxanes and showed statistically significant improvement in PFS and OS.[7,22] The second trial, the THERESA study, compared T-DM1 to treatment of physicians' choice after progression on at least two lines of HER2 targeted therapy for advanced/metastatic disease, demonstrated significant improvements in both PFS and OS with T-DM1 compared to treatment of physicians' choice.[8,23] A third study, the MARIANNE study, was a 3-arm phase III clinical trial of T-DM1 plus placebo versus T-DM1 plus pertuzumab versus trastuzumab plus taxane as first line treatment in HER2-positive progressive or recurrent locally advanced or metastatic breast cancer patients. Data from the MARIANNE trial concluded that T-DM1 and T-DM1 plus pertuzumab were both non-inferior (but not superior) to taxane plus trastuzumab in the studied patient population.[9] All of these studies reported that T-DM1 was tolerated well by the study population with no unacceptable safety signals. Additionally, a previous phase 2 trial showed that administration of 17 cycles of T-DM1 after an anthracycline regimen was feasible and was not associated with unacceptable toxic effects in patients with HER2-positive early breast cancer.[24] As such, pERC has previously recommended reimbursement of T-DM1 for treatment of metastatic breast cancer following at least one line of HER2 targeted therapy in advanced or metastatic setting based mainly on the EMELIA study.

Long term outcomes of systemic therapy used in adjuvant and neo-adjuvant settings in breast cancer are comparable based on existing meta-analysis (although several of the included trials were conducted before the era of tumour receptor profiling and targeted therapies). Neoadjuvant (pre-operative) chemotherapy plus targeted HER-2 antibody therapy is considered a standard of care for locally advanced, unresectable tumours. In early stage HER2+ breast cancer, the main rationale for neoadjuvant systemic treatment is: (a) to shrink local tumor in order to facilitate less extensive (potentially breast conservation and less nodal surgery), (b) to target any microscopic distant disease early, and (c) to assess response of the tumor to systemic treatment directly (in vivo). Clinical data has demonstrated that patients with HER-2 positive cancer that receive adjuvant chemotherapy in a timely manner have better outcomes; as such, these patients may in fact benefit from pre-operative therapy, although no prospective data exists to support this. In addition, patients that achieve pathologic complete response (pCR) after neoadjuvant treatment have a better overall survival compared to those who do not achieve such response, including those with HER2+ disease.[11] This information offers prognostic value to a patient's care. The extent of improvement in pathologic complete response with a treatment in a randomized study that is necessary to achieve a meaningful improvement in long term outcomes is still unknown.

Nevertheless, a significant proportion of women with HER2+ breast cancer who undergo neoadjuvant systemic therapy with trastuzumab containing regimens do not achieve pathologic

complete response. These patients are at a relatively high risk of breast cancer recurrence and death from breast cancer. Since the availability of trastuzumab, there have been no new therapies that have been proven in this group of patients to improve their cancer outcomes, specifically by better targeting what is postulated to be a high burden of residual micro metastatic disease. Therefore, development of more effective therapy leading to a decrease in cancer recurrence and improvement in cure in this patient population is required and is desired by patients. Recently, a phase III randomized controlled study, the KATHERINE trial was reported. The KATHERINE study was designed to evaluate the use of adjuvant T-DM1 (versus trastuzumab) in patients who had HER2-positive early breast cancer and residual invasive cancer at surgery after completion of neoadjuvant chemotherapy plus HER2-targeted therapy. Trastuzumab emtansine received FDA approval for this indication in May 2019. The KATHERINE study is the basis of the current CADTH review.

2.3 Evidence-Based Considerations for a Funding Population

The philosophy behind treatment of metastatic breast cancer and early stage breast cancer are different. In metastatic breast cancer virtually every person receiving the treatment has a potentially fatal disease whereas a vast majority of patients treated in adjuvant setting are already cured with current standard of care therapy (in KATHERINE, 77% of patients in the control arm did not have an event at the time of analysis). If reimbursed, a large population of "cured" patients therefore need to be treated with T-DM1 (instead of trastuzumab) to achieve a delay in recurrence in a relatively small population, without complete knowledge of whether this approach will make patients live longer or better: overtreatment in early stage breast cancer therefore has potential for considerable harms due to side effects, resource utilization, inconvenience of treatment on quality of life, and financial sustainability for the system. Hence the long-term benefit risk ratio of such treatments is important to determine.

The evidence-based population suitable for consideration of T-DM1 in the early breast cancer includes:

1. Histologically confirmed, HER2-positive, nonmetastatic, invasive primary breast cancer
2. Clinical stage at presentation: T1–4, N0–3, M0 (Patients with T1a/bN0 tumors will not be eligible)
3. Patients had to have completed at least six cycles (total duration of at least 16 weeks) of a conventional preoperative chemotherapy regimen containing a minimum of 9 weeks of taxane-based therapy and 9 weeks of trastuzumab therapy (Slightly shorter duration in case of dose dense regimens)
4. Surgical removal of all clinically evident disease in the breast and lymph nodes
5. Patients should have residual invasive disease detected pathologically in the surgical specimen of the breast or axillary lymph nodes after completion of taxane-based neoadjuvant chemotherapy administered with HER2 targeted therapy
6. Adequate baseline hepatic, renal, and bone marrow functions
7. Normal left ventricular ejection fraction (LVEF) (≥55 percent as measured on echocardiography or multiple gated acquisition [MUGA] scanning)
8. Patients with concurrent severe, uncontrolled systemic disease, serious active infections, female patients that are currently pregnant or lactating, have history of intolerance, including Grade 3 to 4 infusion reaction or hypersensitivity to trastuzumab or murine proteins were excluded from the study.

Current patient population eligible for adjuvant use of T-DM1 may differ from those enrolled into the KATHERINE trial in that: Majority of patients in KATHERINE study (>80%) used trastuzumab as single agent neo-adjuvant HER2 targeted therapy with only minority (<20%) receiving trastuzumab plus another HER2 targeted therapy. Use of a second HER2 targeted therapy such as pertuzumab

has increased since the conduct of KATHERINE study due to recent approval by FDA of pertuzumab in neo-adjuvant and adjuvant settings. Of important note, due to chronological sequence of development of HER2 targeted therapies, evidence is currently lacking regarding efficacy of HER2 targeted therapies, including T-DM1, in population of patients that develop metastatic setting after exposure to T-DM1 in adjuvant setting.

2.4 Other Patient Populations in Whom the Drug May Be Used

The following patient groups may also be considered when generalizing the results of this review:

- Inflammatory breast cancer
- Male breast cancer

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient groups provided input on trastuzumab emtansine (Kadcyla) for HER2-positive early breast cancer and their input is summarized below: Rethink Breast Cancer (RBC) and The Canadian Breast Cancer Network (CBCN).
RBC conducted online patient surveys between June 12th and July 12th, 2019. The survey asked questions about the impact of breast cancer on the lives of patients, the effects of current treatments and their willingness to accept side effects for improved health outcomes. The survey also included specific questions directed to patients that have experience with trastuzumab emtansine. Potential respondents were identified through messages to RBC's mailing list as well as the Young Women's Network and partner organizations. Messages were also posted on Facebook and Twitter as well as the Breastcancer.org, Cancer Connection and Cancer Survivors Network online discussion forums. A total of 31 women completed the patient survey. Of these respondents, 9 were from Canada (representing British Columbia, Ontario & Saskatchewan), 5 were from the United States and 17 chose not to answer. All 31 respondents had a diagnosis of HER2-positive early breast cancer and 6 respondents had treatment experience with trastuzumab emtansine. No caregivers were consulted.

The CBCN obtained information through a CBCN online survey conducted in 2017, the survey results of which are published in The Lived Experience Report. This online survey was distributed in English and French to Canadians who had experienced a breast cancer diagnosis. The survey questions were comprised of a combination of scoring options and free-form commentary. Patients were contacted through CBCN's communication channels including social media, organization website and e-newsletters. A total of 278 early-stage breast cancer patients responded to the survey. Data for this submission came specifically from the survey respondents who were diagnosed with HER2-positive early stage breast cancer, which was a total of 55 patients. There was at least 1 respondent from all provinces and territories, except for Nunavut and Yukon. Most patients were from Ontario (n=12) and there were 12 respondents that did not disclose their geographical location. None of the patients in this survey indicated that they had experience with trastuzumab emtansine. Slightly more than half of the patients were aged 30-49 (n=33), whereas 22 patients were aged 50-69. There were no patients under 30 years of age or over 70 years of age included in the survey. The CBCN also conducted a review of current studies and grey literature to identify issues and experiences that are commonly shared among women living with breast cancer.

From a patient's perspective, HER2-positive early breast cancer has a significant physical and psychological impact on the lives of patients, their caregivers and loved ones. The disease limits the ability of patients to work and engage in their daily tasks. Current treatments for HER2 breast cancer include a combination of surgery, chemotherapy, targeted therapy, and radiation. Some of the most significant side effects of current therapies reported by patients are cardiac toxicity, fever, fatigue, diarrhea, muscle and joint pain, and nausea. The CBCN also commented that there are significant financial challenges endured by patients of HER2-positive early stage breast cancer due to loss of income, drug and travel costs. RBC was able to recruit survey respondents who had previous experience with trastuzumab emtansine, the majority of whom spoke highly favourable of the drug. Most of these patients reported that trastuzumab emtansine had significantly improved their quality of life and helped control the disease, as they found the drug very tolerable with minimal side effects. Also, no patient reported any difficulty accessing the drug. The CBCN and RBC both concluded that reduced risk of recurrence and ability to manage side effects were some of the most important patient values. Respondents from both RBC and CBCN however, also mentioned that they are willing to tolerate some minimal side-effects in exchange of a decreased risk of recurrence. CBCN commented that since the side effects of trastuzumab emtansine are tolerable and reversible, this drug is an optimal option for HER2-positive early breast cancer as it aligns very well with their values.

Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification.

Please see below for a summary of specific input received from the patient advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with HER2-positive early breast cancer

The patients surveyed by RBC were at different phases of the disease and treatment process as follows:

- Five of the 31 respondents were currently receiving first-line treatment
- Five had no evidence of disease for more than two years
- Four indicated that they were in a different phase of treatment
- Four were under surveillance following treatment
- Four had no evidence of disease for less than six months
- Four had no evidence of disease for between six months and two years
- Two were receiving third-line treatment or higher
- One was receiving second-line treatment
- One was receiving treatment after recurrence
- One respondent didn't answer the question

The most commonly reported cancer symptom was fatigue (89%, n=18), followed by insomnia (39%), nausea, diarrhea and constipation (28% each).

The CBCN reported that early stage HER2-positive breast cancer has a significant impact on the lives of patients and their families, affecting both their physical and emotional well-being. Most patients with early-stage disease will undergo a variety of treatments that may include surgery, chemotherapy, targeted therapy, and radiation. These treatments not only disrupt their daily life but also have many side effects that are coupled with the emotional impact of breast cancer. The CBCN reported that HER2-positive breast cancer represents approximately 20% of all breast cancers and is associated with an aggressive natural history. Thus, patients are more mindful of the risk of recurrence and increased risk of death with this diagnosis. Over 90% of respondents to the CBCN 2017 survey indicated that reducing the risk of cancer returning and the effectiveness of treatments were the most important considerations. Quality of life was also indicated as a key factor in selecting treatments, with 58% indicating that it was very important and 28% indicating that it was important. Minimal side effects were another important factor, with 32% indicating this was very important and 39% indicating that it was important. The CBCN additionally commented that it's important for new therapies for HER2-positive breast cancer to reduce the risk of recurrence without negatively impacting quality of life. The ability to properly manage side effects is critical to minimize the impact on a patient's quality of life and daily living. Below are some key patient comments:

> *"I wanted a treatment that had the best chance of beating the cancer the first time"*
>
> *"I am a mother to 3 children. I wanted to be aggressive in order to increase my changes of survival"*

3.1.2 Patients' Experiences with Current Therapy for HER2-positive breast cancer

All 31 respondents of the RBC survey provided information about the treatments that they had undergone since their diagnosis. Trastuzumab was by far the most common form of treatment as illustrated in Table 1. Similarly, the CBCN reported that most patients receive a combination of anti-HER2 therapy with trastuzumab, in addition to standard chemotherapy.

Table 1. Treatments Received by Patients Since Diagnosis

Treatments Received	n	Treatments Received	n
Trastuzumab (Herceptin)	29	Epirubicin (Pharmarubicin)	3
Docetaxel (Taxotere)	16	Fluorouracil (Adrucil)	3
Paclitaxel (Taxol)	14	Zoledronic acid (Zometa)	2
Cyclophosphamide (Cytoxan)	13	Goserelin (Zoladex)	2
Doxorubicin (Adriamycin)	13	Capecitabine (Xeloda)	2
Pertuzumab (Perjeta)	6	Lapatinib (Tykerb)	1
Carboplatin (Paraplatin)	6	Leuprorelin (Lupron)	1
Tamoxifen (Nolvadex)	5	Exemestane (Aromasin)	1

The most commonly reported side effects of these treatments reported in the RBC survey were: fatigue (90%, n=31), followed by diarrhea (60%), insomnia (60%) and headaches (50%). The most difficult to tolerate side effects were reported to be fatigue, diarrhea, bone pain, brain fog, constipation, mouth sores and nausea. The respondents were also asked to rate how much they agreed that previous therapies, excluding trastuzumab emtansine, were able to manage their breast cancer symptoms (see Table 2). On a scale of 1 (strongly disagree) to 10 (strongly agree), the average score was 6.1 (n=23).

Table 2: Respondent ratings on how much they agreed that previous therapies, excluding trastuzumab were able to manage their breast cancer symptoms.

Rating	Responses n, (%)	Rating	Responses n, (%)
1	3, (13.04)	6	3, (13.04%)
2	1, (4.35%)	7	5, (21.74%)
3	0, (0.00%) 0	8	1, (4.35%)
4	0, (0.00%)	9	1, (4.35%)
5	3, (13.04%)	10	6, (26.09%)

The CBCN commented that patients experienced a broad range and severity of side effects from currently available therapies for HER2-positive breast cancer. Patients were willing to manage and endure some toxicity to reduce their risk of recurrence; however, acceptability and tolerability

varied among patients. Some of the side effects of therapies for HER2-positive breast cancer reported in the CBCN 2017 survey were: cardiac toxicity, fever, fatigue, diarrhea, muscle and joint pain, and nausea.

The RBC survey asked patients to evaluate the importance of different outcomes for their breast cancer treatment on a scale of 1 (not important) to 5 (very important). Respondents ranked all outcomes as important but prioritized long-term health outcomes, with all patients giving the highest score to preventing recurrence, and 28 of 31 (90%) patients doing the same with controlling disease (see Table 3). One patient commented the following: *"To keep cancer at bay or gone forever means everything."*

Table 3: Respondent evaluations on importance of difference outcomes for treatment

Importance of outcome	1 - not important	2	3	4	5 – very important	Average
Controlling disease	0.00% 0	0.00% 0	0.00% 0	9.68% 3	90.32% 28	4.90 31
Reducing symptoms	3.23% 1	0.00% 0	35.48% 11	16.13% 5	45.16% 14	4.00 31
Maintaining quality of life	0.00% 0	0.00% 0	3.23% 1	12.90% 4	83.87% 26	4.80 31
Managing side effects	0.00% 0	3.23% 1	22.58% 7	32.26% 10	41.94% 13	4.13 31
Preventing recurrence	0.00% 0	0.00% 0	0.00% 0	0.00% 0	100.00% 31	5.00 31

Similar to the results of the RBC survey, a majority (90%) of the patients from the CBCN survey indicated that reducing the risk of recurrence and the effectiveness of treatments were the most important considerations. The CBCN commented on the challenge of managing early-stage HER2 positive breast cancer as patients have limited treatment options available to them. As HER2 positive breast cancers have been clinically demonstrated to have a higher risk of recurrence than HER2 normal tumors, the goal of therapy is to target cancer cells in the body and reduce the risk of disease recurrence.

The CBCN further commented on the financial burden of treating and managing breast cancer. Research on the financial impact of breast cancer identified that 80% of breast cancer patients reported a negative financial impact due to their illness, 44% of patients have used their savings and 27% have taken on debts to cover costs. These findings were reported to be consistent with the responses in the CBCN's survey of 55 HER2-positive early stage breast cancer patients. Specific financial challenges, as reported in the RBC survey, included lost income due to work absence (63%, n=31), followed by parking costs (33%), drug costs and travel costs (20% each). A total of 48% of respondents reported that they required financial assistance due to the costs associated with cancer and its treatment.

3.1.3 Impact of HER2-positive early breast cancer and Current Therapy on Caregivers

The CBCN commented that the diagnosis of HER2-positive breast cancer not only has a significant impact on the life of patients, but also their families. No information from caregivers was sought by CBCN and RBC.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Trastuzumab Emtansine (TDM1)

Six of the 31 patients of the RBC survey had received trastuzumab emtansine for treatment of HER2-positive early breast cancer, none of whom had any difficulty accessing the drug. The patients were asked to rate the change in their quality of life on trastuzumab emtansine compared to other therapies they had received, on a scale of 1 (much worse) to 5 (much better). While respondents felt that trastuzumab emtansine had improved their quality of life in all areas, its effect on controlling disease and maintaining quality of life was especially dramatic (see Table 4).

Table 4. Respondent ratings on change in quality of life on trastuzumab compared to other therapies

Change to quality of life on trastuzumab emtansine	1 – much worse	2	3	4	5 – much better	Average
Metastatic cancer symptoms (%), n	0.00% 0	0.00% 0	50.00% 3	16.67% 1	33.33% 2	3.83 6
Drug side effects (%), n	16.67% 1	16.67% 1	16.67% 1	16.67% 1	33.33% 2	3.33 6
Maintaining quality of life (%), n	0.00% 0	16.67% 1	16.67% 1	0.00% 0	66.67% 4	4.17 6
Controlling disease (%), n	0.00% 0	0.00% 0	33.33% 2	0.00% 0	66.67% 4	4.33 5

Three of the six patients (50%) reported that trastuzumab emtansine helped to manage their cancer symptoms, specifically breast pain, nausea, constipation, fatigue and insomnia. Nausea, anemia, peripheral sensory neuropathy, thrombocytopenia and reduced heart function were all identified as side effects. When asked how much they could tolerate the side effects associated with trastuzumab emtansine on a scale of 1 (completely intolerable) to 10 (completely tolerable), the average rating was 9 which indicated that these respondents found trastuzumab emtansine very tolerable, with one patient commenting, *"Overall, it was one of the easiest meds to tolerate"*. One patient, however, reported that she found the side effects difficult to tolerate without assigning a numerical value. Respondents were also asked if they would be willing to tolerate new side effects from new drugs to extend life expectancy. On a scale of 1 (will not tolerate side effects) to 10 (will tolerate significant side effects), respondents gave an average score of 8.6 supporting the conclusion that patient values prioritize long-term health outcomes. One patient commented, *"Pretty bad quality of life for about a week after each infusion, but those weeks are worth a lifetime a good health."*

Additionally, the RBC survey asked the 6 patients if they would recommend trastuzumab emtansine to other patients with early breast cancer. All six patients responded with a yes. The following are some of the comments made when asked to elaborate.

- *"Means I can live longer."*
- *"It literally saved my life.'*

- *"Kept me stable for almost 19 months; SEs were minimal and felt best I had in several years."*
- *"If it's the standard of care for your type of cancer, why wouldn't you take it and run with the one that works ASAP."*
  The CBCN was unable to connect with any patients who had treatment experience with trastuzumab emtansine.

3.3 Additional Information

The CBCN reiterated the importance of having an option for this very specific and small subset of patients that are at higher risk of recurrence. Given the efficacy of the treatment, and that reducing the risk of recurrence is of utmost importance to this patient population, the CBCN concluded that trastuzumab emtansine aligns with patient values. The CBCN highly recommends that this is taken into consideration when funding decision are being made.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Clarity on eligible patient population

Economic factors:

- Additional healthcare resources for monitoring and management of adverse events

Please see below for more details.

4.1 Factors Related to Comparators

PAG identified that for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual disease after pre-operative systemic treatment, patients are treated with trastuzumab. KATHERINE trial compared trastuzumab emtansine to trastuzumab, which is a relevant comparator.

4.2 Factors Related to Patient Population

PAG is seeking clarity on patients who would be eligible for treatment, if trastuzumab emtansine is recommended for reimbursement, whether the specific trial inclusion and exclusion criteria would be applied or the broader funding criteria. PAG identified that it would also be important to have clarity on patient eligibility in the following clinical settings:

- Patients who had prior trastuzumab plus pertuzumab (or other HER2-targeted therapy) as this is not funded as neoadjuvant therapy in any jurisdiction
- Patients with T1a/bN0 tumours
- Male breast cancer

If recommended for reimbursement, the following subgroup of patients, would need to be addressed on a time-limited basis:

- Patients currently receiving adjuvant trastuzumab. If it is appropriate to switch these patients, is there an appropriate time frame (i.e., patients <6 months into adjuvant treatment versus between months 9 and 12)?
- PAG is seeking guidance on whether it would be appropriate to switch patients from adjuvant trastuzumab to trastuzumab emtansine within the 12 week timeframe as per KATHERINE trial, and for timeframes beyond 12 weeks, should these patients switch to trastuzumab emtansine or remain on trastuzumab?
- Patients who recently completed their one year of adjuvant trastuzumab.

There is a potential for indication creep into the neoadjuvant setting (i.e., pre-operative).

4.3 Implementation Factors

PAG noted that the two vial sizes of 100 and 160mg would allow for vial sharing and minimize drug wastage. However, vial sharing may not be feasible in smaller outpatient cancer centres. Less patients utilize trastuzumab emtansine compared to trastuzumab. This will increase costs given drug wastage, as vial sharing would not be to the same extent as trastuzumab and stability is not as long as trastuzumab. Trastuzumab emtansine and trastuzumab look-alike and sound-alike; therefore, pharmacies would also need to ensure safety measures are in place to prevent dispensing errors.

As trastuzumab emtansine is funded in the metastatic setting, there is familiarity with the preparation, administration and monitoring of trastuzumab emtansine. This would be an enabler. However, use of trastuzumab emtansine will shift from the metastatic to adjuvant setting which will result in greater volume of patients.

PAG noted as there is a greater total number of cycles with trastuzumab emtansine, there would be additional healthcare resources (i.e., nursing, pharmacy, physician, and clinic visits) compared with trastuzumab. Trastuzumab emtansine is also not as well tolerated as trastuzumab and there would be increased monitoring and treatment (e.g., dose modifications, bloodwork for myelosuppression, administration of growth factor support) of adverse effects (e.g., neutropenia, neuropathies) required.

Trastuzumab emtansine, being an intravenous drug, would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of toxicities. Intravenous chemotherapy drugs would be fully funded in all jurisdictions for eligible patients, which is an enabler for patients.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the appropriate place in therapy for trastuzumab emtansine and if trastuzumab emtansine is recommended for reimbursement:

- Appropriate metastatic treatments for patients who progress during or shortly after completing (e.g., ≤6 months) trastuzumab emtansine (e.g., trastuzumab emtansine, pertuzumab plus trastuzumab) and sequencing of these treatment options?
- Would it be reasonable to treat with trastuzumab emtansine in the metastatic setting after receiving adjuvant trastuzumab emtansine? What would be the appropriate timeframe (i.e., between adjuvant treatment and development of metastatic disease) for re-treatment with trastuzumab emtansine subsequently?
- Guidance on number of anti-HER2 therapies that should be available in the metastatic setting.

In the KATHERINE trial, patients who discontinued trastuzumab emtansine early because of toxic effects could complete 14 cycles of trial treatment with trastuzumab at the discretion of the investigator. PAG is seeking guidance on whether the cap of 14 total cycles should be considered if trastuzumab emtansine is recommended for reimbursement, and if 14 total cycles of anti-HER2 therapy should be completed within a specific timeframe.

4.5 Companion Diagnostic

HER-2 testing is already available.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

The following registered clinicians provided input on trastuzumab emtansine (Kadcyla) for early breast cancer: A total of two clinician inputs were received representing a total of 4 clinicians (three oncologists and one pharmacist) - 1 single clinician input from Ottawa and 1 joint clinician input from the Cancer Care Ontario (CCO) Breast Drug Advisory Committee (DAC) representing two oncologists and one pharmacist.

All clinicians agreed that the eligibility criteria for the KATHERINE trial were applicable to clinical practice. The clinicians from CCO Breast DAC reported that trastuzumab emtansine has a significant benefit over the standard treatment of trastuzumab alone and is considered a promising treatment that addresses an unmet need in a high-risk population. Furthermore, the CCO Breast DAC reported that the toxicity associated with trastuzumab emtansine was not excessive, and it is a treatment that should be prioritized since it can prevent several patients from relapsing. The single clinician input noted that trastuzumab emtansine may not be appropriate for patients who have concomitant contraindications to standard trastuzumab (e.g., cardiac dysfunction). All clinicians providing input agreed that the number of anti-HER2 therapies should be advised by clinical trial evidence and practice guidelines. With respect to companion diagnostic testing, the single clinician input stated that patients would have had standard HER2 testing at diagnosis using standard accepted methodologies; Clinicians from CCO Breast DAC however noted that this is not being done as part of routine practice in Ontario.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for Early Breast Cancer

Both the single clinician and the CCO Breast DAC input indicated that for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual disease after pre-operative systemic treatment, patients are to be treated with trastuzumab. The single clinician input noted that the usual standard of ongoing adjuvant trastuzumab (Herceptin) for 18 doses over 1 year is currently funded and that this would remain the standard if trastuzumab emtansine is not available. The CCO Breast DAC commented that trastuzumab + pertuzumab is currently not funded in the neoadjuvant or adjuvant setting in Ontario.

5.2 Eligible Patient Population

Both clinician inputs agreed that the eligibility criteria of the KATHERINE trial are reasonable and can be applied to practice. The single clinician input further added that the patient population of the trial addressed an unmet need, and there was no additional population for whom the therapy would be considered. The CCO Breast DAC predicted that a great number of patients would receive neoadjuvant treatment if trastuzumab emtansine (T-DM1) funding becomes available.

5.2.1 Implementation Question: The eligibility criteria for the KATHERINE trial included a specific patient population compared to the broader funding request. In clinical practice, is there evidence to extend the use of adjuvant trastuzumab emtansine to (provided all other eligibility criteria are met):

a) Patients who had prior trastuzumab plus pertuzumab (or other HER2-targeted therapy) as this is not funded as neoadjuvant therapy in any jurisdiction
b) Patients with T1a/bN0 tumours
c) Male breast cancer

    a) Both clinician inputs agreed that it would be reasonable to extend the use of trastuzumab emtansine to patients who had received prior trastuzumab and

pertuzumab (or other HER2-targeted therapy). Both clinician inputs also noted that patients who received trastuzumab with pertuzumab or another HER2-targeted therapy benefitted from adjuvant trastuzumab emtansine, as per the results of the KATHERINE trial. The single clinician additionally added that pertuzumab has a very small added value of longer-term disease-free survival (DFS), and thus, excluding patients who received prior pertuzumab from receiving trastuzumab emtansine would be inappropriate given that the absolute DFS benefit of trastuzumab emtansine is more robust.

b) The CCO Breast DAC indicated that patients with T1a/bN0 generally have good outcomes in terms of being lower-risk patients, and that the benefit of TDM-1 treatment may not outweigh the potential risk of toxicities. Both inputs indicated trastuzumab emtansine would be used in patients as per the KATHERINE trial. The individual clinician input further added that it is unclear if the overall benefit is worthwhile for patients with very small residual disease burden at surgery; however, in the absence of prospective evidence in that subgroup of patients, the benefit cannot be ruled out.
c) The CCO Breast DAC supported the use of trastuzumab emtansine in male patients, as male patients were included in the KATHERINE trial and there is no reason to suspect that the outcomes in these patients would be different.

5.3 Relevance to Clinical Practice

The individual clinician input indicated that trastuzumab emtansine would be used in clinical practice as per the KATHERINE trial. Aside from patients having concomitant contraindications to the standard trastuzumab (e.g., cardiac dysfunction), there are no additional clinical characteristics that would exclude patients from the consideration of trastuzumab emtansine, including the persistence of peripheral neuropathy symptoms from previous taxane chemotherapy (unless these symptoms worsened while on trastuzumab emtansine, in which case treatment would be discontinued). Patients would need to demonstrate sufficient CBC (blood count) parameters post previous chemotherapy, as defined in the eligibility criteria of the KATHERINE trial.

5.4 Sequencing and Priority of Treatments with Trastuzumab Emtansine (TDM1)

5.4.1 Implementation Question: Please consider the optimal sequencing of treatment for patients with HER2-positive breast cancer. In clinical practice, if trastuzumab emtansine was available

a) Appropriate metastatic treatments for patients who progress during or shortly after completing (e.g., ≤6 months) trastuzumab emtansine (e.g., trastuzumab emtansine, pertuzumab plus trastuzumab) and sequencing of these treatment options?
b) Would it be reasonable to treat with trastuzumab emtansine in the metastatic setting after receiving adjuvant trastuzumab emtansine? What would be the appropriate timeframe (i.e., between adjuvant treatment and development of metastatic disease) for re-treatment with trastuzumab emtansine subsequently?
c) Guidance on number of anti-HER2 therapies that should be available in the metastatic setting.

a) Per the individual clinician input, patients progressing on adjuvant trastuzumab emtansine or within 6 months of completing adjuvant treatment would be considered for taxane/trastuzumab/pertuzumab combination treatment or lapatinib/vinorelbine, lapatinib/capecitabine combinations, or treatment based on promising clinical trials. The

CCO Breast DAC advised that if a patient received trastuzumab emtansine and recurred during treatment or shortly thereafter, it would not be beneficial to retreat the patients with trastuzumab emtansine. Patients would follow the normal metastatic paradigm (e.g., taxane, pertuzumab, trastuzumab).

b) The individual clinician input advised that it would be reasonable to retreat patients with trastuzumab emtansine in the setting of metastatic disease arising 6 months or more after adjuvant therapy, but after initial standard taxane/trastuzumab/pertuzumab therapy. The CCO Breast DAC acknowledged that there are questions about response to subsequent therapies in the metastatic setting, but that there is no evidence to suggest that patients are not eligible for the usual standard metastatic treatment options. The joint clinician input also noted that trastuzumab emtansine is not funded in the first line metastatic setting.

c) The individual clinician input advised that ideally, HER2 targeted therapy should be a part of at least 3 lines of systemic therapy for metastatic disease. However, it could be included in additional lines of therapy in combination with newer, promising investigational agents, if available on study. The CCO Breast DAC stated that the number of anti-HER2 therapies should be based on clinical evidence.

5.5 Companion Diagnostic Testing

Both inputs stated that patients would have had standard HER2 testing at diagnosis using standard accepted methodologies to determine neoadjuvant eligibility. The individual clinician input noted that the key biomarker is the clinical response (or lack thereof) to neoadjuvant therapy. The CCO Breast DAC reported that HER2 biomarker testing on a core biopsy is not done 100% of the time in Ontario to determine neoadjuvant eligibility.

5.6 Additional Implementation Questions

5.4.2 In the KATHERINE trial, patients who discontinued trastuzumab emtansine early because of toxic effects could complete 14 cycles of trial treatment with trastuzumab at the discretion of the investigator. In clinical practice, should the cap of 14 total cycles be considered if trastuzumab emtansine is recommended for reimbursement? Is there evidence to inform whether the 14 total cycles of anti-HER2 therapy should be completed within a specific timeframe?

The single clinician input advised that clinicians treat each case in an evidence-based manner following the protocol in the KATHERINE trial. Patients would be able to tolerate the completion of 14 cycles with trastuzumab alone, unless the toxicity was cardiac, which is rare. Similarly, the CCO Breast DAC stated that most clinicians will use their discretion, and if a patient experiences significant toxicity, they will not be retreated. Guidelines should be similar to the rules for interrupting adjuvant trastuzumab.

5.7 Additional Information

Not applicable.

6 SYSTEMATIC REVIEW

6.1 Objectives

The primary objective of this review is to evaluate the efficacy and safety of trastuzumab emtansine (Kadcyla) for the adjuvant treatment of HER2-positive early breast cancer patients who have residual invasive disease following neoadjuvant taxane and trastuzumab-based treatment.

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 6.1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of trastuzumab emtansine should be included.	Adult patients (≥18 years of age) with early stage, HER2-positive breast cancer with residual disease following preoperative systemic treatment Subgroups: - Age - ECOG PS (0 vs. 1) - Hormone receptor status (ER and PgR) - Pre-operative HER-2 directed therapy (trastuzumab vs. trastuzumab + additional HER-2 directed therapy) - Clinical stage at presentation - Primary tumor stage at surgery - Menopausal status	Trastuzumab Emtansine	Trastuzumab	Primary: - **DFS** Secondary: - OS - **HRQoL** Safety: - AEs - SAEs - WDAEs

Abbreviations:
AEs = adverse events; **DFS** = disease free survival; **ECOG PS** = Eastern Cooperative Oncology Group Performance Status; **ER** = estrogen receptor; **HER2** = human epidermal growth factor receptor; **HRQoL** = health-related quality of life; **OS** = overall survival; **PgR** = progesterone receptor; **RCT** = Randomized controlled trial; **SAEs** = serious adverse events; **WDAEs** = withdrawals due to adverse events

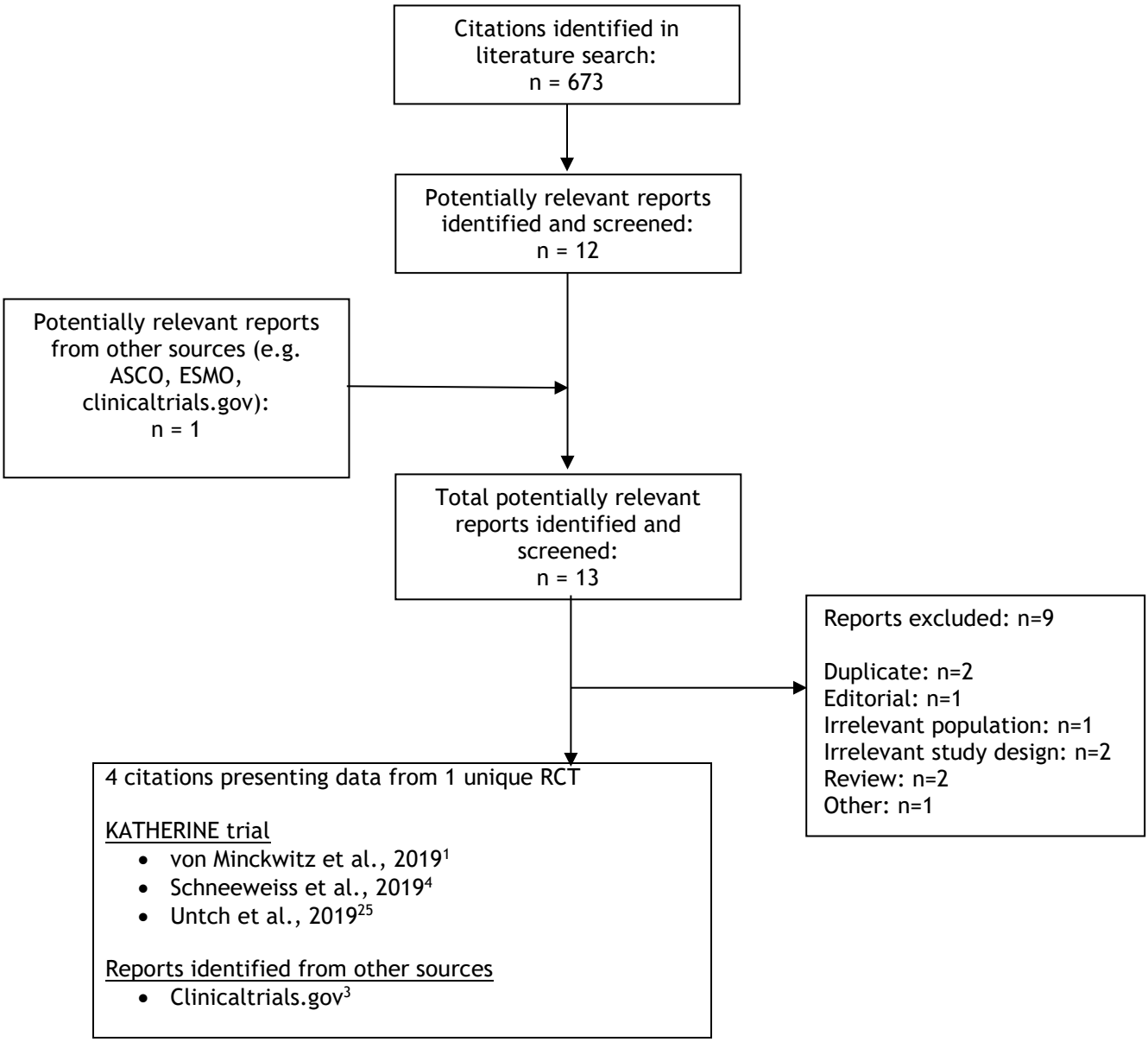
* *Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 13 potentially relevant reports identified, 4 citations reporting data from one randomized controlled trial (RCT) were included in the pCODR systematic review[1,3,4,25], and 9 citations were excluded[26-33]. Studies were excluded because they contained duplicate data[27], were an editorial[30], included an irrelevant population[26], included an irrelevant study design[28,32], were a review[29,33], and other (content out of scope of the systematic review objective)[31].

Figure 6.1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the KATHERINE trial were also obtained through requests to the Submitter by pCODR.[2,13]

6.3.2 Summary of Included Studies

One randomized controlled trial (RCT), the KATHERINE trial, met the selection criteria for this systematic review. Key trial characteristics including study design, eligibility criteria, intervention details, and trials outcomes are summarized in Table 6.2.

6.3.2.1 Detailed Trial Characteristics

Table 6.2. Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study:[1,3,13] KATHERINE NCT01772472 **Characteristics:** Phase III, superiority, open-label, randomized (1:1), active-controlled, trial N = 1486 randomized (743 in both arms) N = 1469 treated (trastuzumab emtansine=739; trastuzumab=720) **Setting:** 268 sites in 28 countries (Canada, Argentina, Austria, Belgium, Brazil, China, Colombia, Czech Republic, France, Germany, Greece, Guatemala, Hong Kong, Ireland, Israel, Italy, Mexico, Panama, Peru, Serbia, South Africa, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom, United States) **Patient Enrolment Dates:** April 2013 to December 2015 **Data cut-off:** July 25th, 2018 **Final Analysis Date:** To be conducted after ~367 deaths occurred **Funding:** Hoffman-La Roche Limited	<u>Key Inclusion Criteria:</u> • ≥18 years of age with histologically confirmed invasive breast carcinoma • HER2-positive breast cancer based on pre-treatment biopsy, or if insufficient, based on residual tissue from surgery (synchronous bilateral invasive disease eligible if both lesions HER2-positive) • Clinical stage: T1-2, N0-3, M0 (T1a/bN0 ineligible) • Completion of 6 cycles of preoperative treatment with a duration of 16 weeks, including 9 week of trastuzumab & 9 weeks of taxane-based chemotherapy (can be concurrent and >1 HER2 therapy allowed) • Adequate excision of clinically evident disease in breast and lymph nodes as defined in protocol • Pathological evidence of residual invasive carcinoma in the breast or axillary lymph nodes following completion of preoperative therapy • ≤ 12 weeks between surgery and randomization date • Known hormone receptor status • ECOG 0 or 1 • Adequate organ function <u>Key Exclusion Criteria:</u> • Stage IV (metastatic breast cancer) • History of prior (ipsi or contralateral) breast cancer except LCIS • Clinically evidence gross residual disease or recurrent disease following preoperative therapy and surgery • PD during preoperative therapy • History of other malignancy within 5 years (except treated in-situ cervix carcinoma, non-melanoma skin carcinoma, stage I uterine cancer, or other non-breast malignancies) • NCI CTCAE v.4.0 grade ≥2 peripheral neuropathy • Cumulative exposure exceeding 480 mg/m^2 of epirubicin or 240 mg/m^2 BSA of doxorubicin/other anthracyclines	<u>Intervention:</u> Trastuzumab emtansine 3.6 mg/kg q3w by IV infusion for 14 cycles <u>Comparator:</u> Trastuzumab 6 mg/kg q3w for 14 cycles by IV infusion for 14 cycles	<u>Primary:</u> • iDFS <u>Secondary:</u> • iDFS including second primary non-breast cancer • DFS • OS • DRFI <u>Tertiary:</u> • HRQoL <u>Safety</u> • AEs • SAEs • WDAEs • Dose interruptions and modifications • Deaths • Cardiac events

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	• Cardiopulmonary dysfunction (symptoms ≥ grade 2 of LV dysfunction, cardiac arrythmia, or cardiac ischemia; uncontrolled angina, serious cardiac arrythmia, or clinically significant valvular disease; LVEF <50%; history of grade ≥3 CHF; history of decrease in LVEF to <40% or symptomatic CHF during preoperative therapy; MI ≤12 months prior to randomization; or requirement of continuous oxygen therapy) • Prior treatment with T-DM1 • Severe or uncontrolled systemic disease (CVD, ulcers, etc.) • Major surgery or significant traumatic injury within 28 days of randomization • Known liver disease including HBV, HCV, autoimmune hepatic disorders, & sclerosing cholangitis • HIV infection • History of intolerance, infusion reaction, or hypersensitivity to trastuzumab or murine proteins • Active, unresolved infections at screening		

Abbreviations:
AE = adverse events; BSA = body surface area; CHF = congestive heart failure; CTCAE = Common Terminology Criteria for Adverse Events; CVD = cardiovascular disease; DFS = disease-free survival; DRFI = distant recurrence-free interval; ECOG = Eastern Cooperative Oncology Group Performance Status; HBV = hepatitis B virus; HCV = hepatitis C virus; HER2 = human epidermal factor receptor 2; HIV = human immunodeficiency virus; HRQoL = health-related quality of life; iDFS = invasive disease-free survival; IV = intravenous; kg = kilogram; LCIS = lobular carcinoma in situ; LV = left ventricular; LVEF = left ventricular ejection fraction; M = metastasis; m^2 = square metre; mg = milligram; MI = myocardial infarction; N = nodes (number of lymph nodes involved); NCI = National Cancer Institute; OS = overall survival; PD = progressive disease; Q3W = every 3 weeks; T = tumor size; SAE = serious adverse event; T-DM1 = trastuzumab emtansine; v. = version; WDAE = withdrawal due to adverse event

Table 6.3. Select quality characteristics of included studies of trastuzumab emtansine in patients with early breast cancer

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
KATHERINE	T-DM1 vs. trastuzumab	iDFS	1484	1486	1:1 via IVRS/IWRS permuted-block randomization scheme	Yes	No, open-label	Yes	No	No	Yes

Abbreviations:
IVRS = interactive voice response system; IWRS = interactive web response system; T-DM1 = trastuzumab emtansine
iDFS = invasive disease-free survival; IVRS = interactive voice response system; IWRS = interactive web response system; T-DM1 = trastuzumab emtansine

a) Trials

KATHERINE was an international, open-label, phase III, randomized, active-controlled, superiority trial of trastuzumab emtansine (T-DM1) versus trastuzumab in the adjuvant setting for patients with HER2-positive primary breast cancer with pathological residual disease in the breast or axillary lymph nodes following preoperative therapy.[1] This study was conducted at 268 sites in 28 countries, which are listed in Table 6.2, and included 58 Canadian patients representing the provinces of Ontario, Quebec, Alberta, and British Columbia.[13]

Trial Design

Screening and Randomization

Patients were assessed for eligibility during a 30 day screening period, and key inclusion and exclusion criteria are outlined in Table 6.2. Briefly, patients must have had neoadjuvant therapy (preoperative therapy) with at least 9 weeks of HER2-directed therapy that included trastuzumab and at least 9 weeks of taxane therapy for a total of 16 weeks in total of systemic treatment (or if dose-dense chemotherapy regimen, at least 6-8 weeks of taxane-based therapy and 8 weeks of trastuzumab). HER2-directed therapy and chemotherapy could be given concurrently, and patients may have received more than one HER2-directed therapy. Patients could have received anthracycline and alkylating agents as part of the neoadjuvant therapy. HER2 status was confirmed centrally prior to trial enrollment using the pre-treatment biopsy or surgical sample.

Eligible patients were randomized in a 1:1 ratio to receive open-label treatment with trastuzumab emtansine (hereafter, referred to as T-DM1) or trastuzumab through an interactive voice response (IVRS) or interactive web response (IWRS) system, and first dose of treatment as planned on the day of randomization, but no later than 5 business days after randomization. Patients were randomized using a permuted block randomization scheme.[1] The block size was 4.[13] Randomization was stratified by:

- Clinical stage at presentation: inoperable (stage T4NxM0 or TxN2-3M0) versus operable (stages T1-3N0 to 1M0)
- Hormone receptor status: estrogen receptor (ER) or progesterone receptor (PR) positive versus ER or PR negative/unknown
- Preoperative HER2-directed therapy: trastuzumab versus trastuzumab plus additional HER2-directed agents
- Pathologic nodal status evaluated after preoperative therapy: node positive versus node negative/not done[1]

Treatment

Patients assigned to T-DM1 received 3.6 mg/kg intravenously every 3 weeks for 14 cycles and patients assigned to trastuzumab received 6 mg/kg every 3 weeks. Patients were administered radiotherapy and hormonal therapy (if hormone-receptor positive) in addition to study treatment according to institutional standards as well as the following guidelines outlined in the study protocol:

- Hormonal therapy (such as aromatase inhibitors, tamoxifen, etc.) was initiated in applicable patients at presentation
- Whole breast irradiation was required for patients undergoing breast-conserving surgery

- Regional node irradiation was required if at initial diagnosis there was T3 or T4 disease and/or N2 or N3 disease in both patients undergoing breast-conserving surgery and post-mastectomy patients, also recommended if there was residual disease in lymph nodes
- For post-mastectomy patients that did not meet criteria above, radiotherapy was at discretion of investigator based on institutional standards[1]

Treatment Discontinuation

Treatment was discontinued prior to 14 cycles if there was pregnancy; disease recurrence; symptomatic congestive heart failure (CHF); 2 consecutive or 3 intermittent dose delays due to asymptomatic decrease in left ventricular ejection fraction (LVEF); inability to receive T-DM1 after 2 dose reductions due to toxicity; unacceptable toxicity; intercurrent, non-cancer related illness that prevents continuation of protocol or follow-up; major protocol violation; repeated patient noncompliance; investigator opinion that continuation would compromise patient's well-being; withdrawal of patient consent, or study termination by the Sponsor.[1]

Follow-up

Patients who discontinued treatment attended a study treatment discontinuation visit 30 days after last dose of study drug for evaluations that included laboratory assessment, physical examination, vital signs assessment, adverse event (AE) monitoring, concomitant medication reporting, and health-related quality of life (HrQOL) assessment. Patients were to be followed for 10 years for assessments, which included monitoring AEs, laboratory and physical assessments, concomitant medications, and optional pharmacokinetic (PK) assessments. Mammograms of any remaining breast tissue were to be performed at least annually during follow-up. HrQOL assessments were completed every 6 months for a year and patients were followed for pregnancy at 3 and 6 months following the study discontinuation visit. Cardiac monitoring by echocardiogram or multigated acquisition (MUGA) scan was scheduled at 3,6, 12, 18, 24, 36, 48, and 60 months during survival follow-up. If disease recurrence occurred, patients were to be out of the study schedule and followed annually for survival for up to 10 years. [1]

Disease Assessments

Disease status was assessed by investigators based on clinical assessments was to be documented from randomization, and every 3 months while on study treatment up to 2 years, and then every 6 months from 3-5 years, and annually from 6-10 years.[1] Clinical assessments included vital signs measurement, physical examination, radiologic evaluation (included a bilateral mammogram and/or magnetic resonance imaging [MRI] with at least an annual mammogram of any remaining breast tissue), and laboratory assessment. When possible, disease recurrence was to be confirmed pathologically.[13] If disease recurrence occurred at any point in the study, then patients were to be out of the study schedule and followed once a year until the 10 years for survival and new relapse events for secondary endpoints.

Disease recurrence included local invasive recurrence (ipsilateral breast after previous lumpectomy or ipsilateral after prior mastectomy) confirmed by positive histology or cytology; regional recurrence (not including tumor in the opposite breast) confirmed by positive histology or cytology, or radiologic evidence (positron emission tomography [PET], computed tomography [CT], or magnetic resonance imaging [MRI] if no biopsy performed); distant recurrence (tumor in other areas such as skin, bone, bone marrow, lung, liver, and central nervous system)

confirmed by cytology, histology, aspirate, biopsy, bone scan, MRI, CT, or PET as applicable and outlined in the protocol; contralateral invasive breast cancer confirmed by positive cytology or histology; second non-breast primary malignancy (other than basal or squamous cell carcinoma of the skin, carcinoma in-situ of the cervix) confirmed histologically; and death without recurrence. Though ipsilateral and contralateral lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS) were not considered as recurrence, these were noteworthy events to be recorded during follow-up. [1]

Sample Size

Sample size was determined based on the primary endpoint of invasive disease-free survival (iDFS) with 1484 patients planned for enrollment. To detect a hazard ratio (HR) of 0.75 in iDFS, representing a 6.5% improvement in 3-year iDFS from 70% in the trastuzumab arm to 76.5% in the T-DM1 arm, approximately 384 iDFS events were required to achieve 80% power at a 2-sided significance level with $\alpha = 0.05$. The final iDFS analysis is planned after 384 events have occurred, which is projected at 64 months from the first patient enrolled in the study. With a sample size of 1484 and a 10 year follow-up period, the study has 56% power to detect a HR of 0.8, which represents a 2.8% improvement in 3-year overall survival (OS) from 85% in the trastuzumab arm to 87.8% in the T-DM1 arm at a 2-sided significance level with $\alpha = 0.05$.[1]

Study Endpoint and Statistical Analyses

Primary Endpoint – Invasive Disease-Free Survival

The primary efficacy endpoint of iDFS was defined as the time between randomization and date of first occurrence of an iDFS event. iDFS events were defined as any of one of the following occurrences:

- Ipsilateral invasive breast tumor recurrence
- Ipsilateral local-regional invasive breast cancer recurrence (i.e., invasive breast cancer in the axilla, regional lymph nodes, chest wall and/or skin of the ipsilateral breast)
- Distant recurrence (i.e., evidence of breast cancer in any anatomic site other than two mentioned above with histological confirmation or clinical diagnosis)
- Contralateral invasive breast cancer
- Death attributable to any cause

Patients who did not have an event were censored at the date last known to be alive and event free on or prior to the clinical data cut-off date (July 25th, 2018). Cox proportional hazards model stratified by the protocol-defined stratification factors, which included clinical stage at presentation (inoperable vs. operable), hormone receptor status (ER or PR positive vs. ER or PR negative/unknown), preoperative HER2-directed therapy (trastuzumab vs. trastuzumab plus additional HER2-directed agents), and pathologic nodal status after preoperative therapy (node positive vs. node negative/not done), were used to estimate the HR between the two treatment arms and the 95% confidence interval (CI). The log-rank test stratified by the protocol-defined factors was also conducted to compare iDFS between the two treatment arms. The Kaplan-Meier (K-M) approach will be used to estimate 3-year iDFS rates and corresponding 95% CIs for each treatment arms. A sensitivity analysis using the unstratified log-rank test was also conducted. A testing hierarchy was used to control the overall type I error rate at 5% of the IA and final analysis of iDFS.[1]

Secondary Endpoints

Secondary endpoints included:

- Invasive disease-free survival including second primary non-breast cancer: This outcome was defined in the same way as the primary endpoint of iDFS, but included a second primary non-breast invasive cancer as an event. Non-melanoma skin cancers and carcinoma in-situ of any disease site were not included in this definition.
- Disease-free survival (DFS): This was defined as the time between randomization and the date of first occurrence of an iDFS event including second primary non-breast cancer as an event or contralateral/ipsilateral ductal carcinoma in situ.
- Overall survival (OS): This was defined as the time from randomization to death due to any cause.
- Distant recurrence-free interval (DRFI): This was defined as the time between randomization and the date of distant breast cancer recurrence.

All secondary endpoints were analyzed similar to the primary endpoint to estimate the 3-year event rates (for OS, the 5-year survival rate) for each treatment arm and the HR (with 95% CI) between the 2 treatment arms. The type I error rate of the IAs and final analysis of OS was controlled at 5% by a testing hierarchy procedure.[1]

Interim Analyses and Multiplicity

One interim analysis (IA) and one final analysis of iDFS was planned. At the IA, the iDFS was tested using the Lan-Mets alpha spending function and O'Brien-Fleming boundary, which controlled for multiplicity, so the overall type I error rate was maintained at the 5% level for the iDFS primary endpoint. Table 6.4 summarizes the planned iDFS analyses. If the test is found significant at the IA, the independent data monitoring committee (IDMC) recommended releasing primary endpoint results prior to the targeted 384 events, and the study would continue until 10 years of follow-up with an updated iDFS analysis at 384 events.[1]

Table 6.4. Summary of planned interim and final analyses for invasive disease-free survival in the KATHERINE trial

Analysis of IDFS	No. of events	Efficacy Stopping Boundary [a]	Estimated Timing [b]
Interim	257	p<0.0124 or observed HR<0.732	48 months
Final	384	p<0.0462 or observed HR<0.816	64 months

HR=hazard ratio; IDFS=invasive disease-free survival.

[a] p-value will be based on 2-sided stratified log-rank test.

[b] Time from the enrollment of first patient to data cutoff.

Source: The New England Journal of Medicine, von Minckwitz G, et al, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, 380(7), 617-628. Copyright ©2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

There were three planned IAs for OS and one final analysis of OS, summarized in Table 6.5. The overall type I error rate for OS IAs was controlled at 0.05 using the

Lan-DeMets alpha spending function with an O'Brien-Fleming boundary. The boundaries used at each interim and final analysis would depend on the timing of the analyses and number of deaths included in the analyses.[1]

Table 6.5. Summary of the planned interim and final analyses of overall survival in the KATHERINE trial

Analysis Of OS	No. Of Events	Efficacy Stopping Boundary [a]	Estimated Timing [b]
Interim 1 (at interim IDFS)	150	p<0.0009 or observed HR<0.5826	48 months
Interim 2 (at final IDFS)	206	p<0.0053 or observed HR<0.6785	64 months
Interim 3	279	p<0.0184 or observed HR<0.754	88 months
Final	367	p<0.0435 or observed HR<0.8099	119 months

HR=hazard ratio; IDFS=invasive disease-free survival; OS=overall survival.
[a] p-value will be based on 2-sided stratified log-rank test.
[b] Time from the enrollment of first patient to data cutoff.

Source: The New England Journal of Medicine, von Minckwitz G, et al, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, 380(7), 617-628. Copyright ©2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

Safety

Patients who received any amount of study treatment were included in the safety analyses based on the treatment patients actually received. Safety of study treatments were assessed through treatment exposure, summaries of adverse events (AEs), serious AEs (SAEs), cardiac-specific AEs, LVEF measurement, and laboratory test results routinely throughout the study.[1]

Health-related Quality of Life

HrQOL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 (QLQ-C30) and the EORTC breast cancer module (EORTC-QLQ-BR23). The EORTC-QLQ-C30 is a validated and reliable self-report measure that consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social); three symptom scales (fatigue, nausea/vomiting, and pain); global health status/quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scale scores can be obtained for the multi-item scales.[1] Table 6.6 includes the changes that were considered clinically meaningful from the EORTC QLQ-C30:

Table 6.6. Clinically meaningful cut-offs used for assessing scales from the EORTC QLQ-C30

Scales	Clinically meaningful deterioration from baseline
Global health status/quality of life	Decrease of ≥ 10 points
Patient functioning •Physical •Emotional (not analyzed) •Role •Cognitive •Social (not analyzed)	 Decrease of ≥ 10 points Decrease of ≥ 10 points Decrease of ≥ 14 points Decrease of ≥ 7 points Decrease of ≥ 10 points
Symptom scales •Fatigue •Nausea/Vomiting •Pain	 Increase of ≥ 10 points Increase of ≥ 11 points Increase of ≥ 11 points
Single items •Dyspnea •Insomnia •Appetite loss •Constipation •Diarrhea •Financial difficulties (not analyzed)	 Increase of ≥ 11 points Increase of ≥ 9 points Increase of ≥ 14 points Increase of ≥ 15 points Increase of ≥ 15 points Increase of ≥ 10 points

Source: Roche Checkpoint Responses, 2019[13]

EORTC QLQ-BR23 comprises of 23 questions assessing disease symptoms, side effects of treatment (surgery, chemotherapy, radiotherapy, and hormonal treatment), body image, sexual functioning, and future perspectives among breast cancer patients with varying disease stages and treatment modalities. The EORTC-QLQ-BR23 includes 5 multiple-item scales to assess systemic therapy side effects, arm symptoms, breast symptoms, body image, and sexual functioning, and single items assess sexual enjoyment, hair loss, and future perspective.[1] Table 6.7 includes the changes that were considered clinically meaningful from the EORTC QLQ-BR23:

Table 6.7. Clinically meaningful cut-offs used for assessing scales from the EORTC QLQ-BR23

Scales	Clinically meaningful deterioration from baseline
Multi-item Scales •Systemic therapy side effects •Body image (not analyzed) •Sexual functioning (not analyzed) •Arm symptoms (not analyzed) •Breast symptoms (not analyzed)	 Increase of ≥ 10 points Increase of ≥ 10 points Increase of ≥ 10 points Increase of ≥ 10 points Increase of ≥ 10 points
Single Item Scales •Upset by Hair loss •Sexual enjoyment (not analyzed) •Future perspective (not analyzed)	 Increase of ≥ 10 points Increase of ≥ 10 points Increase of ≥ 10 points

Source: Roche Checkpoint Responses, 2019[13]

Summary statistics of absolute scores and the change from baselines were summarized at each assessment time point for the treatment arms. Only patients with a baseline assessment and at least one post-baseline assessment were included in this analysis, and treatment effect changes over time and treatment-by-time interaction were explored using repeated measures mixed-effects models.

The EuroQoL EQ-5D-3L was also used to assess HRQoL, which is a five-item questionnaire (includes questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three categories (no problem, moderate problem, severe problems), which was used to support economic modelling.

Protocol Amendments

A total of five protocol amendments to the protocol were made (first version issued on October 19th, 2012), and are summarized in the table below[2]:

Protocol Version, Date	Summary of Changes
Version 2, April 2013	• Clarification and details of IHC and ISH assays used for determining HER2 status • Inclusion of patients who had received dose-dense chemotherapy regimens, provided at least 8 weeks of taxane-based therapy and at least 8 weeks of trastuzumab had been given • Revision of language to differentiate radiotherapy for T3 disease with and without lymph node involvement • Recommendations for hormonal therapy were revised to allow 5 to 10 years, rather than only 5 years, of tamoxifen therapy as a result of changing practice guidelines • Guidelines for managing the specific adverse events of nodular regenerative hyperplasia and interstitial lung disease were added. • For nodular regenerative hyperplasia, a new appendix for guidelines for liver biopsy was added • Radiotherapy-related toxicity was split into interstitial lung disease and skin toxicity, in order to differentiate between radiation-induced and drug-induced toxicities • Text on use of strong/potent CYP3A4/5 inhibitors was revised to provide further instruction to investigators, and remove erythromycin from the list of examples as it is only a moderate CYP3A4/5 inhibitor, not a potent inhibitor • Suspected transmission of an infection agent by the study drug was added as an adverse event of special interest
Version 3, September 2013	• The duration of patient monitoring following first dose of trastuzumab emtansine was changed from 60 minutes to 90 minutes • Assessment of total protein at baseline was added to the list of assessments because it was inadvertently omitted • Requirements for long-term reporting of concomitant medication, adverse events and serious adverse events were clarified • Detail on severe/fatal hemorrhage was added under the identified risk of hematologic toxicity
Version 4, March 2014	• Addition of language to allow shorter duration of an escalated dose-dense administration of paclitaxel

Protocol Version, Date	Summary of Changes
	• Inclusion criteria were revised to clarify that if pre-chemotherapy LVEF assessments were not conducted, the screening LVEF assessment must be at least 55% in order for the patient to be eligible • Dose modifications related to increases in AST and for thrombocytopenia were revised. • Guidelines for Grade 1-2 pneumonitis were updated such that to require diagnosis of drug-related ILD/pneumonitis should lead to permanent discontinuation of trastuzumab emtansine treatment.
Version 5, July 2014	• Issued rapidly after Version 4, to correct a small but significant error in language in the general inclusion criteria, and indicate that LVEF should be ≥50% prior to receiving neoadjuvant chemotherapy instead of after receiving neoadjuvant chemotherapy • Local version of protocol created in Argentina for local requirements regarding pregnancy testing and HIV testing
Version 6, October 2015	• Data that became available from the Phase III study TDM4788g/BO22589 was included in the background section. • The reporting of left ventricular systolic dysfunction events as SAEs was clarified • Pregnancy reporting requirements were updated, in line with the Global Enhancement Pharmacovigilance Pregnancy Program

Funding

The trial was funded by Hoffman-LaRoche/Genetech. Four of the 29 authors reported only non-financial support (medical writing support) from the Sponsor during study conduct, with one reporting a dinner meeting to discuss the study. An additional 5 authors were directly employed by Hoffman-La Roche and owned stock and/or equity in the company. The remaining 20 authors reported receiving financial compensation from the Sponsor in the form of grants and personal fees for consulting, travel (including accommodations to attend meetings), honoraria (for advisory boards, lectures, and/or speaking), education, and research funding. Three of the 20 authors reported this financial compensation went to their institution.[1]

b) Populations

A total of 1486 patients were randomly assigned to receive T-DM1 or trastuzumab (743 patients in each treatment arm). The median age in both treatment arms was 49 years, ranging from 24-79 years in the T-DM1 arm and 23 to 80 in the trastuzumab arm.[1] Almost all patients were female, with the exception of 2 male patients in the T-DM1 arm and 3 male patients in the trastuzumab arm.[2] Overall, demographic and clinical characteristics were well balanced between treatment arms with the majority of patients reporting White race/ethnicity (n=1082; 72.8%), with a clinical stage at presentation of operable breast cancer (n=1111; 74.8%), ER and/or PR positive (n=1074; 72.3%), and a prior treatment regimen involved anthracycline (n=1143, 76.9%).[1] Most patients had a baseline Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 (trastuzumab: n= 613, 82.5%;

trastuzumab emtansine: n = 597; 80.3%) compared to a ECOG PS of 1 (trastuzumab: n= 130, 17.5%; trastuzumab emtansine: n=146; 19.7%). There were 399 (53.7%) patients that were premenopausal and 344 (46.3%) patients that were postmenopausal in the T-DM1 treatment arm compared to 413 (55.6%) and 330 (44.4%) premenopausal and postmenopausal women, respectively, in the trastuzumab arm.[2] Most patients in both treatment arms had neoadjuvant HER2-directed therapy with trastuzumab alone (n=1196; 80.5%), and a similar proportion of patients in the T-DM1 arm (133; 17.9%) and trastuzumab arm (n=139; 18.7%) had trastuzumab plus pertuzumab.[1] Demographic and clinical characteristics are presented in Table 6.8.

Overall, 1195 (80.4%) of patients had HER2 status confirmed by pre-surgical sample, and 289 (19.4%) of patients had HER2 status confirmed centrally by surgical sample. The proportion of patients with HER2 status confirmed centrally by pre-surgical sample (81.2% in the trastuzumab arm vs. 79.7% in the T-DM1 arm) and surgical sample (18.6% in the trastuzumab arm vs. 20.3% in the T-DM1 arm) was similar between treatment arms. There were 2 patients in the trastuzumab arm with unknown HER2 status (one was randomized with missing HER2 status, but was assessed as positive during re-randomization and another patient's HER2 status could not be confirmed centrally).[13]

Table 6.8. Demographic and clinical characteristics at baseline in the KATHERINE trial

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Trastuzumab Group (N=743)	T-DM1 Group (N=743)
Median age (range) — yr	49 (23–80)	49 (24–79)
Race or ethnic group — no. of patients (%)†		
White	531 (71.5)	551 (74.2)
Asian	64 (8.6)	65 (8.7)
Black	19 (2.6)	21 (2.8)
American Indian or Alaska Native‡	50 (6.7)	36 (4.8)
Multiple or unknown	79 (10.6)	70 (9.4)
Clinical stage at presentation — no. of patients (%)		
Inoperable breast cancer§	190 (25.6)	185 (24.9)
Operable breast cancer¶	553 (74.4)	558 (75.1)
Hormone-receptor status — no. of patients (%)		
Estrogen-receptor–negative and progesterone-receptor–negative or status unknown	203 (27.3)	209 (28.1)
Estrogen-receptor–positive, progesterone-receptor–positive, or both	540 (72.7)	534 (71.9)
Previous use of anthracycline — no. of patients (%)	564 (75.9)	579 (77.9)
Neoadjuvant HER2-targeted therapy — no. of patients (%)		
Trastuzumab alone	596 (80.2)	600 (80.8)
Trastuzumab plus pertuzumab	139 (18.7)	133 (17.9)
Trastuzumab plus other HER2-targeted therapy‖	8 (1.1)	10 (1.3)

* Additional baseline characteristics are listed in Table S1 in the Supplementary Appendix. Percentages may not total 100 because of rounding. HER2 denotes human epidermal growth factor receptor 2, and T-DM1 trastuzumab emtansine.
† Race or ethnic group was reported by the investigators.
‡ The American Indian category includes North, Central, and South American Indians.
§ Inoperable breast cancer was defined as tumor stage T4, nodal stage Nx, and metastasis stage M0 or tumor stage Tx, nodal stage N2 or N3, and metastasis stage M0.
¶ Operable breast cancer was defined as tumor stage T1 to T3, nodal stage N0 or N1, and metastasis stage M0.
‖ Other HER2-targeted agents were neratinib, dacomitinib, afatinib, and lapatinib.

Source: The New England Journal of Medicine, von Minckwitz G, et al, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, 380(7), 617-628. Copyright ©2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

c) Interventions

A total of 1460 patients were treated, with 740 in the T-DM1 treatment arm and 720 in the trastuzumab arm. There were 23 patients who did not receive the randomly assigned treatment in the trastuzumab arm and 4 patients in the T-DM1 arm, of which three patients are being followed for disease recurrence and survival. One patient was randomized to T-DM1, but was administered 9 cycles of trastuzumab and was included in the trastuzumab safety population. There was one patient who was randomized twice in error, initially to trastuzumab and then to T-DM1 and was included in the trastuzumab intention-to-treat population and the T-DM1 safety population. There was one patient that was randomized to trastuzumab and treated with 13 cycles of trastuzumab and 1 cycle of T-DM1 in error, and thus was included in the T-DM1 safety population.[1] In the trastuzumab arm, a larger number of patients (n=17) withdrew prior to receiving their randomly assigned therapy compared to the T-DM1 arm (n=2). Other reasons in the trastuzumab arm for not receiving the randomly assigned treatment included a protocol violations (n=4) and inadequate venous access (n=1), and in the trastuzumab arm other reasons included ineligible (n=1) and recurrence noted prior to first dose of study drug (n=1).[13]

All treatments were administered intravenously. Patients assigned to T-DM1 received 3.6 mg per kilogram of body weight and patients assigned to trastuzumab received 6 mg per kilogram of body weight once every 3 weeks for 14 cycles. A loading dose of 8 mg per kilogram of body weight was administered if more than 6 weeks had elapsed since the preceding dose of trastuzumab.

A total of 71.4% (n=528) of patients in the T-DM1 treatment arm and 81.0% (n=583) of patients in the trastuzumab arm received all 14 cycles of assigned treatment, representing approximately a 10% difference in treatment completion between treatment arms.[1] The median duration of treatment both arms was 10 months, ranging from 1 to 12 in the T-DM1 arm 1 to 13 months in the trastuzumab arm. The median number of treatment cycles was 14 in both arms.[2] Patients who discontinued T-DM1 early because of toxic effects could complete 14 cycles of trial treatment with trastuzumab, and of 133 (17.9%) patients who discontinued treatment early, 71 (9.6%) switched to trastuzumab of whom 63 (8.5%) completed a total of 14 cycles of HER2-targeted treatment.[1] The median duration of treatment with trastuzumab after the switch from T-DM1 was 5 months (range: 1-10), with patients completing 1-11 cycles of trastuzumab. The 8 patients who did not complete a total of 14 cycles of HER2-targeted therapy were not switched over to another HER2-targeted therapy.[2]

Previous Anticancer Therapies and Breast Cancer Surgery

Previous neoadjuvant treatments for breast cancer were balanced across the treatment arms and prior treatments are summarized in Table 6.9. In both treatment arms, the median time between surgery and randomization was 1.6 months. The type of definitive surgery between treatment arms was similar and the majority (60%) of patients underwent simple, radical, or modified radical mastectomy.[2] Prior breast cancer surgery is summarized in Table 6.10.

Table 6.9. Previous therapies for eBC in the KATHERINE trial

	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
Cumulative Dose of Prior Anthracyclines [mg/m2] (for Patients with known dose)		
n	522	525
Mean (SD)	268.7 (98.03)	263.9 (100.77)
Median	282.0	295.0
Min - Max	9 - 600	2 - 488
Prior Therapy Type		
Chemo (Anthracycline)	564 (75.9%)	579 (77.9%)
Chemo (Non-Anthracycline)	743 (100.0%)	743 (100.0%)
Hormonal	524 (70.5%)	528 (71.1%)
Trastuzumab	743 (100.0%)	743 (100.0%)
HER2-directed therapy other than trastuzumab	147 (19.8%)	143 (19.2%)
Other	1 (0.1%)	2 (0.3%)
Overall Clinical Response after Neoadjuvant Therapy		
Complete response	82 (11.0%)	74 (10.0%)
Partial response	501 (67.4%)	499 (67.2%)
Stable disease	72 (9.7%)	59 (7.9%)
Unknown but no progression	86 (11.6%)	110 (14.8%)
Not applicable	2 (0.3%)	1 (0.1%)
Prior Therapy Administered		
Trastuzumab		
n	743	743
Trastuzumab overall	743 (100.0%)	743 (100.0%)
Other HER2-targeted agents		
n	147	143
Afatinib	2 (0.3%)	4 (0.5%)
Lapatinib	5 (0.7%)	6 (0.8%)
Neratinib	1 (0.1%)	1 (0.1%)
Pertuzumab	139 (18.7%)	133 (17.9%)
Taxanes overall		
n	743	743
Docetaxel	424 (57.1%)	407 (54.8%)
Nanoparticle Paclitaxel	6 (0.8%)	6 (0.8%)
Paclitaxel	331 (44.5%)	350 (47.1%)
Other agents		
*cisplatin/*cyclophosphamide/*epirubicin/*etoposide/ Fluorouracil	0	3 (0.4%)
Bevacizumab	1 (0.1%)	1 (0.1%)
Bkm120	0	1 (0.1%)
Blinded Bkm120	0	1 (0.1%)
Capecitabine	1 (0.1%)	0
Carboplatin	147 (19.8%)	138 (18.6%)
Cisplatin	6 (0.8%)	4 (0.5%)
Cyclophosphamide	426 (57.3%)	440 (59.2%)
Cyclophosphamide/Fluorouracil	1 (0.1%)	1 (0.1%)
Cyclophosphamide/Fluorouracil/Methotrexate	1 (0.1%)	0
Doxorubicin	199 (26.8%)	194 (26.1%)
Epirubicin	366 (49.3%)	389 (52.4%)
Fluorouracil	140 (18.8%)	142 (19.1%)
Methotrexate	4 (0.5%)	3 (0.4%)
Pirarubicin	2 (0.3%)	0
Tegafur	1 (0.1%)	0
Vinorelbine	1 (0.1%)	0

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Note that due to a transcriptional error the regimen *cisplatin + epirubicin +fluorouracil (FEC) is showing as *cisplatin/*cyclophosphamide/*epirubicin/*etoposide/Fluorouracil in this table; patients received the standard FEC combination and did not receive either cyclophosphamide or etoposide.

Source: Table 19 CSR, p. 97/5878[2]

Table 6.10. Prior breast cancer surgery by treatment arm in the KATHERINE trial, ITT population

	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
Time to definitive surgery (in months from randomization)		
n	743	743
Mean (SD)	-1.85 (1.41)	-1.92 (2.32)
Median	-1.61	-1.64
Range	-14.2 - 9.3	-49.3 - 10.8
Patients with any type of definitive breast cancer surgery	743 (100.0%)	743 (100.0%)
Lumpectomy/partial mastectomy	297 (40.0%)	295 (39.7%)
Simple/radical/modified radical mastectomy	446 (60.0%)	448 (60.3%)
Other surgeries and biopsies	663 (89.2%)	665 (89.5%)
Reconstructive surgery	57 (7.7%)	68 (9.2%)
Re-excision of surgical margins	24 (3.2%)	30 (4.0%)
Sentinel node biopsy/axillary sampling	270 (36.3%)	263 (35.4%)
Axillary dissection	360 (48.5%)	367 (49.4%)
Biopsy	552 (74.3%)	557 (75.0%)

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Note that for the range in time to definitive surgery, the maximums are positive: this is due to data entry error of the date of surgery (5 patients).

Source: Table 20 CSR, P. 98/5878[2]

Concomitant Medications

Prohibited concomitant medications included other anticancer therapies, including cytotoxic chemotherapy, radiotherapy (except for adjuvant therapy for breast cancer after completion of chemotherapy), immunotherapy, biological/targeted anticancer therapy, and other investigational gents. Concomitant use of strong CYP 3A4/5 inhibitors with T-DM1 was to be avoided, and if required, patients were to be closely monitored. Excessive alcohol intake was also to be avoided.[1]

Adjuvant radiotherapy and concomitant hormonal therapy was allowed as specified in the protocol and outlined earlier in this section. Briefly, hormonal therapy was required for hormone receptor positive patients. As outlined in Table 6.11, 525 (70.9%) patients and 512 (71.1%) of patient in the T-DM1 and trastuzumab arms received at least one treatment with hormonal therapy, which was generally consistent with the total population of patients that were hormone receptor positive (10 patients in the trastuzumab arm and 7 patients in the T-DM1 arm who were HR positive did not receive hormonal therapy for unknown reasons).[2,13] The most common classes of hormonal therapy were anti-estrogens and aromatase inhibitors. There were no major differences between treatment arms in anti-estrogens, and tamoxifen was the most commonly used anti-estrogen (n=347 [46.9%] in the T-DM1 arm and n=321 [44.7%] in the trastuzumab arm). There were more patients in the trastuzumab arm who received an aromatase inhibitor (n=261, 36.3%) than the T-DM1 arm (n=235; 31.8%), primarily due to more patients

receiving letrozole (n=158, 21.9%) in the trastuzumab arm than the T-DM1 arm (n=125; 16.9%).

Whole breast irradiation and regional node irradiation (if T3 or T4 and/or N2 or N3 disease at initial diagnosis) was required for patients undergoing breast-conserving surgery. Regional node irradiation (same requirement as breast-conserving surgery patients) was also required for post-mastectomy patients. For both breast-conserving surgery patients and post-mastectomy patients, regional node irradiation was also recommended if there was residual disease in lymph nodes. Radiotherapy received was balanced between treatment arms and is summarized in Table 6.12.[2]

Table 6.11. Summary of hormonal therapy received concomitantly by treatment arm in the KATHERINE trial, safety population

	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
Total number of patients with at least one treatment	512 (71.1%)	525 (70.9%)
Overall total number of treatments	652	633
ANTI-ESTROGENS		
Total number of patients with at least one treatment	322 (44.7%)	347 (46.9%)
Total number of treatments	348	361
TAMOXIFEN	321 (44.6%)	345 (46.6%)
FULVESTRANT	4 (0.6%)	2 (0.3%)
TOREMIFENE CITRATE	1 (0.1%)	1 (0.1%)
AROMATASE INHIBITORS		
Total number of patients with at least one treatment	261 (36.3%)	235 (31.8%)
Total number of treatments	304	272
LETROZOLE	158 (21.9%)	125 (16.9%)
ANASTROZOLE	100 (13.9%)	95 (12.8%)
EXEMESTANE	41 (5.7%)	42 (5.7%)

Multiple uses of a specific medication for a patient were counted once in the frequency for the medication. Likewise, multiple uses within a specific medication class for a patient were counted once in the frequency for the medication class.Includes medications recorded on the 'Adjuvant hormone therapy' eCRF page.
All patients received these agents in the adjuvant setting with the following exceptions: Tamoxifen: 2 patients(1013, trastuzumab arm and 2997, T-DM1 arm); Fulvestrant: all patients; Letrozole: (1756 and 7301, both in the trastuzumab arm); Exemestane (7453, T-DM1 arm).
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Note: patients received these agents in the adjuvant setting with the following given in the recurrent disease setting: Tamoxifen: 2 patients (1 in trastuzumab arm and 1 in the trastuzumab emtansine arm); Fulvestrant: 6 patients; Letrozole: 2 patients (both in the trastuzumab arm); Exemestane: (1 patient in the trastuzumab emtansine arm).

Source: p. 100/5878 CSR, Table 21[2]

Table 6.12. Summary of radiation therapy received concomitantly by treatment arm in the KATHERINE trial, safety population

	Trastuzumab (N=720)	Trastuzumab Emtansine (N=740)
Total number of patients with adjuvant radiotherapy	590 (81.9%)	623 (84.2%)
Site		
n	590	623
R Chest Wall	149 (20.7%)	147 (19.9%)
L Chest Wall	151 (21.0%)	152 (20.5%)
R breast	141 (19.6%)	172 (23.2%)
L breast	164 (22.8%)	169 (22.8%)
R axilla/Super Clavicular	162 (22.5%)	150 (20.3%)
L axilla/Super Clavicular	177 (24.6%)	165 (22.3%)
Internal Mammary	56 (7.8%)	61 (8.2%)
Tumor Bed	123 (17.1%)	122 (16.5%)
Other	89 (12.4%)	92 (12.4%)

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Source: p. 100/5878 CSR, Table 22[2]

Subsequent Anticancer Treatments

Almost double the patients in the trastuzumab arm (n=131; 18.2%) compared to the T-DM1 arm (n=72; 9.7%) received follow-up anticancer therapies. This was primarily due to more patients in the trastuzumab arm receiving further HER2-targetted therapies. Specifically, 83 (11.5%) in the trastuzumab arm received subsequent trastuzumab compared to 35 patients in the T-DM1 arm (n=35; 4.7%), and 48 (6.7%) received subsequent pertuzumab in the trastuzumab arm compared to 11 (1.5%) patients in the T-DM1 arm. A higher proportion of patients in the trastuzumab arm also received taxanes (n=71, 9.9%) compared to the T-DM1 arm (n=17, 2.3%), with 5.3% (n=38) of patients receiving paclitaxel and 4.7% (n=34) of patients receiving docetaxel in the trastuzumab arm compared to 1.2% (n=9) and 1.1% (n=8) receiving paclitaxel and docetaxel, respectively, in the T-DM1 arm. A total of 33 patients (4.6%) in the trastuzumab arm compared to 4 (0.5%) patients in the T-DM1 arm received subsequent therapy with T-DM1. A similar number of patients in both treatment arms received a subsequent tyrosine kinase inhibitor (TKI), with 20 (2.8%) patients in the trastuzumab arm and 19 (2.6%) in the T-DM1 arm receiving subsequent lapatinib.[2]

d) Patient Disposition

The patient disposition diagram is outlined in Figure 6.2. A total of 1925 patients were screened for eligibility, of which 439 were ineligible. Reasons for ineligibility included inadequate establishment of HER2-positive status (n=186), inadequate organ function (n=63), patient declined to participate (n=57), and other reasons (n=133).[1] Some examples of other reasons for ineligibility included the screening period was exceeded, incomplete, or re-screening was needed (n=23); the interval of 12 weeks between date of surgery and date of randomization was exceeded (n

=18); pathologic evidence of residual invasive carcinoma in the breast or axillary lymph nodes following completion of preoperative therapy (n=12); and fluorescence in situ hybridization (FISH) determination of HER2 status by TARGOS Molecular Pathology not done or ready in time (n=7).[13] A total of 1486 patients were randomized, 743 to each treatment arm. A total of 740 patients received study treatment with T-DM1 (739 randomised to T-DM1 and 1 randomised to trastuzumab) and 720 patients with trastuzumab (719 randomised to trastuzumab and 1 randomised to T-DM1). There were 23 patients in the trastuzumab arm who were randomized and did not receive planned study medication and 4 in the T-DM1 arm.[1] Of the 23 patients that did not receive randomized study treatment in the trastuzumab arm, 17 participants withdrew consent, 4 patients had a protocol violation, 1 patient was re-randomized to the T-DM1 arm, and 1 patient did not have adequate venous access. Of the 4 patients who were randomized to the T-DM1 arm and did not receive treatment, 2 patients withdrew, 1 was ineligible, and 1 had recurrence prior to the first dose of study drug.[13] However, since 1 patient was re-randomized from trastuzumab to T-DM1 and was treated with T-DM1, the total safety population in the T-DM1 arm was 740.

More patients in the T-DM1 treatment discontinued study treatment prematurely due to AEs (n=133, 18.0%) compared to the trastuzumab arm (n=15; 2.1%).

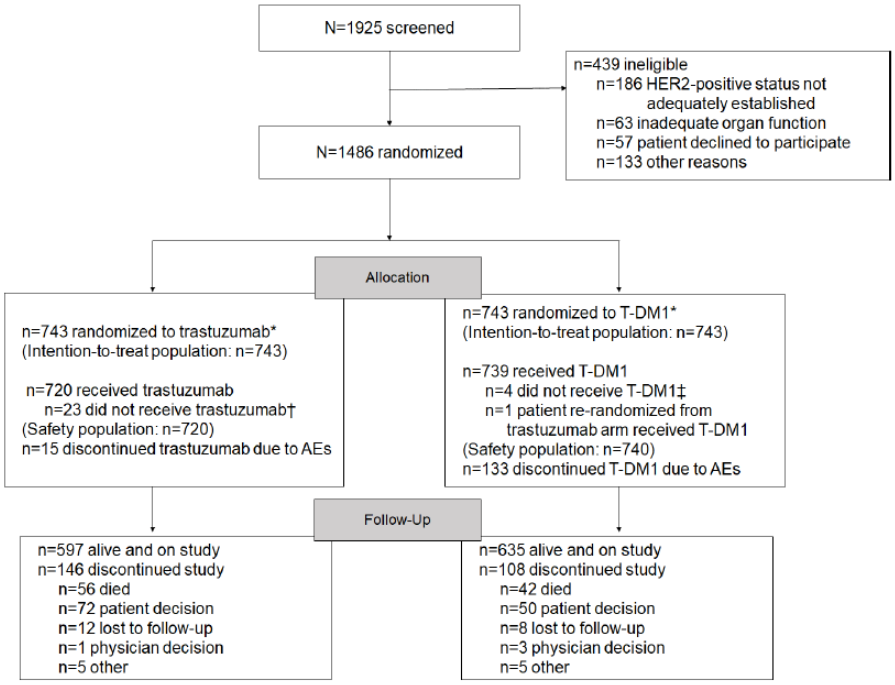
As of the interim data cut-off date of July 25th, 2018, all patients had completed treatment and a total of 635 (85.5%) patients in the T-DM1 arm and 597 (80.3%) patients in the trastuzumab arm were alive and on study. A total of 108 (14.5%) patients had permanently discontinued the study without further follow up in the T-DM1 arm, whereas 146 (19.7%) patients had permanently discontinued the study without further follow up in the trastuzumab arm.[2,14] The most common reason for permanent discontinuation was patient decision in both arms, with more patients deciding to discontinue in the trastuzumab arm (n=72; 9.7%) compared to the T-DM1 arm (n=50; 6.7%). The most common reason for voluntary withdrawal was personal reasons/patient wish, with 15 patients in the trastuzumab arm compared to 8 patients in the T-DM1 arm reporting this reason. Other reasons for voluntary withdrawal in the T-DM1 included patient no longer wished to be treated (n=8), side effects (n=7), and withdrawal of consent (n=5). Other reasons for voluntary withdrawal in the trastuzumab arm included withdrawal of consent (n=10), patient had one year of trastuzumab and did not want additional treatments (n=8), and patient refused to continue to treatment (n=6).[13] Patient decision/voluntary withdrawal was followed by death as the most common reason patients discontinued study, with 56 (7.5%) deaths in the trastuzumab arm and 42 (5.7%) deaths in the T-DM1 arm.[1]

Protocol Deviations

Protocol deviations are summarized in Table 6.13. There were more patients in the T-DM1 arm with a major protocol deviation (n=156; 21%) compared to the trastuzumab arm (n=93; 12.5%). Major exclusion criteria deviations were balanced between treatment arms (1.6% vs. 0.8% in the trastuzumab vs. T-DM1 arms, respectively), as were major inclusion criteria deviations (9.7% vs. 10.6% in the trastuzumab vs. T-DM1 arms, respectively). Lack of signed informed consent was the most common inclusion criteria deviation, which included 13 (1.7%) patients in the trastuzumab arm and 15 (2.0%) patients in the T-DM1 arm. The difference between treatment arms in protocol deviations was driven by major on-study protocol deviations, which occurred in 83 (11.2%) of patients in the T-DM1 arm compared to 9 (1.2%) patients in the trastuzumab arm. There were 78 (10.5%)

patients that did not have their dose held or reduced as per protocol in the T-DM1 arm compared to 4 (0.5%) patients in the trastuzumab arm.[2]

Figure 6.2. Patient disposition diagram for the KATHERINE trial



Source: The New England Journal of Medicine, von Minckwitz G, et al, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, 380(7), 617-628. Copyright ©2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

Table 6.13. Protocol deviations in the KATHERINE trial by treatment arm, ITT population

Protocol Deviations of Interest	Trastuzumab (N=743)	Trastuzumab Emtansine (N=743)
No. Of Patients With At Least One Protocol Deviation	93 (12.5%)	156 (21.0%)
Major Exclusion Criteria Deviation	12 (1.6%)	6 (0.8%)
Major Inclusion Criteria Deviation	72 (9.7%)	79 (10.6%)
Major On-Study Protocol Deviation	9 (1.2%)	83 (11.2%)
Major Exclusion Criteria Deviation		
Patients With At Least One Exclusion Criteria Deviation	12 (1.6%)	6 (0.8%)
Active Liver Disease: 15	0	2 (0.3%)
Active, Unres Infections Requiring Treatment: 18	4 (0.5%)	0
Exceed Cumulative Dose Of Anthracyclines: 9	1 (0.1%)	0
Hbv/Hcv But Liver Tests Not Repeated In Scr: 15	6 (0.8%)	1 (0.1%)
History Of Other Malignancy In Last 5 Years: 6	0	1 (0.1%)
Pd By Inv At End Of Preoperative Systemic Chemo: 4	1 (0.1%)	0
Prohibited Cardiopulmonary Dysfunction: 10	0	2 (0.3%)
Major Inclusion Criteria Deviation		
Patients With At Least One Inclusion Criteria Deviation	72 (9.7%)	79 (10.6%)
<=12 Wks From Primary Surgery To Randomization: 7	6 (0.8%)	6 (0.8%)
Adequate Anc, Platelets, Hemoglobin: 13a-C	1 (0.1%)	2 (0.3%)
Adequate Ast, Alt, Bilirubin, Alk: 13f-H	4 (0.5%)	10 (1.3%)
Adequate Coagulation Labs: 13e	8 (1.1%)	7 (0.9%)
Adequate Contraception Methods: 14	0	3 (0.4%)
Adequate Creatinine: 13d	0	2 (0.3%)
Adequate Excision Of Breast And Lymph Disease: 5	7 (0.9%)	6 (0.8%)
Adequate Organ Function Missing Required Labs: 13	10 (1.3%)	7 (0.9%)
Adequate Systemic Chemo And Tras Prior To Sx: 4	7 (0.9%)	6 (0.8%)
Confirmed Her2-Positive Bc By Central Lab: 1	5 (0.7%)	6 (0.8%)
Documented Hbv And Hcv Status Per Protocol: 16	10 (1.3%)	9 (1.2%)
Inadequate Baseline Lvef: 13.I	3 (0.4%)	7 (0.9%)
Negative Pregnancy Test Per Protocol: 15	3 (0.4%)	0
No Icf/Signed Icf Approved By Irb/Ec: 9	13 (1.7%)	15 (2.0%)
Pathologic Evidence Of Residual Inv Disease: 6	1 (0.1%)	0
Major On-Study Protocol Deviation		
Patients With At Least One Major On-Study Protocol Deviation	9 (1.2%)	83 (11.2%)
Dose Delay > 42 Days For Toxicity	0	1 (0.1%)
Dose Deviating >20% Of Planned Dose	1 (0.1%)	0
Dose Not Reduced/Held Per Protocol	4 (0.5%)	78 (10.5%)
Drug Not Discontinued Despite Meeting Criteria	1 (0.1%)	0
Received Incorrect Study Medication	1 (0.1%)	2 (0.3%)
Received Prohibited Concomitant Medication	1 (0.1%)	0
Sae Not Reported Within The Expected Timelines	1 (0.1%)	3 (0.4%)

Source: CSR Table 12; p. 83/5878[2]

e) Limitations/Sources of Bias

Key limitations and sources of bias include:

- The primary outcome of the trial, iDFS, has not been validated in the published literature, thus, the strength of the association between this surrogate outcome and OS is unknown. In addition, there are varying definitions for iDFS and DFS in the literature, which make cross-trial comparisons challenging for analysis and interpretation. As per STEEP, and more recently, as per the DATECAN (Definition for the Assessment of Time-to-event Endpoints in CANcer trials) initiative, the definition of iDFS was recommended to include second primary non-breast invasive cancer as an event for a more conservative approach.[12,34] However, a more narrow definition that excluded a second primary as an event was used in the KATHERINE trial, which has certain limitations, for example, distant recurrences may have been misdiagnosed as a second primary, and thus would have be excluded as an iDFS event providing a more and estimate of iDFS that favours the T-DM1 arm. Although secondary analyses with the STEEP definition for iDFS and DFS (which included in-situ breast cancers in

the definition) were conducted and were consistent with the primary analysis, these analyses were not controlled for multiplicity. A recent meta-analysis was conducted to explore the validity of DFS as a surrogate for OS in patients with HER2-positive, early breast cancer in trials of adjuvant trastuzumab using both patient-level associations (i.e., whether patients with prolonged DFS are more likely to have prolonged OS) and trial-level associations (i.e., whether treatment-induced changes in the surrogate endpoint are accompanied by proportional changes in the final endpoint) as outcomes.[35] The patient-level associations between DFS and OS were found to be valid (r_s = 0.90; 95% CI: 0.89-0.90) as per IQWIG guidance, however the trial-level associations indicated unclear validity with an R^2 of 0.75 (95% CI; 0.50-1.00).[35,36] Trial-level validation is typically the method most suited for regulatory approval for validation of a surrogate endpoint.[36] However, it must be noted that this validation study involved eight trials with varying definitions of DFS (some definitions of DFS were consistent with the definition of iDFS).

- The study design was open-label, which is susceptible to reporting and performance biases as patients and investigators were not blinded to study treatment. All outcomes were investigator-assessed, of which most were confirmed either pathologically, radiologically, or using both methods (2 cases of distant recurrence in the trastuzumab arm and 1 case of distant recurrence in the T-DM1 arm were not confirmed pathologically or radiologically which could mean these tests were not done or that the test was negative).[13] However, reporting biases remain a concern with the potential for delaying pathological or radiological confirmation of an iDFS events in the T-DM1 arm based on the open-label design. It should be noted that there were a higher proportion of protocol deviations related to investigators not holding or reducing the dose of T-DM1 as per protocol (10.5% vs. 0.5% in the T-DM1 and trastuzumab arms, respectively), which indicated some degree of investigator bias as well as deviation bias in the T-DM1 arm.[2] An analysis to assess for deviation bias related to dosing was conducted by the sponsor. The iDFS analysis excluding the 10.5% (n=78) and the 0.5% (n=4) of patients in the T-DM1 and trastuzumab arms, respectively, with a deviation of not having dose reduced or held as per protocol resulted in a HR consistent with the primary iDFS analysis (HR: 0.50; 95% CI: 0.39, 0.66). The impact of deviation bias can be considered minimal on efficacy outcomes.[13]
- Though deviation bias related to not holding or reducing doses as per protocol may be minimal on efficacy outcomes observed in the trial, it may not be reflective of how the drug will be administered in clinical practice. In theory, if clinicians prescribe the drug as per protocol in practice (and thus, hold or reduce doses due to toxicity) in a much larger population, it could result in the drug being less efficacious in the "real-world" setting.
- Irrespective of the fact that 10.5% of patients that did not have their doses held or reduced in the T-DM1 arm due to toxicity, there were still a higher proportion of patients in the T-DM1 arm that required a dose reduction (10.4% required a one-level dose reduction and 3.9% required a two-level dose reduction, compared to no patients in the trastuzumab arm); dose interruption (14.3% compared to 5.1% in the trastuzumab arm); and discontinued treatment due to an AE (18.0% compared to 2.1%

in the trastuzumab arm).[2] This is indicative of a higher proportion of toxicities in the T-DM1 arm overall, and the proportion of dose interruptions or reductions may be underestimated due to the higher proportion of protocol deviations related to not holding or reducing doses for toxicities in this treatment arm.

- Patients who discontinued T-DM1 treatment early (i.e., due to toxicity) were able to crossover to trastuzumab. Of 133 (17.9%) patients who discontinued T-DM1 treatment early, 71 (9.6%) switched to trastuzumab.[1] Post-hoc exploratory analyses adjusting for crossover to trastuzumab of the primary endpoint of iDFS (HR: 0.47; 95% CI: 0.36, 0.62) and secondary endpoint of OS (HR: 0.69; 95% CI: 0.45, 1.05), revealed results that were consistent with the primary analysis.[13] The potential confounding of crossover to trastuzumab in the T-DM1 arm was considered to have a minimal effect on the overall efficacy results, however limitations of the analytical method selected for the adjustment may have introduced bias. HRQoL also may have been impacted by crossover of T-DM1 patients to trastuzumab. [redacted][2] HRQoL assessments of the T-DM1 arm at specific cycles included all patients (those that crossed over and those that did not), and thus could potentially be confounded by crossover. *(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 3rd, 2020 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)*
- Double the patients in the trastuzumab arm compared to the T-DM1 arm received follow-up anticancer therapies. More patients in the trastuzumab arm (11.5%) received subsequent trastuzumab compared to the T-DM1 arm (4.7%), and 6.7% of patients received subsequent pertuzumab in the trastuzumab arm compared to 1.5% of patients in the T-DM1 arm. A higher proportion of patients in the trastuzumab arm also received taxanes (9.9%) compared to the T-DM1 arm (2.3%). A total of 4.6% of patients in the trastuzumab arm compared to 0.5% patients in the T-DM1 arm received subsequent therapy with T-DM1.[2] The imbalance of subsequent therapies between treatment arms may confound the results in an unknown direction. Discussion with the CGP revealed that subsequent therapies in the trastuzumab arm were not reflective of clinical practice (for example, T-DM1 is an established subsequent therapy following trastuzumab in the recurrent setting), which may indicate investigator bias in prescribing patterns due to the open-label nature of the study design and may bias the results in favour of T-DM1.
- There were more patients in the trastuzumab arm who received an aromatase inhibitor (n=261, 36.3%) than the T-DM1 arm (n=235; 31.8%), primarily due to more patients receiving letrozole (n=158, 21.9%) in the trastuzumab arm than the T-DM1 arm (n=125; 16.9%).[2] As per discussion with the Clinical Guidance Panel, this was not predicted to affect outcomes, and thus the potential confounding is predicted to be limited.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Efficacy analyses were performed using the intention-to-treat population, which included all patients who were randomized, regardless of treatment received. A total of 1,486 patients were included in the intention-to-treat (ITT) population.[1] As of the data cut-off date of July 25th, 2018, the median duration of follow-up was 41.4 months (range, 0.1 to 62.7) in the T-DM1 arm and 40.9 months (range, 0.1 to 62.6) in the trastuzumab arm.[1,3]

Primary Endpoint – Invasive Disease-Free Survival (iDFS)

The primary endpoint of the study was met at the prespecified IA for iDFS. A total of 91 (12.2%) iDFS events occurred in the T-DM1 arm compared to 165 (22.2%) iDFS events in the trastuzumab arm. The site of first invasive disease event is summarized in Table 6.14, with more distant recurrences occurring in the trastuzumab arm (n=121, 16.3%) compared to the T-DM1 arm (n=78; 10.5%). The estimated invasive disease-free event rate at 3 years was 88.3% (95% CI: 85.8, 90.7) in the T-DM1 arm and 77.0% (95% CI: 73.8, 80.3) in the trastuzumab arm. [1,2] There was a 50% reduction in the risk of an iDFS event with the T-DM1 treatment arm compared to the trastuzumab arm (unstratified HR: 0.50; 95% CI: 0.39, 0.64; p<0.001), and the K-M curves as illustrated in Figure 6.3., Panel A.[1]

The stratified analyses as initially planned were not reported due to stratum with <5 patients, and thus it was deemed that robust stratified analyses could not be conducted and instead, unstratified analyses were reported as the primary results as per the pre-specified statistical analysis plan. Stratum with less than 5 patients included patients that were inoperable, negative for hormone receptor status, received trastuzumab plus an additional HER2-directed agent, and were negative/not done for nodal status; and patients that were inoperable, had positive hormone receptor status, received trastuzumab plus an additional HER2-directed agent, and were negative/not done for nodal status. The stratified analyses with all 4 stratification factor were performed nonetheless and confirmed the robustness of the primary unstratified analyses results, as the results were highly consistent (HR: 0.482; 95% CI: 0.373, 0.622). The sponsor further supplemented this with a reduced stratification factor model, although cited the difficulty in selecting which stratification factor to exclude. Statistical methods, specifically the stepwise selection option in the PHREG model statement in SAS, were used and that resulted in exclusion of factor 3 (pre-operative therapy stratification factor),and the results were consistent with the primary analysis (HR: 0.481; 95% CI: 0.372, 0.622). Finally, 4 stratified models including only one of the stratification factors were run with each model resulting in HRs that ranged from 0.48 to 0.49, which further confirmed the robustness and appropriateness of running unstratified analyses for the primary results.[13]

Two sensitivity analyses were performed where patients were 1) censored at the time they began a new anticancer therapy before experiencing an iDFS event; and 2) censored at the time they discontinued study treatment due to any reason before experiencing an iDFS event. Both analyses were consistent with the primary analysis and are presented in Table 6.15.[2]

Subgroup analyses of iDFS also showed a consistent benefit across stratification factors and other subgroups, presented in Figure 6.4 and 6.5. Of note, the confidence interval crossed 1 in the ≥65 years of age subgroup; in the subgroup of patients that received preoperative therapy with trastuzumab and additional HER2-

directed agent(s); tumor stage of T4 at definitive surgery; regional lymph node stage of N4 or not evaluable; patients that reported Black or African American, or Asian, or American Indian or Alaska Native, or unknown races; primary tumor stage at initial diagnosis of cT4, cT4a, cT4B, or cT4c, or cT4d; and regional lymph node stage at initial diagnosis of cN3. Sensitivity or subgroup analyses are not powered to detect statistically significant differences, and thus should be considered exploratory.[1]

Approximately 9.6% of patients in the T-DM1 arm crossed over to trastuzumab, and 8.5% completed 14 cycles of HER2-targeted therapy with trastuzumab. Since HER2-targeted therapy in the adjuvant setting has a known beneficial treatment effect, it would be unethical to withhold if patients could not complete T-DM1 for reasons such as toxicity. However, given trastuzumab has a known beneficial treatment effect and crossover occurred prior to the occurrence of an iDFS event for at least the 8.5% of patients that completed HER2 therapy with trastuzumab, the treatment effect in the T-DM1 arm may be overestimated as it is confounded by this crossover.

Thus, a post-hoc exploratory analysis of iDFS adjusting for crossover of the T-DM1 arm to trastuzumab using rank-preserving structural failure time (RPSFT) methodology was also conducted and the unstratified results were consistent with the primary analysis (HR: 0.47; 95% CI: 0.36, 0.62; P <0.001).[13] While detailed information on the conduct of this analysis is not available, it may be subject to some limitations. Briefly, the application of this method would involve adjusting the survival time of the T-DM1 arm as if crossover never occurred. The causal effect of trastuzumab relative to T-DM1 would be estimated as a relative increase/decrease in OS. This constant factor is assumed to be equal for all patients who cross over, regardless of the timing of the switch – however, if there is an enhanced treatment benefit of sequencing trastuzumab after T-DM1 or if patients who crossover have worse prognosis due to inability to tolerate T-DM1, this would violate the "constant treatment effect" assumption and it could be in favour of the trastuzumab arm or T-DM1 arm. Rank is also preserved with this methodology, so if a patient in the trastuzumab arm experienced an iDFS event prior to a T-DM1 patient before survival time is adjusted, this would still be the case in the post adjustment. If there was a beneficial treatment effect of crossover from T-DM1 to trastuzumab to delay an iDFS event, this aspect of the RPSFT methods would bias in favour of T-DM1. Additional methods to adjust for crossover should have been explored to supplement the findings.

Though there were a higher proportion of patients that numerically experienced CNS recurrence as a first iDFS event in the T-DM1 arm (n=44; 5.9%) compared to the trastuzumab arm (n=32; 4.3%), exploratory analyses of OS post-CNS recurrence revealed no significant difference between treatment arms in OS (HR: 1.07; 95% CI: 0.60, 1.91). The 3-year OS event free rate was 24.2% (95% CI: 5.05, 43.3) in the T-DM1 arm and 25.4% (95% CI: 6.81, 44.0) in the trastuzumab arm in patients with CNS recurrence.[25]

Table 6.14. The site of first invasive disease-free survivaliDFS event in the KATHERINE trial, ITT populaton

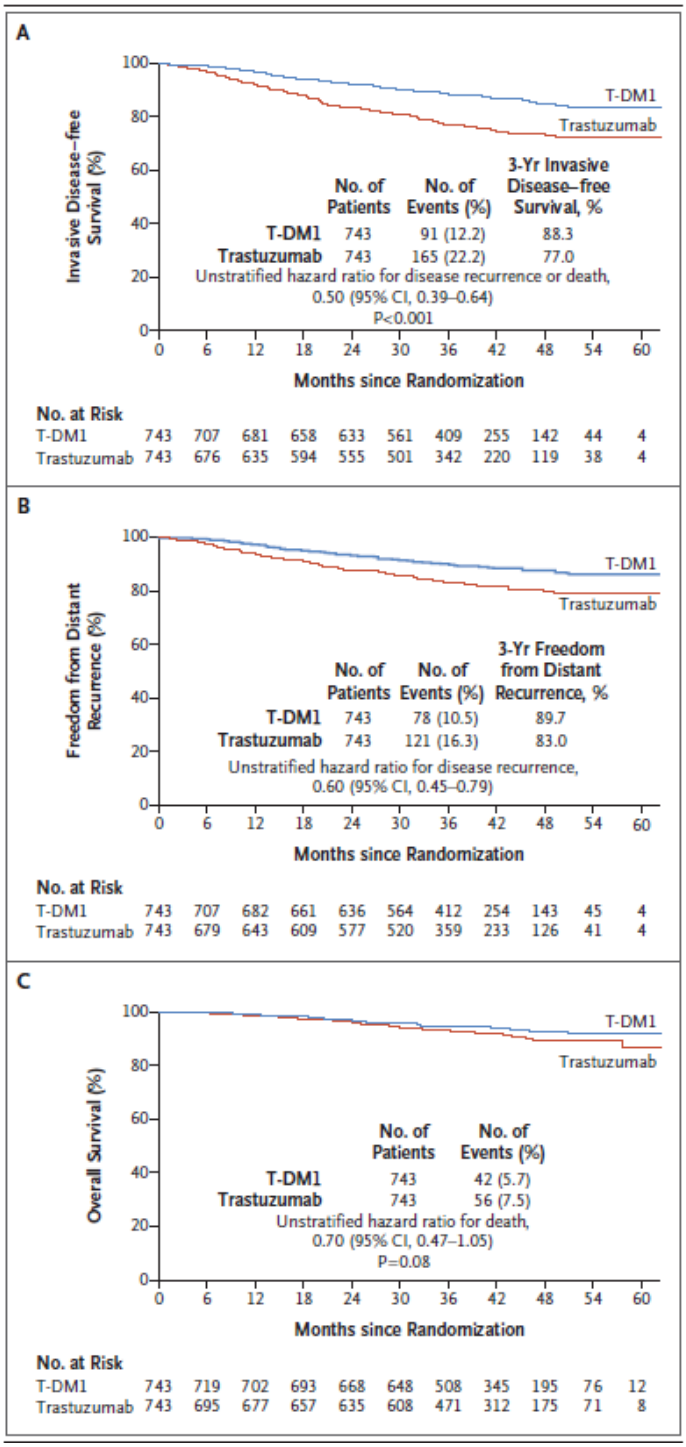
Event	Trastuzumab (n=743)	T-DM1 (n=743)
	no. of patients (%)	
Any invasive-disease event[†]	165 (22.2)	91 (12.2)
Category of first invasive-disease event		
Distant recurrence	118 (15.9)	78 (10.5)
Central nervous system recurrence	32 (4.3)	44 (5.9)
Locoregional recurrence	34 (4.6)	8 (1.1)
Contralateral breast cancer	10 (1.3)	3 (0.4)
Death without previous event	3 (0.4)	2 (0.3)

[*]Patients who experienced an additional invasive-disease event within 61 days of their first event are reported in the category according to the following hierarchy: distant recurrence (central nervous system recurrence is a subset of distant recurrence), locoregional recurrence, contralateral breast cancer, and death without a previous event. T-DM1 denotes trastuzumab emtansine.

[†]Six additional patients (two in the trastuzumab arm and four in the T-DM1 arm) had an invasive-disease event under the standardized definitions for efficacy end points (STEEP) definition, which includes second primary non-breast cancer.

Source: The New England Journal of Medicine, von Minckwitz G, et al, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, 380(7), 617-628. Copyright ©2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

Figure 6.3. Kaplan-Meier estimates of A) invasive disease-free survival B) distant recurrence-free survival, and C) overall survival based on the interim analysis, ITT population



Source: The New England Journal of Medicine, von Minckwitz G, et al, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, 380(7), 617-628. Copyright ©2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

Table 6.15. Sensitivity analyses results for invasive disease-free survival, ITT population

Analysis	3-year IDFS event-free rates (95% CI)		HR for IDFS	95% CI
	Trastuzumab (N=743)	Trastuzumab emtansine (N=743)		
Assessment of Robustness				
Censoring for new anti-cancer Therapy	77.4% (74.2, 80.7)	88.1% (85.5, 90.7)	0.51	0.39, 0.66
Censoring for Discontinuation of Study Treatment	81.6% (78.3, 84.8)	90.2% (87.6, 92.8)	0.54	0.39, 0.74

Source: CSR p. 108/5878; Table 26[2]

Figure 6.4. Subgroup analyses of invasive disease-free survival

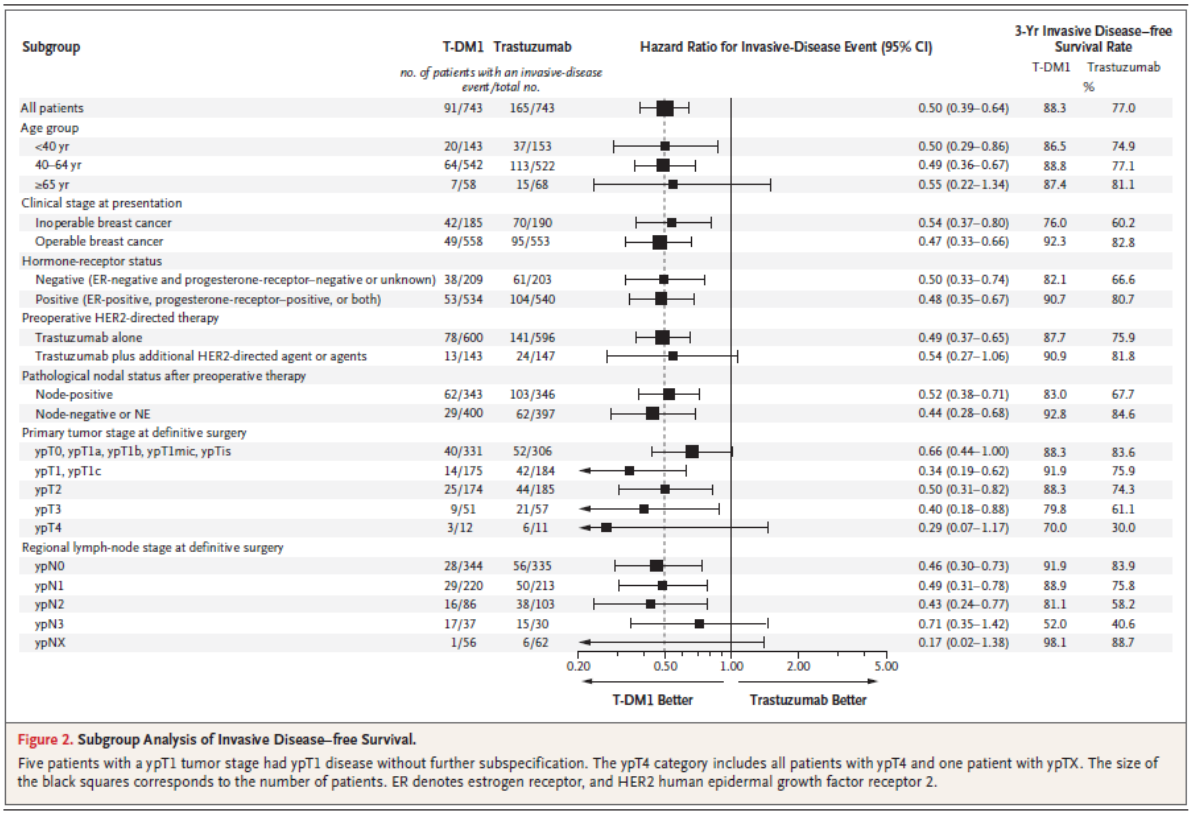
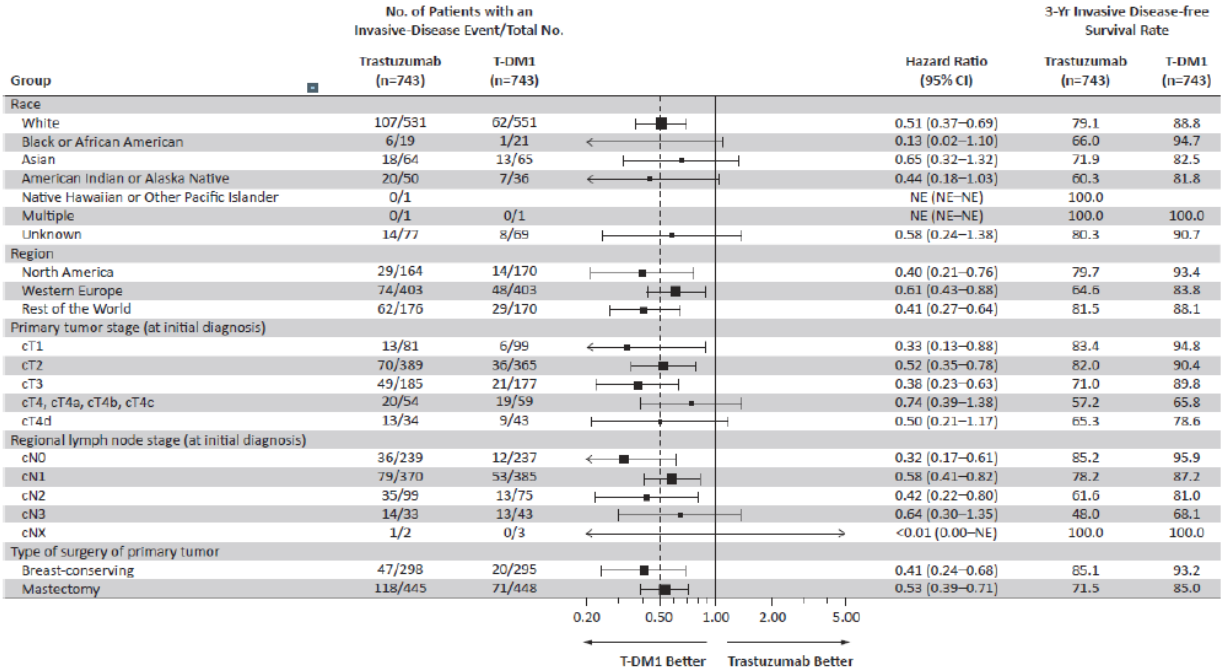


Figure 2. Subgroup Analysis of Invasive Disease–free Survival.

Five patients with a ypT1 tumor stage had ypT1 disease without further subspecification. The ypT4 category includes all patients with ypT4 and one patient with ypTX. The size of the black squares corresponds to the number of patients. ER denotes estrogen receptor, and HER2 human epidermal growth factor receptor 2.

Source: The New England Journal of Medicine, von Minckwitz G, et al, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, 380(7), 617-628. Copyright ©2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

Figure 6.5. Additional subgroup analyses of invasive disease-free survival



Source: The New England Journal of Medicine, von Minckwitz G, et al, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, 380(7), 617-628. Copyright ©2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

Secondary Endpoints

For secondary endpoints (i.e., iDFS, DFS, and DFSI), if >1 iDFS event are reported in the category associated with their earliest iDFS event. If >1 are reported on the same date, then patients are reported in the category according to the following hierarchy: distant recurrence (including central nervous system), locoregional occurrence, contralateral breast cancer, second primary non-breast invasive cancer, or death without primary event.[2] The median months and 95% CIs for K-M estimates have not been reached for all secondary outcomes.[13]

Invasive disease-free survival including second primary non-breast cancer (STEEP definition)

The iDFS analysis including a second primary non-breast cancer as an iDFS event (STEEP definition) was consistent with the primary analysis, as shown in Table 6.16. There were 95 (12.8%) patients in the T-DM1 arm and 167 (22.5%) patients in the trastuzumab arm that had an iDFS event with this definition. There was a 49% (unstratified HR: 0.51; 95% CI: 0.40, 0.66) reduction in the risk of an iDFS event with this definition in the T-DM1 arm compared to the trastuzumab. The estimated 3-year event rate for iDFS was 87.7% (95% CI: 85.2, 90.2) in the T-DM1 arm and 76.9% (95% CI: 73.7, 80.1) in the trastuzumab arm.[1]

Disease-free survival

The DFS definition included a second primary non-breast cancer event or contralateral or ipsilateral ductal carcinoma in situ as an event, and the DFS analysis was consistent with the primary iDFS results (Table 6.16). There were 98

(13.2%) patients with a DFS event in the T-DM1 arm and 167 (22.5%) in the trastuzumab arm. There was a 47% reduction in the risk of a DFS event in the T-DM1 arm compared to the trastuzumab arm. The estimated 3-year event rate for DFS was 87.4% (95% CI: 84.9, 89.9) in the T-DM1 arm and 76.9% (95% CI: 73.6, 80.1) in the trastuzumab arm.[1]

Overall survival

There were 42 deaths (5.7%) in the T-DM1 treatment arm and 56 (7.5%) deaths in the trastuzumab arm. As shown in Figure 6.3, Panel C (above section) and Table 6.16, there was no statistically signficiant difference in OS between treatment arms (HR: 0.70; 95% CI: 0.47, 1.05; p = 0.0848) in the IA, and OS data are immature.[1] The 5-year OS rates were estimated as 92.1% (95% CI: 89.4, 94.7) in the T-DM1 arm and 86.8% (95% CI: 81.0, 92.6) in the trastuzumab arm.[2] The K-M curves are illustrated in Figure 6.3C (above section).

A post-hoc exploratory analysis of OS adjusting for crossover of the T-DM1 arm to trastuzumab was also conducted and the unstratified results were consistent with the primary analyses (HR: 0.69; 95% CI: 0.45, 1.05; p = 0.0848).[13]

Distant reccurrence-free interval

A total of 78 (10.5%) distant recurrence events had occurred in the T-DM1 arm compared to 121 (16.3%) events in the trastuzumab arm, as shown in Table 6.16. Of note, this number is different that the number of distant recurrences shown in Table 6.14 as it includes the classification of distant reccurrence based on first occurrence of an iDFS event presenting as distant reccurence. In Table 6.14, patients who experienced an additional invasive disease event within 61 days of their first event were reported in the category according to the following hierarchy: distant recurrence (including central nervous system), locoregional occurrence, contralateral breast cancer, and death without a previous event.[1] The 61-day window was selected to assign weight to events with poorer prognosis within a reasonable period of time after an event with better prognosis (for example, ipsilateral breast recurrence), however it was not used in this analysis.[13]

As illustrated in Figure 6.3, Panel B (above section), there was a 40% reduction in distant recurrence events with T-DM1 compared to trastuzumab (HR: 0.60; 95% CI: 0.45, 0.79). The 3-year event rate was estimated at 89.7% (95% CI: 87.4, 92.0) in the T-DM1 arm and 83.0% (95% CI: 80.1, 85.9) in the trastuzumab arm.[1]

Table 6.16. Summary of secondary efficacy endpoints in the KATHERINE trial, ITT population

End Point	Trastuzumab (n=743)	T-DM1 (n=743)
Invasive-disease–free survival (STEEP definition)		
Patients with an event— no. of patients (%)	167 (22.5)	95 (12.8)
3-year event-free rate—% (95% CI)	76.9 (73.7–80.1)	87.7 (85.2–90.2)
Hazard ratio (95% CI)	0.51 (0.40–0.66)	
Disease-free survival		
Patients with an event— no. of patients (%)	167 (22.5)	98 (13.2)
3-year event-free rate—% (95% CI)	76.9 (73.6–80.1)	87.4 (84.9–89.9)
Hazard ratio (95% CI)	0.53 (0.41–0.68)	
Distant recurrence-free interval		
Patients with an event— no. of patients (%)	121 (16.3)	78 (10.5)
3-year event-free rate—% (95% CI)	83.0 (80.1–85.9)	89.7 (87.4–92.0)
Hazard ratio (95% CI)	0.60 (0.45–0.79)	
Overall survival		
Patients with an event— no. of patients (%)	56 (7.5)	42 (5.7)
Hazard ratio (95% CI)	0.70 (0.47–1.05)	
P-value (log-rank)‡	0.0848	

*CI denotes confidence interval, STEEP standardized efficacy end points, and T-DM1 trastuzumab emtansine.

†No statistical adjustments were made for multiple comparisons.

‡The boundary for statistical significance in this prespecified interim analysis was P<0.000032, corresponding to a hazard ratio of less than 0.43.

Source: The New England Journal of Medicine, von Minckwitz G, et al, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, 380(7), 617-628. Copyright ©2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

Quality of Life

Overall, 640 (86%) and 612 (82%) patients in the trastuzumab and T-DM1 arms, respectively, has a valid baseline and ≥ 1 post-baseline HrQOL assessment completed. The completion rates for the EORTC QLQ-C30 and EORTC-BR23 were consistently over 70% during the follow-up period.

Baseline scores were similar between treatment groups and are illustrated in Figure 6.6. The maximum possible score is 100, and scores for function scales that range

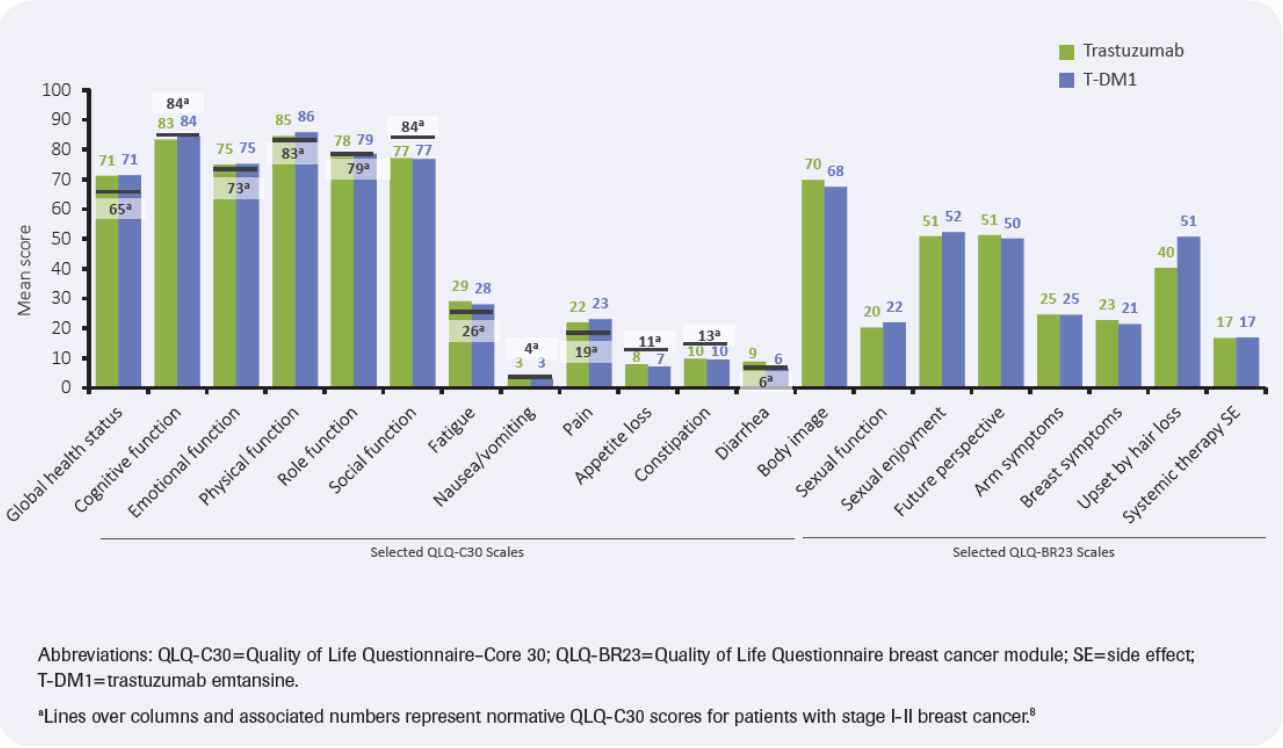
between 75-86 reflect moderate levels of functioning. For symptom scales (e.g., nausea/vomiting, appetite loss, pain, constipation, etc.), low score represents low to moderate levels of symptoms at baseline.

Mean changes from baseline over the course of the study were similar for global health status, cognitive functioning, physical functioning, and fatigue, as shown in Figure 6.7. There were no clinically meaningful changes from baseline for global health status in both treatment arms at Cycle 5, 11, treatment discontinuation, or at 6 and 12 month follow-up.[4] [redacted][2] *(Non-disclosable information was used in this pCODR Guidance Report and the sponsor requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until July 3rd, 2020 or until notification by the sponsor that it can be publicly disclosed, whichever is earlier.)*

Additionally, emotional, social, and role functioning from the EORTC QLQ-C30 and body image, future prospect, and sexual functioning scores from the EORTC QLQ-BR23 had similar mean changes from baseline. The 9 symptom scales from the EORTC QLQ-C30 and the 4 symptom scales from the EORTC QLQ-BR23 also had similar mean change scores from baseline. There were some increases in baseline score for fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and systemic therapy side effects, however these changes were not considered clinically meaningful and generally returned to baseline after treatment discontinuation.

As shown in Table 6.17, there were more patients in the T-DM1 treatment arm that reported a clinically meaningful deterioration in role function (49% vs. 41% in the trastuzumab arm), appetite loss (38% vs. 28% in the trastuzumab arm), constipation (47% vs. 38% in the trastuzumab arm), fatigue (66% vs. 61% in the trastuzumab arm), nausea/vomiting (39% vs. 30% in the trastuzumab arm), and systemic therapy side effects (49% vs. 36% in the trastuzumab arm) at any point in the study. A higher proportion of patients in the trastuzumab arm reported a clinically meaningful deterioration in diarrhea (27% vs. 22% in the T-DM1 arm) at any point in the study. The proportions of patients reporting a clinically meaningful deterioration in these scales is illustrated in Figure 6.8.[4]

Figure 6.6. Baseline scale scores from the EORTC QLQ-C30 and QLQ-BR23, KATHERINE trial

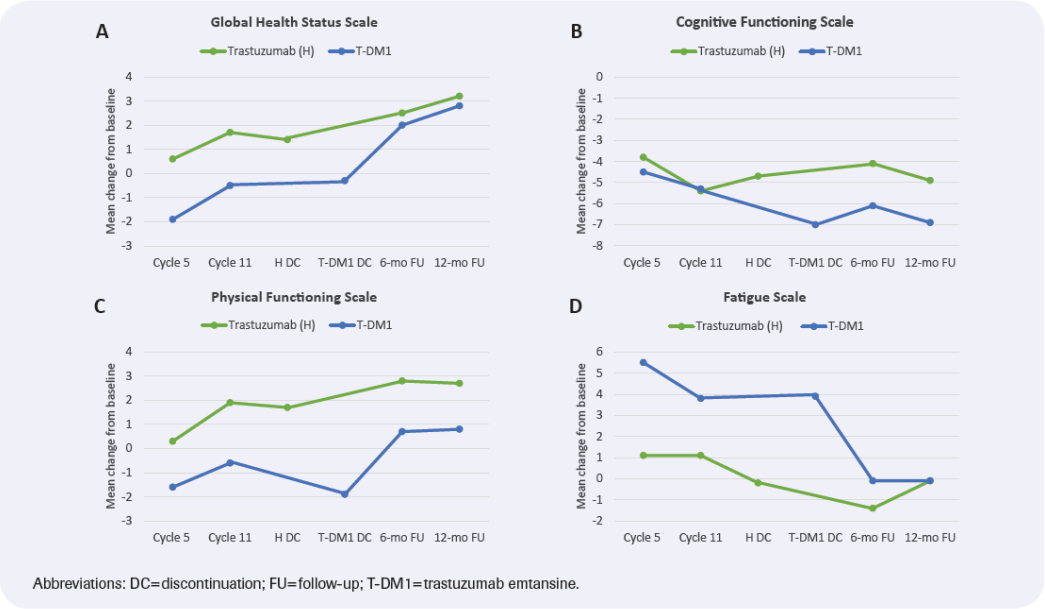


Abbreviations: QLQ-C30=Quality of Life Questionnaire–Core 30; QLQ-BR23=Quality of Life Questionnaire breast cancer module; SE=side effect; T-DM1=trastuzumab emtansine.

[a]Lines over columns and associated numbers represent normative QLQ-C30 scores for patients with stage I-II breast cancer.[8]

Source: Schneeweiss A, Loibl S, Mamounas EP, et al. Patient-reported outcomes from KATHERINE: a phase III study of adjuvant trastuzumab emtansine vs trastuzumab in patients with residual invasive disease after neoadjuvant therapy for HER2-positive breast cancer [poster]. In: pan-Canadian Oncology Drug Review sponsor submission: Kadcyla (trastuzumab emtansine), 100 mg and 160 mg single-use vial injection. Hoffman-La Roche Limited. Mississauga (ON): Hoffman-La Roche Limited; 2019 Jul 2.[4]

Figure 6.7. Mean change in score from baseline over time in the EORTC QLQ-C30 A) global health status scale, B) cognitive functioning scale, C) physical functioning scale, and D) fatigue scale, in the KATHERINE trial



Abbreviations: DC=discontinuation; FU=follow-up; T-DM1=trastuzumab emtansine.

Source: Schneeweiss A, Loibl S, Mamounas EP, et al. Patient-reported outcomes from KATHERINE: a phase III study of adjuvant trastuzumab emtansine vs trastuzumab in patients with residual invasive disease after neoadjuvant therapy for HER2-positive breast cancer [poster]. In: pan-Canadian Oncology Drug Review sponsor submission: Kadcyla (trastuzumab emtansine), 100 mg and 160 mg single-use vial injection. Hoffman-La Roche Limited. Mississauga (ON): Hoffman-La Roche Limited; 2019 Jul 2.[4]

Table 6.17. Patients reporting a clinically meaningful deterioration at any assessment point in selected scales from the EORTC QLQ-C30 and QLQ-BR23 questionnaires, KATHERINE trial

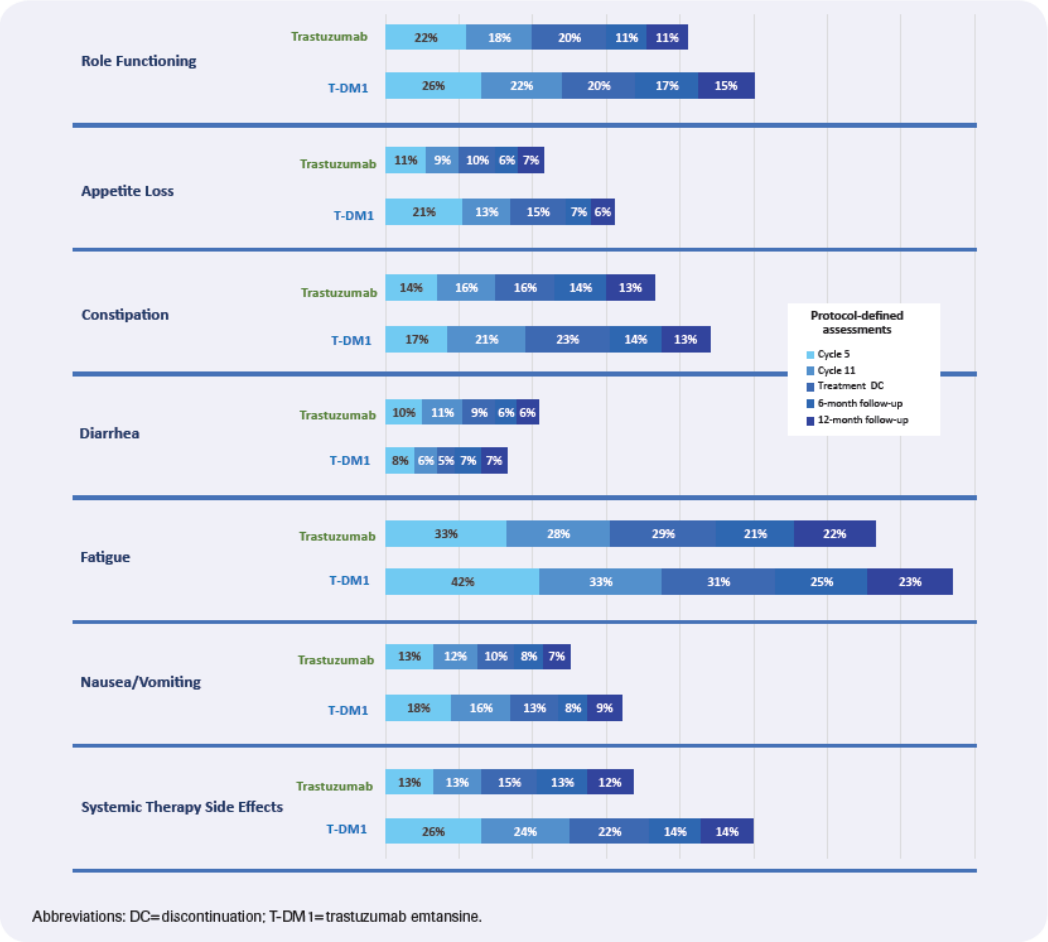
	Trastuzumab (n=743)	T-DM1 (n=743)
Role functioning	41%	49%
Appetite loss	28%	38%
Constipation	38%	47%
Fatigue	61%	66%
Nausea/vomiting	30%	39%
Systemic therapy side effects	36%	49%
Diarrhea	27%	22%

Abbreviations: T-DM1=trastuzumab emtansine.

Source: Schneeweiss A, Loibl S, Mamounas EP, et al. Patient-reported outcomes from KATHERINE: a phase III study of adjuvant trastuzumab emtansine vs trastuzumab in patients with residual invasive disease after neoadjuvant therapy for HER2-positive breast cancer [poster]. In: pan-Canadian Oncology Drug Review sponsor submission: Kadcyla (trastuzumab emtansine), 100 mg and 160 mg single-

use vial injection. Hoffman-La Roche Limited. Mississauga (ON): Hoffman-La Roche Limited; 2019 Jul 2.[4]

Figure 6.8. Proportion of patients reporting a clinically meaningful deterioration in selected scales from the EORTC QLQ-C30 and QLQ-BR23 questionnaires at each assessment point, KATHERINE trial



Source: Schneeweiss A, Loibl S, Mamounas EP, et al. Patient-reported outcomes from KATHERINE: a phase III study of adjuvant trastuzumab emtansine vs trastuzumab in patients with residual invasive disease after neoadjuvant therapy for HER2-positive breast cancer [poster]. In: pan-Canadian Oncology Drug Review sponsor submission: Kadcyla (trastuzumab emtansine), 100 mg and 160 mg single-use vial injection. Hoffman-La Roche Limited. Mississauga (ON): Hoffman-La Roche Limited; 2019 Jul 2.[4]

Harms Outcomes

Treatment Exposure

The median total treatment duration in the T-DM1 arm was 10 months (range 1-12 months) and in the trastuzumab arm it was 10 months (range 1-13 months).[2] As summarized in Table 6.18, there were no patients in the trastuzumab arm that required a dose reduction, whereas in the T-DM1 arm 77 (10.4%) patients had one dose-level reduction and 29 (3.9%) patients had second dose-level reduction.[1] A total of 90 (12.2%) of patients had a dose reduction due to an AE. Common reasons

for a dose reduction in the T-DM1 arm included platelet count decreased (n=23; 3.1%) and blood bilirubin increased (n=20; 2.7%).[2] There were 106 (14.3%) patients that experienced at least 1 AE leading to a dose interruption in the T-DM1 arm compared to 37 (5.1%) patients in the trastuzumab arm. Common reasons for a dose interruption in the T-DM1 arm included platelet count decreased (n=14; 1.9%) and aspartate aminotransferase (AST) increased (n=12; 1.6%), whereas in the trastuzumab arm it was ejection fraction decreased (n=11; 1.5%).[2]

A total of 15 (2.1%) patients discontinued trastuzumab due to an AE, whereas 133 (18.0%) patients discontinued T-DM1 due to an AE.[1] AEs leading to discontinuation in the T-DM1 arm included platelet count decreased (n=31; 4.2%), blood bilirubin increased (n=19; 2.6%), AST increased (n= 23; 1.6%), alanine aminotransferase increased (n=11; 1.5%), peripheral sensory neuropathy (n=11; 1.5%), and ejection fraction decreased (n=9; 1.2%). In the trastuzumab arm, the main AE leading to treatment discontinuation was ejection fraction decreased (n=10; 1.4%).[2] As mentioned in the previous section, of the 133 patients that discontinued T-DM1 early, 71 had switched to trastuzumab.[1]

Adverse Events (AEs)

There were more patients in the T-DM1 arm that experienced any AE (n=731; 98.8%) and grade ≥3 AEs (n=190; 25.7%) compared to the trastuzumab arm (any grade AEs: n=672, 93.3%; grade ≥3 AEs: n=111, 15.4%). Adverse events that occurred in at least 10% of patients in either treatment arm are shown in Table 6.19.[1] Almost double the patients in the T-DM1 arm that had a treatment-related AE of any grade (n=641; 86.6%) compared to the trastuzumab arm (n=326; 45.3%). A total of 101 (13.6%) of patients in the T-DM1 arm had treatment-related AEs grade ≥3 compared to 18 (2.5%) patients in the trastuzumab arm.[2]

The most commonly occurring any grade AEs in both treatment arms was fatigue (T-DM1: n=366, 49.5% vs. trastuzumab: n=243, 33.8%). In the T-DM1 arm, fatigue was followed by nausea that occurred in 41.6% of patients (compared to 13.1% in the trastuzumab arm); decreased platelet count that occurred in 28.5% of patients (compared to 2.4% in the trastuzumab arm); increased aspartate aminotransferase that occurred in 28.4% of patients (compared to 5.6% in the trastuzumab arm); and headaches that occurred in 28.4% of patients (compared to 16.9% in the trastuzumab arm. In the trastuzumab arm, fatigue was followed by radiation-related skin injury that occurred in 27.6% of patients (compared to 25.4% in the T-DM1 arm); arthralgia that occurred in 20.6% of patients (compared to 25.9% in the T-DM1 arm); hot flashes that occurred in 20.3% of patients (compared to 12.8% in the T-DM1 arm; and headaches (as outlined previously).[1]

As shown in Table 6.20, the most commonly occurring grade ≥3 AE was decreased platelet count, which occurred in 5.7% (n=42) of patients in the T-DM1 arm and 0.3% (n=2) of patients in the trastuzumab arm. This was followed by hypertension, which occurred in 2.0% (n=15) and 1.2% (n=9) of patients in the T-DM1 and trastuzumab arms, respectively. Radiation-related skin injury occurred in 1.4% (n=10) and 1.0% (n=7) in the T-DM1 and trastuzumab arms, respectively. Peripheral sensory neuropathy ≥ grade 3 occurred in 1.4% (n=10) of patients in the T-DM1 arm and in no patients in the trastuzumab arm.[1]

The most common treatment-related AEs that were more frequently reported (with at least a 10% difference) in the T-DM1 arm compared to the trastuzumab arm included:

- Fatigue (36.2% vs. 13.1% in the T-DM1 and trastuzumab arms, respectively)

- Nausea (34.5% vs. 4.0%)
- Platelet count decreased (26.9% vs. 1.3%)
- AST increased (25.1% vs. 2.4%)
- ALT increased (20.8% vs. 2.9%)
- Headache (15.8% vs. 3.5%)
- Epistaxis (15.7% vs. 1.4%)
- Peripheral sensory neuropathy (12.4% vs. 1.1%)

Other commonly occurring treatment-related AEs included arthralgia, which occurred in 12.0% of patients in the T-DM1 arm compared to 5.0 % in the trastuzumab arm.[2]

Serious adverse events (SAEs)

SAEs occurred in 94 (12.7%) patients in the T-DM1 arm compared to 58 (8.1%) patients in the trastuzumab arm. The most common SAEs included mastitis and decreased platelet count. Mastitis occurred in 8 (1.1%) patients in the T-DM1 arm and 6 (0.8%) in the trastuzumab arm, and decreased platelet count occurred in 10 (1.4%) patients in the T-DM1 arm and no patients in the trastuzumab arm.[2]

Deaths

There was 1 (0.1%) patient who died in the T-DM1 arm due to an AE and no patients that died in the trastuzumab arm. This patient had a low platelet count and fell at home and died of intracranial hemorrhage.[1,2]

Six additional deaths occurred outside of the 30 days following the last study treatment dose that were not considered related to study treatment, which included 4 deaths occurred in the trastuzumab arm and 2 deaths in the T-DM1 arm. Reasons for death in the trastuzumab arm included pneumonia (n=2) and cerebrovascular event (n=1), and in the T-DM1 arm reasons included cerebrovascular event with renal insufficiency (n=1) and death after osteosynthesis (n=1). In the trastuzumab arm, and additional patient died due to encephalitis infection, that was erroneously marked as death due to AE on the electronic case report form.[2]

Additional Information

Additional analyses exploring peripheral neuropathy and thrombocytopenia were conducted. Baseline neuropathy was found to be similar between treatment arms (22.7% and 21.4% in the T-DM1 and trastuzumab arms, respectively), and there was a slightly higher incidence of peripheral neuropathy in those with baseline neuropathy in the T-DM1 arm (36.3%) than those without (31.1%), whereas incidence of peripheral neuropathy was similar in those with (17.5%) and without baseline neuropathy (16.8%) in the trastuzumab arm. Baseline neuropathy was associated with longer median duration of peripheral neuropathy (352-337 days) and lower resolution rate (66-64%) compared to those without baseline neuropathy (median duration: 243-232 days; resolution rate: 81-83%). In the T-DM1 arm, prior treatment with platinum chemotherapy was associated with higher thrombocytopenia incidence (36%) compared to those without prior platinum chemotherapy (27%), and median duration (33 days in those with prior platinum vs. 29 days in those without) and resolution rate (95% in those with prior platinum vs. 96% in those without) of grade 3-4 thrombocytopenia was similar regardless of prior

platinum. Thrombocytopenia rate was 2.4% in the trastuzumab arm, and thus further analyses were not conducted.[25]

Table 6.18. Summary of treatment exposure in the KATHERINE trial, safety population

	Trastuzumab (n=720)	T-DM1 (n=740)
Cycles of trastuzumab or T-DM1 completed	*no. of patients (%)*	
14 cycles	583 (81.0)	528 (71.4)
≥11 cycles	618 (85.8)	579 (78.2)
≥7 cycles	664 (92.2)	637 (86.1)
≥4 cycles	683 (94.9)	677 (91.5)
Dose reductions		
No dose reduction	0	634 (85.7)
Dose reduction by one level (3.0 mg/kg)	0	77 (10.4)
Dose reduction by two levels (2.4 mg/kg)	0	29 (3.9)
Cycle of first dose reduction		
Cycle 1	0	0
Cycle 2	0	9 (1.2)
Cycle 3	0	11 (1.5)
Cycle 4–7	0	35 (4.7)
Cycle 8–11	0	34 (4.6)
Cycle 12–14	0	17 (2.3)
Completed 14 cycles of any study treatment†	583 (81.0)	593 (80.1)

*T-DM1 denotes trastuzumab emtansine.

†Includes patients who discontinued T-DM1 early and switched to trastuzumab to complete a total of 14 cycles of treatment. Patients discontinuing trastuzumab early did not switch to T-

Source: The New England Journal of Medicine, von Minckwitz G, et al, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, 380(7), 617-628. Copyright ©2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

Table 6.19. Summary of adverse events in the KATHERINE trial, safety population

Table 2. Summary of Adverse Events in the Safety Population.*

Event	Trastuzumab Group (N=720)	T-DM1 Group (N=740)
	no. of patients (%)	
Any adverse event	672 (93.3)	731 (98.8)
Grade ≥3 adverse event	111 (15.4)	190 (25.7)
Adverse event leading to death†	0	1 (0.1)
Serious adverse event	58 (8.1)	94 (12.7)
Adverse event leading to discontinuation of trial drug‡	15 (2.1)	133 (18.0)
Grade ≥3 adverse event that occurred in ≥1% of patients in either group		
Decreased platelet count	2 (0.3)	42 (5.7)
Hypertension	9 (1.2)	15 (2.0)
Radiation-related skin injury	7 (1.0)	10 (1.4)
Peripheral sensory neuropathy	0	10 (1.4)
Decreased neutrophil count	5 (0.7)	9 (1.2)
Hypokalemia	1 (0.1)	9 (1.2)
Fatigue	1 (0.1)	8 (1.1)
Anemia	1 (0.1)	8 (1.1)

* Listed are adverse events with an onset that occurred from the first dose of any trial treatment through 30 days after the final dose of trial treatment and adverse events with an onset in the follow-up period that were determined by the investigators to be related to the trial drug or trial procedure. Patients may have had more than one adverse event.

† One patient with a platelet count of 55,000 per cubic millimeter fell at home and died of an intracranial hemorrhage.

‡ The most common adverse event leading to discontinuation of the trial drug in the trastuzumab group was a decreased ejection fraction in 10 of 720 patients (1.4%). The most common adverse events leading to discontinuation of the trial drug in the T-DM1 group were a decreased platelet count in 31 of 740 patients (4.2%), an increased blood bilirubin level in 19 patients (2.6%), an increased aspartate aminotransferase level in 12 patients (1.6%), an increased alanine aminotransferase level in 11 patients (1.5%), peripheral sensory neuropathy in 11 patients (1.5%), and a decreased ejection fraction in 9 patients (1.2%).

Source: The New England Journal of Medicine, von Minckwitz G, et al, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, 380(7), 617-628. Copyright ©2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

Table 6.20. Adverse events of any grade occurring in 10% of patients in either treatment arm in the KATHERINE trial, safety population

Adverse Event	Trastuzumab (n=720)				T-DM1 (n=740)			
	no. of patients (%)							
	Any Grade	Grade 1	Grade 2	Grade 3†	Any Grade	Grade 1	Grade 2	Grade 3†
Fatigue	243 (33.8)	189 (26.3)	53 (7.4)	1 (0.1)	366 (49.5)	247 (33.4)	111 (15.0)	8 (1.1)
Nausea	94 (13.1)	74 (10.3)	18 (2.5)	2 (0.3)	308 (41.6)	244 (33.0)	60 (8.1)	4 (0.5)
Platelet count decreased†	17 (2.4)	14 (1.9)	1 (0.1)	1 (0.1)	211 (28.5)	105 (14.2)	64 (8.6)	27 (3.6)
Aspartate aminotransferase increased	40 (5.6)	36 (5.0)	2 (0.3)	2 (0.3)	210 (28.4)	171 (23.1)	35 (4.7)	4 (0.5)
Headache	122 (16.9)	94 (13.1)	27 (3.8)	1 (0.1)	210 (28.4)	165 (22.3)	45 (6.1)	0
Arthralgia	148 (20.6)	114 (15.8)	34 (4.7)	0	192 (25.9)	143 (19.3)	48 (6.5)	1 (0.1)
Radiation skin injury	199 (27.6)	121 (16.8)	71 (9.9)	7 (1.0)	188 (25.4)	98 (13.2)	80 (10.8)	10 (1.4)
Alanine aminotransferase increased	41 (5.7)	35 (4.9)	4 (0.6)	2 (0.3)	171 (23.1)	136 (18.4)	32 (4.3)	3 (0.4)
Epistaxis	25 (3.5)	24 (3.3)	1 (0.1)	0	159 (21.5)	143 (19.3)	16 (2.2)	0
Peripheral sensory neuropathy	50 (6.9)	39 (5.4)	11 (1.5)	0	138 (18.6)	90 (12.2)	38 (5.1)	10 (1.4)
Constipation	59 (8.2)	51 (7.1)	8 (1.1)	0	126 (17.0)	105 (14.2)	20 (2.7)	1 (0.1)
Myalgia	80 (11.1)	64 (8.9)	16 (2.2)	0	114 (15.4)	84 (11.4)	27 (3.6)	3 (0.4)
Vomiting	37 (5.1)	25 (3.5)	10 (1.4)	2 (0.3)	108 (14.6)	80 (10.8)	24 (3.2)	4 (0.5)
Insomnia	86 (11.9)	64 (8.9)	21 (2.9)	1 (0.1)	101 (13.6)	80 (10.8)	21 (2.8)	0
Cough	86 (11.9)	71 (9.9)	15 (2.1)	0	100 (13.5)	81 (10.9)	18 (2.4)	1 (0.1)
Dry mouth	9 (1.3)	9 (1.3)	0	0	100 (13.5)	92 (12.4)	7 (0.9)	1 (0.1)
Influenza-like illness	87 (12.1)	70 (9.7)	16 (2.2)	1 (0.1)	100 (13.5)	81 (10.9)	19 (2.6)	0
Hot flush	146 (20.3)	118 (16.4)	26 (3.6)	2 (0.3)	95 (12.8)	82 (11.1)	13 (1.8)	0
Pain	92 (12.8)	73 (10.1)	19 (2.6)	0	93 (12.6)	72 (9.7)	21 (2.8)	0
Diarrhea	90 (12.5)	61 (8.5)	27 (3.8)	2 (0.3)	91 (12.3)	64 (8.6)	21 (2.8)	6 (0.8)
Pain in extremity	70 (9.7)	52 (7.2)	15 (2.1)	3 (0.4)	86 (11.6)	68 (9.2)	18 (2.4)	0
Stomatitis	27 (3.8)	21 (2.9)	5 (0.7)	1 (0.1)	80 (10.8)	66 (8.9)	13 (1.8)	1 (0.1)
Pyrexia	29 (4.0)	25 (3.5)	4 (0.6)	0	77 (10.4)	67 (9.1)	10 (1.4)	0
Anemia	60 (8.3)	54 (7.5)	5 (0.7)	1 (0.1)	74 (10.0)	47 (6.4)	19 (2.6)	8 (1.1)

*T-DM1 denotes trastuzumab emtansine.

†All adverse events listed were grade 3 except for platelet count decreased which includes 0.1% grade 4 in the trastuzumab arm and 2.0% grade 4 in the T-DM1 arm.

Source: The New England Journal of Medicine, von Minckwitz G, et al, Trastuzumab emtansine for residual invasive HER2-positive breast cancer, 380(7), 617-628. Copyright ©2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[1]

6.4 Ongoing Trials

There were two ongoing trials identified as relevant to this review, the ATOP trial and the ATEMPT trial. The ATOP trial, while does not fit the systematic review protocol (nonrandomized trial), may provide future insights on treating older patients with T-DM1 with eBC. The ATEMPT trial is an open-label, randomized, active-controlled, Phase II trial

exploring trastuzumab emtansine compared to trastuzumab and paclitaxel in the adjuvant setting for patients with HER2-positive eBC.

Table 6.21: Ongoing trials of trastuzumab emtansine in early breast cancer in the adjuvant setting

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study:[37] NCT03587740 ATOP trial **Characteristics:** Open-label, non-randomized, single arm, Phase II trial **Estimated enrolment:** N = 82 **Number of centres and number of countries:** 13 sites across the US **Patient Enrolment Dates:** August 22nd, 2018 (ongoing) **Estimated primary study completion:** January 31st, 2022 **Estimated study completion:** January 31st, 2025 **Funding:** Dana-Farber Cancer Institute	Key Inclusion Criteria: • Local and central histologically or cytologically confirmed HER2-positive disease (DCIS components should not be counted in determination of HER2 status • Older adults ≥60 years of the time of study registration • Histologically or cytologically confirmed Stage I-III breast cancer • Known ER/PR status • Standard chemo/trastuzumab declined by patient or physician deemed patient not a candidate for standard therapy due to concerns related to toxicity or provider/patient preference • All tumor removed by modified radical mastectomy or a segmental mastectomy (management of axillary lymph nodes up to treating physician) • ECOG PS 0-2 • Baseline EF ≥50% by MUGA or echocardiogram performed ≤60 days • Adequate laboratory values Key Exclusion Criteria: • Evidence of metastatic disease • Baseline staging not required to rule out metastatic disease, ordered at physician's discretion • Locally advanced tumors at T4, including tumors fixed to the chest wall, peau d'orange, skin ulcerations/nodules, or clinical inflammatory changed • Stage III HER2-negative cancer in the contralateral breast • Positive HBV and/or HCV must meet requirements for ALT, AST, total bilirubin, INR, PTT, and alkaline phosphatase • Acute liver disease • Significant, active cardiopulmonary dysfunction within 60 days of study initiation or a prior history of: NCI CTCAE v. 4.0 grade ≥3 CHF; angina pectoris required medication; high-risk uncontrolled arrhythmias; significant symptoms related to LVEF, arrythmia, or ischemia; MI; uncontrolled hypertension; evidence of transmural	Intervention: Trastuzumab emtansine, every 3 weeks by IV infusion with 21 consecutive days defined as a treatment	Primary: • 5-year iDFS Secondary: • Recurrence-free survival (2 years) • OS • Sit of first recurrence • Incidence rate of cardiac-related AEs (LVEF) • Incidence rate of cardiac-related AEs (cardiac death) • Incidence rate of cardiac-related AEs (decreased EF) • Tertiary: • PFS by RECIST 1.1 • OS

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	infarction on ECG; requirement for oxygen therapy • Concurrent second malignancy or past malignancy with >30% estimated risk of relapse in next 5 years • Prior treatment with T-DM1 or any trastuzumab therapy • Neoadjuvant chemotherapy (> 4 weeks of tamoxifen or other hormonal therapy for adjuvant for this malignancy) • Cumulative exposure to prior anthracyclines that exceed the protocol defined dose		
Study:[38] NCT01853748 ATEMPT trial **Characteristics:** Open-label, randomized, active-controlled, Phase II trial **Estimated enrolment:** N = 512 **Number of centres and number of countries:** 85 sites across the US **Patient Enrolment Dates:** May 2013 (recruitment completed) **Estimated primary study completion:** January 2020 **Estimated study completion:** December 2021 **Funding:** Dana-Farber Cancer Institute	<u>Key Inclusion Criteria:</u> • HER2-positive (local and central confirmation) stage I histologically confirmed invasive carcinoma of the breast • Known ER/PR status • Bilateral breast cancers that individually meet eligibility criteria allowed • Multifocal or multicentric disease are eligible if each tumor meets eligibility criteria • History of ipsilateral DCIS eligible if treated with wide-excision alone without radiation therapy, contralateral DCIS not eligible • ≤ 90 days since most recent breast surgery for this breast cancer • All tumor removed by modified radical mastectomy or segmental mastectomy (lumpectomy) either a sentinel node biopsy or axillary dissection with margins clear of invasive cancer or DCIS • Received up to 4 weeks of tamoxifen or other hormonal therapy for adjuvant therapy for this cancer • Prior oophorectomy for cancer prevention allowed • No contraindication to radiation if undergoing lumpectomy <u>Key Exclusion Criteria:</u> • Use of potent CYP3A4 inhibitors during study treatment period • Excessive alcohol intake (>3 beverages a day) • Locally advanced tumors at diagnosis • History of previous invasive breast cancer • History of prior chemotherapy in the past 5 years • History of prior trastuzumab in prior paclitaxel therapy	<u>Intervention</u> Trastuzumab emtansine every 3 weeks by IV for 17 cycles (total 51 weeks) <u>Comparator</u> Paclitaxel and trastuzumab once a week by IV for 12 weeks, beginning week 13, trastuzumab will be administered as monotherapy by IV every 3 weeks for 13 cycles	<u>Primary:</u> • 2-year DFS <u>Secondary:</u> • 2-year DFS by tumor size (<1 cm or ≥1 cm) and hormone receptor status • Percentage of patients with grade 3-4 cardiac dysfunction • Percentage of participants with T-DM1 induced grade 2-4 thrombocytopenia • Percentage of patient with amenorrhea at specific time points • OS

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	• Active, unresolved infection • Active liver or cardiac disease • History of different malignancy unless disease-free for 5 years or at low risk for recurrence; cervical cancer in situ, basal or squamous cell carcinoma of the skin		

Abbreviations:
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; cm = centimetre; DCIS = ductal carcinoma breast cancer; DFS = disease-free survival; ECOG PS = Eastern Cooperative Oncology Performance Status; EF = ejection fraction; ER = estrogen receptor; HBV = hepatitis B virus; HCV = hepatitis C virus; HER2 = human epidermal growth factor receptor 2; iDFS = invasive-disease free survival; INR = international normalized ratio; IV = intravenous; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition scan; OS = overall survival; PR = progesterone receptor; PTT = partial thromboplastin time; T-DM1 = trastuzumab emtansine; US = United States

7 SUPPLEMENTAL QUESTIONS

There were no supplemental questions identified for this review.

8 COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Breast Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on trastuzumab emtansine (Kadcyla) for early breast cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via Ovid platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** June 2019**, Embase** 1974 to 2019 July 09**, Ovid MEDLINE(R) ALL** 1946 to July 09, 2019

#	Searches	Results
1	(Kadcyla* or Kadccyla* or Ado-trastuzumab* or (trastuzumab* adj3 (emtansin* or emtasin*)) or (trastuzumab* adj3 dm 1) or (trastuzumab* adj3 dm1) or pro 132365 or pro132365 or tmab mcc dm1 or t dm 1 or t dm1 or huN901-DM1 or RG-3502 or SE2KH7T06F).ti,ab,ot,kf,kw,hw,rn,nm.	3500
2	1 use cctr	233
3	1 use medall	676
4	*trastuzumab emtansine/	624
5	(Kadcyla* or Kadccyla* or Ado-trastuzumab* or (trastuzumab* adj3 (emtansin* or emtasin*)) or (trastuzumab* adj3 dm 1) or (trastuzumab* adj3 dm1) or pro 132365 or pro132365 or tmab mcc dm1 or t dm 1 or t dm1 or huN901-DM1 or RG-3502).ti,ab,kw,dq.	2319
6	or/4-5	2352
7	6 use oemezd	1511
8	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	1137387
9	Randomized Controlled Trial/	1043040
10	exp Randomized Controlled Trials as Topic/	299131
11	"Randomized Controlled Trial (topic)"/	163961
12	Controlled Clinical Trial/	556989
13	exp Controlled Clinical Trials as Topic/	311020
14	"Controlled Clinical Trial (topic)"/	10226
15	Randomization/	182657
16	Random Allocation/	199527
17	Double-Blind Method/	412649
18	Double Blind Procedure/	162517

19	Double-Blind Studies/	272166
20	Single-Blind Method/	80174
21	Single Blind Procedure/	35694
22	Single-Blind Studies/	82117
23	Placebos/	338426
24	Placebo/	337416
25	Control Groups/	112500
26	Control Group/	112406
27	(random* or sham or placebo*).ti,ab,hw,kf,kw.	4327297
28	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	835068
29	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	3467
30	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	2898145
31	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	101496
32	allocated.ti,ab,hw.	192214
33	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	126576
34	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	28843
35	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	1062
36	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	12782
37	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	19540
38	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.	142940
39	or/8-38	6130433
40	3 and 39	113
41	7 and 39	505
42	41 and (conference review or conference abstract).pt.	217
43	limit 42 to english language	217

44	limit 43 to yr="2014 -Current"	166
45	remove duplicates from 44	159
46	41 not (conference review or conference abstract).pt.	288
47	2 or 40 or 46	634
48	limit 47 to english language	558
49	remove duplicates from 48	416
50	45 or 49	575

2. **Literature search via PubMed**
A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Items Found
#4	Search #2 AND #3 Filters: English	19
#3	Search publisher[sb]	464437
#2	Search ado-trastuzumab emtansine [Supplementary Concept] OR SE2KH7T06F[rn] OR Kadcyla*[tiab] OR Kadccyla*[tiab] OR Ado-trastuzumab*[tiab] OR trastuzumab emtansin*[tiab] OR OR trastuzumab emtasin*[tiab] OR trastuzumab dm 1[tiab] OR trastuzumab dm1[tiab] OR pro 132365[tiab] OR pro132365[tiab] OR tmab mcc dm1[tiab] OR t dm 1[tiab] OR t dm1[tiab] OR huN901-DM1[tiab] OR RG-3502[tiab] OR trastuzumab conjugate with emtasin*[tiab]	671

3. **Cochrane Central Register of Controlled Trials (CENTRAL)**
(searched via Ovid)

4. **Grey literature search via:**

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Kadcyla/trastuzumab emtansine, breast cancer

Select international agencies including:

US Food and Drug Administration (FDA)
https://www.fda.gov/

European Medicines Agency (EMA)
https://www.ema.europa.eu/

Search: Kadcyla/trastuzumab emtansine, breast cancer

Conference abstracts:

American Society of Clinical Oncology (ASCO)
https://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

Search: Kadcyla/trastuzumab emtansine, breast cancer — last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the PRESS (Peer Review of Electronic Search Strategies) checklist (https://www.cadth.ca/resources/finding-evidence/press).[39]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Kadcyla (trastuzumab emtansine).

Search filters were applied to limit retrieval to randomized controlled trials or controlled clinical trials. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of November 18, 2019.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[40] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

Additional data analyses are not expected for pCODR reviews. If they are required, as determined in consultation with pCODR, provide details on any additional statistical analyses and details on software programs used. If additional data analyses are not conducted, insert the following:

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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