pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Trastuzumab Emtansine (Kadcyla) for Metastatic Breast Cancer

January 10, 2014

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy trastuzumab emtansine (T-DM1; Kadcyla) compared to an appropriate comparator, in patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who have received prior therapy with trastuzumab and a taxane for previous metastatic breast cancer or who developed disease recurrence during or within six months of completing adjuvant therapy with these agents for breast cancer.

T-DM1 (trastuzumab emtansine) is an antibody-drug conjugate that incorporates the HER2-targeted antitumor antibody properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1 (derivative of maytansine).

Trastuzumab emtansine (Kadcyla) has a Health Canada indication for use as a single agent, for the treatment of patients with HER2-positive, metastatic breast cancer who received both prior treatment with Herceptin (trastuzumab) and a taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease, or developed disease recurrence during or within 6 months of completing adjuvant therapy.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one open-label randomized controlled superiority trial, EMILIA, comparing T-DM1 to lapatinib plus capecitabine.[2]

The study randomised 991 patients to T-DM1 (n=495, 3.6 mg/kg i.v. every 21 days until disease progression or unmanageable toxicity) or lapatinib (1250 mg daily, orally) plus capecitabine (n=496, 1000 mg/m^2 every 12 hours, maximum daily dose, 2000 mg/^{2}) on days 1-14, every 21 days. The majority of patients had an ECOG status of 0 (60) or 1(35) and the majority of patients in both arms (84%) had received prior trastuzumab in the metastatic setting only, early breast cancer setting only, or both. Baseline characteristics were similar between the two arms.

Patients were excluded if they had cardiac dysfunction or a history of symptomatic congestive heart failure, serious cardiac arrhythmia requiring treatment, history of myocardial function or unstable angina within 6 months.

The EMILIA study did not blind study participants, treating physicians, or investigators to treatment assignment.

Efficacy

The EMILIA study had two co-primary efficacy endpoints: progression-free survival (as assessed by an independent review committee) and overall survival.[2] The study randomized sufficient patients to meet the sample requirement of 980 patients. Statistically significant differences in overall survival (July 31, 2012 analysis: HR 0.68, 95% CI 0.55 to 0.85; 331 events; Table 2) and in progression-free survival (January 14, 2012 analysis: HR 0.65, 95% CI 0.55 to 0.77; 569 events; Table 2) were demonstrated in favour of the T-DM1 arm compared to the lapatinib-capecitabine arm.[2]

The investigator-assessed PFS showed a statistically significant difference for T-DM1 (median 9.4 months) compared to lapatinib plus capecitabine (median 5.8 months; HR

0.66, 95% CI 0.56-0.77, p<0.001).[2] The effect of T-DM1 was consistent across all 16 pre-specified subgroups with the exception of patients aged 75 years or older. Pre-specified sensitivity analyses by line of therapy demonstrated that in a subgroup of patients receiving third line or later therapy (n=512) there was a statistically significant difference in investigator-assessed PFS in favour of T-DM1 compared to lapatinib plus capecitabine with HR 0.69, 95% CI 0.55 to 0.86.[2] The study did not specify how many patients in this pre-specified subgroup may have been in the third line setting as compared to 4th line or beyond. The rate of objective response was also statistically significantly higher in the T-DM1 arm (43.6% of 397 patients) compared to the lapatinib-capecitabine arm (30.8% of 389 patients; p<0.001). The median time to a decrease of 5 points or more on the FACT-B TOI (Trial Outcome Index) subscale was 7.1 months for the T-DM1 arm compared to 4.6 months for the lapatinib-capecitabine arm, with a HR of 0.80, 95% CI 0.67 to 0.95 (p=0.012). Higher scores on the FACT-B TOI indicate better quality of life.[2]

Harms

A slightly higher proportion of patients in the lapatinib-capecitabine arm experienced grade 3 or above adverse events compared to the T-DM1 arm (57.0% vs. 40.8%; Table 2). Of note, higher proportions of any grade and grade 3 or above diarrhea and palmar-plantar erythrodyesthesia (hand-foot syndrome) occurred in patients in the lapatinib-capecitabine arm compared to the T-DM1 arm (Table 2). Conversely, higher proportions of any grade elevated alanine aminotransferase and any grade or grade 3 or above thrombocytopenia and elevated aspartate aminotransferase occurred in patients in the T-DM1 arm compared to the lapatinib plus capecitabine arm (Table 2).

The proportion of patients who discontinued the study drug due to adverse events was 5.9% in the T-DM1 arm compared to 7.6% and 9.4% for lapatinib and capecitabine, respectively. Dose reductions for T-DM1 occurred in 16.3% of 495 patients and dose reduction for lapatinib and capecitabine occurred in 27.3% and 53.4% of 496 patients, respectively.[2]

Grade 3 left ventricular systolic dysfunction developed in one patient in the T-DM1 arm and in no patients in the lapatinib plus capecitabine arm. The rate of Grade 3 or above bleeding events was 1.4% and 0.8% in the T-DM1 and lapatinib plus capecitabine arms, respectively.[2]

No statistical comparisons were made between the T-DM1 arm and the lapatinib-capecitabine arm for any of the reported safety outcomes.

1.2.2 Additional Evidence

pCODR received input on T-DM1 from the following patient advocacy groups who collaborated and provided one joint input, Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer. Provincial Advisory group input was obtained from five of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

In addition, the following information relevant to the pCODR review of T-DM1 is discussed as supporting information.

- A summary of preliminary results from TH3RESA, a randomized controlled trial comparing T-DM1 to treatment of physician's choice for patients with HER2-positive metastatic breast cancer (MBC) who have received at least two lines of prior HER-2 targeted therapy.
- A critical appraisal of an indirect comparison of T-DM1 with trastuzumab plus capecitabine was conducted.

1.2.3 Interpretation and Guidance

Burden of Illness and Need

Breast cancer is the most commonly diagnosed malignancy in Canadian women, with an estimated incidence of 23,600 new cases in Canada in 2011.[3] Deaths from breast cancer account for 14.4% of all annual cancer deaths (second leading cause of cancer deaths in women) with an estimated 5,100 Canadian women dying from breast cancer in 2011.

In general, women with metastatic breast cancer (MBC) have a 5-year survival rate of 15%, though it is recognized there is a wide variability between patients and between biological subtypes of breast cancer.[4] Approximately 15-20% of all breast cancers have gene amplification or over-expression (or both) of human epidermal growth factor receptor 2 (HER2), a tyrosine kinase transmembrane receptor, resulting in a more aggressive phenotype of breast cancer and a poor prognosis.[5-7] In women with HER2-positive MBC, the use of the anti-HER2 humanized monoclonal antibody trastuzumab, in addition to cytotoxic chemotherapy, as compared to cytotoxic chemotherapy alone, has been found to significantly improve PFS and OS.[8] Thus anti-HER2 treatment is considered a standard approach for HER2-positive MBC.[9] Despite such therapy, the majority of patients with MBC who initially respond to trastuzumab demonstrate disease progression within 1 year of treatment initiation.[8] As such, there remains the need for new and improved targeted therapies both in terms of efficacy and tolerability.

Effectiveness

Treatment with T-DM1 significantly improved progression free survival as determined by independent review and overall survival, both co-primary endpoints of this study.[2] With an absolute improvement of 3.2 months in progression free survival (independent review) and 5.8 months in overall survival, the magnitude of benefit is clinically meaningful. Subgroup analysis of patients from EMILIA that received TDM-1 in the third line or later setting demonstrated an improvement in PFS. In addition, interim analysis from the TH3RESA study showed that third-line patients receiving TDM-1 had improved PFS compared to physician's treatment of choice. Although overall survival data for the TH3RESA study is not yet mature, a trend towards improved OS with TDM-1 was seen. Although the EMILIA study did not blind study participants, treating physicians, or investigators to treatment assignment, the lack of blinding would not have had a significant impact on the co-primary endpoints of progression free survival (determined by independent review) and overall survival.

Safety

In terms of the toxicity spectrum, the percent of patients reporting serious adverse events, and adverse events of all grades were similar between treatment arms however more patients in the lapatinib plus capecitabine experienced greater 3 or greater toxicity and more patients in the lapatinib plus capecitabine arm required a dose reduction compared to patients on the T-DM1 arm.[2]

Grade 3 or greater thrombocytopenia was more common in patients receiving T-DM1 than lapatinib plus capecitabine and was most commonly reported in the first 2 cycles of T-DM1. With does modifications the majority of patients were able to continue treatment. The overall incidence of bleeding events was also higher with T-DM1 compared with lapatinib plus capecitabine.

As there is no safety data on the treatment of patients with cardiac dysfunction, only patients with normal cardiac status should be considered for treatment with T-DM1. Patients with symptomatic brain metastases, or treatment for brain metastases within 2

months were excluded from the EMILIA study and should not be considered for treatment with T-DM1.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to T-DM1 in women with HER2 positive, unresectable, locally advanced or metastatic breast cancer that have previously been treated with trastuzumab and a taxane. This recommendation is based on a single high-quality randomized controlled trial (EMILIA) that demonstrated a clinically and statistically significant benefit in progression-free and overall survival for women treated with T-DM1 compared to lapatinib plus capecitabine. While there were a similar percent of patients reporting serious adverse events in both treatment arms, more patients receiving lapatinib plus capecitabine discontinued treatment due to toxicity.

The Clinical Guidance Panel also considered that from a clinical perspective:

- Metastatic breast cancer is the second leading cause of cancer death in women and there is a need for new and improved systemic therapies, both in terms of efficacy and tolerability

- T-DM1 demonstrated an improvement in progression-free and overall survival in patients previously exposed to trastuzumab and a taxane

- Based on results seen in a subgroup of 3rd line patients in the EMILIA study and preliminary results from the ongoing study TH3RESA, there is evidence for clinical benefit in patients receiving TDM-1 in the third-line or later setting. Therefore, the use of TDM-1 can be considered for patients as a third line treatment of HER-2 positive metastatic breast cancer, whose disease has progressed on a taxane and trastuzumab in one of their previous therapeutic lines. However, these data did not specify how many patients received T-DM1 in the third line setting as compared to 4th line or beyond.

- T-DM1 has a favourable toxicity profile compared to other systemic treatments used in the management of metastatic breast cancer and was better tolerated than lapatinib plus capecitabine

- T-DM1 should be used cautiously in patients with borderline cardiac function (LVEF 50 % at baseline). There is no evidence to support the role of T-DM1 in patients with cardiac dysfunction (LVEF < 50 %). Consideration may be given to the administration of T-DM1 in patients, who with medical management, experience improvement in their cardiac status.

- Dual HER2 blockade with trastuzumab and pertuzumab in combination with docetaxel has been approved for the treatment of women with HER2 + MBC in the first line setting. There is currently no clinical evidence supporting the administration of T-DM1 in women who have progressed after treatment with this regimen (trastuzumab, pertuzumab and docetaxel), however this may be a reasonable treatment option for this small population of patients. The results of two ongoing Phase III randomized controlled trials, with T-DM1 in the first (MARIANNE) and 3rd (TH3RESA) line MBC setting, will provide further information that will help determine the optimal HER2 targeted treatment strategy for this patient population.

2 CLINICAL GUIDANCE

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 metastatic 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 pCODR website,www.pcodr.ca.

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

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on trastuzumab emtansine (Kadcyla) and a summary of submitted Provincial Advisory Group Input on trastuzumab emtansine (Kadcyla) are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

T-DM1 (trastuzumab emtansine) is an antibody-drug conjugate that incorporates the HER2-targeted antitumor antibody properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1 (derivative of maytansine). The antibody (T) and the cytotoxic agent (DM1) are conjugated by a stable linker.[10,11] T-DM1 allows drug delivery to those cells which specifically overexpress HER-2, thereby improving the efficacy while minimizing exposure of the drug to normal tissues (lower toxicity). Phase II studies have demonstrated the clinical activity of T-DM1 in patients with HER2 + MBC.[12-14] Trastuzumab emtansine (Kadcyla) has a Health Canada indication for use a single agent, for the treatment of patients with HER2-positive, metastatic breast cancer who received both prior treatment with HERCEPTIN (trastuzumab) and a taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease, or developed disease recurrence during or within 6 months of completing adjuvant therapy.[1]

Lapatinib (Tykerb) is an oral active small molecule that inhibits the tyrosine kinases of HER2 and the epidermal growth factor receptor type 1 (EGFR). In pre-clinical studies lapatinib was found to be not cross-resistant with trastuzumab.[15,16] A phase III randomized open label study compared lapatinib in combination with capecitabine vs capecitabine alone in women with HER2 + MBC or locally advanced breast cancer who had progressive disease after receiving an anthracycline, a taxane and trastuzumab.[17] The median time to progression, the primary endpoint of the study, was 8.4 months in the combination arm vs 4.4 months in the monotherapy arm (HR 0.47; p <0.001). Based on superior efficacy and reasonable toxicity, the combination of lapatinib and capecitabine was approved and funded for women with HER2 + MBC in the second line setting.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effectiveness of single-agent therapy with trastuzumab emtansine (T-DM1; Kadcyla) compared to an appropriate comparator, in patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who have received prior

therapy with trastuzumab and a taxane for previous metastatic breast cancer or who developed disease recurrence during or within six months of completing adjuvant therapy with these agents for breast cancer.

Outcomes of interest included overall survival, progression-free survival, response rates, time-to-symptom progression, quality of life, and adverse events. Appropriate comparators were lapatinib plus capecitabine, trastuzumab plus vinorelbine, or trastuzumab plus capecitabine. Additional details of the review protocol can be found in Table 3 in Section 6.2.1.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

One study (the EMILIA study) was identified that met the eligibility criteria for this review.[2,18,19] The EMILIA study was a multicentre, open-label randomized controlled superiority trial comparing T-DM1 to lapatinib-capecitabine funded by F. Hoffmann-La Roche and Genentech.[2] A total of 991 patients with HER2-positive unresectable locally advanced or metastatic breast cancer that was previously treated with trastuzumab and a taxane, were randomized to T-DM1 (n=495) or to lapatinib-capecitabine (n=496).[2] A summary of key trial characteristics can be found in Table 1. The baseline characteristics for the T-DM1 arm and the lapatinib-capecitabine arm were similar.

The EMILIA study had three primary endpoints: progression-free survival, overall survival, and safety.[2] The study randomized a sufficient number of patients to meet the sample requirement of 980 patients for the two co-primary efficacy endpoints: progression-free survival and overall survival. Progression-free survival was assessed by independent review according to RECIST criteria. The primary analysis of progression-free survival was to be conducted after 508 independently-assessed events and the final analysis for overall survival after 632 deaths with a planned interim analysis for overall survival at the time of the primary analysis for progression-free survival.[2] Following the first interim analysis for overall survival, the protocol was amended to include a second interim analysis after 50% of the required events had occurred (316 deaths). Stopping boundaries were determined using a Lan De Mets alpha-spending function, with an O'Brien-Fleming boundary. A Cox proportional hazards model, with the stratification factors used for randomization (Table 1), was used to estimate the hazard ratios (HR) and 95% confidence intervals (95% CI). The EMILIA study was included time-to-symptom progression as an endpoint, defined as the time from randomization to the first documentation of a more than 5-point decrease from baseline in the scoring of responses as measured by the Functional Assessment of Cancer Therapy-Breast (FACT-B) instrument using the Trial Outcome Index (TOI) subscale, which includes the physical, functional, and breast subscales.[2]

Table 1. Summary of Trial characteristics of the EMILIA Study[2]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
NCT00829166; TDM4370g/BO21977 EMILIA Study 213 sites worldwide Patients enrolled from February 2009 through October 2011. Data cutoff (primary analysis-PFS): January 14, 2012 Data cutoff (final analysis-OS): July 31, 2012 Enrolled: n=991 Randomized: n=991 Open-label, active control Randomized in a 1:1 ratio (T-DM1:L+C) Randomization was stratified by: A) Geographic area[A] B) Number of prior chemotherapy regimens for unresectable, locally advanced or metastatic breast cancer[B] C) Disease involvement[C] Funded by: F. Hoffmann-La Roche/ Genentech	HER2-positive unresectable locally advanced or metastatic breast cancer that was previously treated with trastuzumab and a taxane and with documented progression. Patients must have progressed during or after their most recent treatment for locally advanced or metastatic breast cancer or within 6 months after treatment for early-stage breast cancer. Age ≥18 years, ECOG PS 0-1, left ventricular ejection fraction of 50% or more at baseline. HER2 status was confirmed centrally by immunohistochemistry (with 3+ being positive), or fluorescence in situ hybridization (with amplification ratio ≥2.0 being positive), or both. **Exclusion criteria:** Prior treatment with T-DM1, lapatinib, or capecitabine.	**Intervention (T-DM1):** T-DM1: 3.6 mg/kg i.v. every 21 days until disease progression or unmanageable toxicity. First dose reduction was to 3.0 mg/kg and the second was to 2.4 mg/kg. Dose escalation was not allowed after a dose reduction. If a toxic event did not resolve to Grade 1 or baseline status within 42 days after the most recent dose, treatment was discontinued. **Control (L+C):** Lapatinib 1250 mg daily, orally plus capecitabine 1000 mg/m^2 every 12 hours (maximum daily dose, 2000 mg/^{2}) on days 1-14, every 21 days. Patients recorded doses in a patient diary. Lapatinib: first dose reduction was to 1000 mg daily and second was to 750 mg daily. Capecitabine: first dose reduction was to 75% of planned daily dose, second was to 50% of that dose. Patients could continue to take one drug if the other was discontinued. If both treatments were delayed for more than 42 days, both drugs were discontinued.	**Primary:** PFS (IRC) OS Safety **Secondary:** PFS (investigator) ORR (IRC and investigator) Time to symptom progression

Notes: **ECOG PS** = Eastern Cooperative Oncology Group Performance Status; **IRC** = independent review committee; **L+C** = lapatinib plus capecitabine; **OR(R)** = objective response (rate); **OS** = overall survival; **PFS** = progression-free survival; **RCT**= randomized controlled trial; **T-DM1**=trastuzumab emtansine.

[A]United States, Western Europe or other.

[B]0 or 1 vs. >1.

[C]Visceral vs. non-visceral.

The EMILIA study did not blind study participants, treating physicians, or investigators to treatment assignment. Given that T-DM1 is an intravenous medication and that lapatinib and capecitabine are both oral agents, implementing blinding in this study may have been difficult. However, this lack of blinding may have had an impact on the results of the trial as both the treating physicians and patients had knowledge of treatment assignment. For instance, almost twice as many patients in the lapatinib-capecitabine arm (n=46) withdrew from the study due to patient decision than in the T-DM1 arm (n=25). This difference may have been due to patients' knowledge of treatment assignment and their perception or expectation of whether the treatment they received should work or not. However, the impact of the lack of blinding of patients, physicians, and investigators on the progression-free survival results would have been minimal as the assessments of tumour response and disease progression were conducted by a blinded independent review committee. In addition, the co-primary endpoint, overall survival, was an objective outcome.

The results of the EMILIA study are summarized in Table 2. Statistically significant differences in overall survival (July 31, 2012 analysis: HR 0.68, 95% CI 0.55 to 0.85; 331 events; Table 2) and in progression-free survival (January 14, 2012 analysis: HR 0.65, 95% CI 0.55 to 0.77; 569 events; Table 2) was demonstrated in favour of the T-DM1 arm compared to the lapatinib-capecitabine arm.[2] The rate of objective response was statistically significantly higher in the T-DM1 arm (43.6% of 397 patients) compared to the lapatinib-capecitabine arm (30.8% of 389 patients; p<0.001). The effect of T-DM1 was consistent across all 16 pre-specified subgroups with the exception of patients aged 75 years or older (Figure 5). Pre-specified sensitivity analyses by line of therapy demonstrated that in a subgroup of patients receiving third line or later therapy (n=512) there was a statistically significant difference in investigator-assessed PFS in favour of T-DM1 compared to lapatinib plus capecitabine with HR 0.69, 95% CI 0.55 to 0.86.[2] The study did not specify how many patients in this pre-specified subgroup may have been in the third line setting as compared to 4th line or beyond.

A statistically significant difference in time-to-symptom progression in favour of the T-DM1 arm was demonstrated in the EMILIA study: the median time to a decrease of 5 points or more on the FACT-B TOI subscale was 7.1 months for the T-DM1 arm compared to 4.6 months for the lapatinib-capecitabine arm, with a HR of 0.80, 95% CI 0.67 to 0.95 (p=0.012). Higher scores on the FACT-B TOI indicate better quality of life.[2]

Key adverse events and harms outcomes can be found in Table 2. No statistical comparisons were made between the T-DM1 arm and the lapatinib-capecitabine arm for any of the reported outcomes. The proportion of patients who experienced any grade of any adverse event was similar in both arms (Table 2). A slightly higher proportion of patients in the lapatinib-capecitabine arm experienced a grade 3 or above adverse event compared to the T-DM1 arm (57.0% versus [vs.] 40.8%; Table 2). Of note, higher proportions of diarrhea (any grade and grade ≥3), palmar-plantar erythrodyesthesia (hand-foot syndrome; any grade and grade ≥3), occurred in patients in the lapatinib-capecitabine arm compared to the T-DM1 arm (Table 2). Conversely, higher proportions of thrombocytopenia (any grade and grade ≥3), elevated alanine aminotransferase (any grade), and elevated aspartate aminotransferase (any grade and grade ≥3) occurred in patients in the T-DM1 arm compared to the lapatinib-capecitabine arm (Table 2). The proportion of patients who discontinued the study drug due to adverse events was 5.9% of 490 patients in the T-DM1 arm compared to 7.6% of 488 patients discontinued lapatinib and 9.4% of 488 patients who discontinued capecitabine. Dose reductions for T-DM1 occurred in 16.3% of 495 patients and dose reduction for lapatinib and capecitabine occurred in 27.3% and 53.4% of 496 patients, respectively.[2]

Table 2. Summary of Key Outcomes From the EMILIA Study.[2]

Efficacy outcome (ITT population)	Analysis	Intervention	Median [months]	HR (95% CI)	p-value	Median follow-up [months]
Overall survival (co-primary outcome)	July 31, 2012	T-DM1 (n=495) Lapatinib+ capecitabine (n=496)	**30.9** **25.1**	**0.68** **(0.55-0.85)**	**p<0.001**†	**18.6**
Progression-free survival by IRC (co-primary outcome)	January 14, 2012	T-DM1 (n=495) Lapatinib+ capecitabine (n=496)	**9.6** **6.4**	**0.65** **(0.55-0.77)**	**p<0.001**	**13**

Harms outcome (safety population)	T-DM1 (n=490)	Lapatinib + capecitabine (n=488)
Discontinued study drug due to AE, n (%)	29 (5.9)	Lapatinib: 37 (7.6) Capecitabine: 46 (9.4)
Any Grade AE, %	95.9	97.7
Grade ≥3 AE, %	40.8	57.0
Diarrhea, % Any grade Grade ≥3	 23.3 1.6	 79.7 20.7
Palmar-plantar erythrodyesthesia, % Any grade Grade ≥3	 1.2 0	 58.0 16.4
Thrombocytopenia, % Any grade Grade ≥3	 28.0 12.9	 2.5 0.2
Elevated alanine aminotransferase, % Any grade Grade ≥3	 16.9 2.9	 8.8 1.4
Elevated aspartate aminotransferase, % Any grade Grade ≥3	 22.4 4.3	 9.4 0.8

Notes: Results for outcomes in **BOLD** type are statistically significant; **AE**=adverse event; **CI**=confidence interval; **HR**=hazard ratio; **IRC**=independent review committee; **ITT**=intent-to-treat; **n**=number of patients; **T-DM1**=trastuzumab emtansine.
†The final overall survival analysis crossed the O'Brien-Fleming stopping boundary (HR=0.73, p=0.0037) and was therefore statistically significant.[2] No interim analyses of PFS were planned or conducted.

2.1.4 Comparison with Other Literature

Relevant literature identified jointly by the pCODR Clinical Guidance Panel and Methods Team and providing supporting information to the systematic review is summarized below. This information has not been systematically reviewed.

Results of the TH3RESA trial were recently published as an abstract[20] and presented[21] at the 2013 European Cancer Congress by Wildiers et al. TH3RESA was a multicenter open-

label randomized phase III trial funded by Hoffmann-La Roche.[22] The trial enrolled patients with HER2-positive metastatic or unresectable locally advanced or recurrent breast cancer who had disease progression after at least two previous HER2-directed therapies (trastuzumab and lapatinib) in the metastatic or unresectable locally advanced or metastatic setting and who had received a taxane in any setting.[20] The investigators randomized 602 patients 2:1 to receive either T-DM1 at 3.6 mg/kg intravenously every 21 days (n=404) or treatment of physician's choice (n=198; chemotherapy, hormonal therapy, biologic drug and/or HER2-directed therapy). The study had two co-primary outcomes: progression-free survival and overall survival. Of note, the abstract publication[20] and the conference presentation[21] reported that the co-primary outcome of progression-free survival was assessed by the investigators, whereas the record available in the ClinicalTrials.gov registry indicates that progression-free survival (as the co-primary outcome) was to have independent tumour assessments.[22] As the abstract publication and presentation report the final analysis of progression-free survival from the TH3RESA trial, it is assumed that the method of assessment reported in the abstract was the method actually used; i.e., that tumour assessments used to progression-free survival were conducted by the investigators.[20,21] The authors reported that after the results of the EMILIA trial were reported, patients in the treatment of physician's choice arm were allowed to crossover to the T-DM1 arm, following disease progression. The date of this change was not reported; however at the data cutoff of February 11, 2013, 44 of 198 patients (22%) crossed over to receive T-DM1 following disease progression on treatment of physician's choice. Many of the details required to ascertain the quality of the study were not reported in the abstract publication (e.g., the method of generating the randomization sequence, allocation concealment, and patient disposition).[20] The presentation at the 2013 European Cancer Congress reported that 36.9% of 198 patients in the treatment of physician's choice arm had discontinued the study (death, 22.2%; withdrawal by patient, 13.1%; physician's decision, 1.0%; other, 0.5%) and that 21.0% of 404 patients in the T-DM1 arm had discontinued the study (death, 15.1%; withdrawal by patient, 4.7%; physician's decision, 0.5%; other, 0.7%).[21] Of note, no information was available on the number of patients lost to follow-up. As the study was open-label (both patients and investigators were not blinded to treatment assignment) and as progression-free survival was assessed by the investigators, there exists the potential for bias in those results as tumour assessments can be subjective. This may have led to assessments of disease progression in favour of T-DM1. As overall survival is an objective outcome, it would not have been subject to the same potential bias. Although the abstract publication did not report the required sample size or the baseline patient characteristics[20], this information was available in the presentation.[21] The final progression-free survival analysis required 324 events with a power of 80% to detect a HR=0.65 and a two-sided alpha=0.5%.[21] The interim overall survival analysis (planned to occur with the final progression-free survival), with 105 events, required a HR<0.363 or p<0.0000013 to stop early for benefit.[21] The final overall survival analysis will occur after 492 events and will have 80% power to detect a HR=0.76 with a two-sided alpha=4.5%.[21] The authors also presented that the treatment arms were balanced for select baseline patient characteristics: age, world region, race, ECOG performance status, estrogen receptor- and/or progesterone receptor-positive diease, visceral involvement, disease extent at study entry (metastatic versus unresectable locally advanced/recurrent), number of prior regimens for advanced breast cancer, and presence of brain metastases at baseline.[21].

Median progression-free survival was significantly longer in the T-DM1 arm (6.2 months) compared to the treatment of physician's choice arm (3.3 months), with a HR=0.528, 95% CI 0.422 to 0.661; p<0.0001.[20] An interim analysis of overall survival reported a non-significant difference, between the study arms, with the median not yet reached in the T-DM1 arm compared to 14.9 months in the treatment of physician's choice arm, with a

HR=0.552, 95% CI 0.369 to 0.826; p<0.0034 (the stopping boundary was HR=0.363 or p<0.0000013).[20,21] The objective response rate was significantly higher in the T-DM1 arm (31.3% of 345 patients; 95% CI 26.5% to 36.5%) compared to the treatment of physician's choice arm (8.6% of 163 patients; 95% CI 5.1% to 13.8%; p<0.0001).[20]

The abstract publication did not report the number of patients included in the safety analysis; however, that information was presented at the 2013 European Cancer Congress, with 184 patients included from the treatment of physician's choice arm and 403 patients from the T-DM1 arm.[21] A lower proportion of patients in the T-DM1 compared to the treatment of physician's choice arm experienced grade 3 or higher adverse events (32.3% vs. 43.5%, respectively), grade 3 or higher neutropenia (2.5% vs. 15.8%) febrile neutropenia (0.2% vs. 3.8%), and diarrhea (0.7% vs. 4.3%).[20] Grade 3 or higher thrombocytopenia occurred in a higher proportion of patients in the T-DM1 arm than in the treatment of physician's choice arm (4.7% vs. 1.6%).[20] Of note, statistical comparisons were not reported for the safety analysis. In addition, a higher proportion of patients in the treatment of physician's choice arm than in the T-DM1 arm experienced adverse events leading treatment discontinuation (10.9% vs. 6.7%, respectively) and adverse events leading to a dose reduction (19.6% vs. 9.4%).[21]

There does exist the possibility of bias in the estimates of both progression-free survival and objective response, in favour of T-DM1, as the abstract publication reported that tumour assessments were conducted by the investigators. Importantly, given the lack of information needed to assess the quality of the TH3RESA trial (i.e., no information on the randomization sequence, allocation concealment, or losses to follow-up) the results need to be interpreted with caution, as it is not possible to determine whether any serious biases exist.

2.1.5 Summary of Supplemental Questions

Critical Appraisal of an Indirect Comparison of Trastuzumab Emtansine (T-DM1) Versus All Available Pharmacological Interventions

The indirect comparison of trastuzumab emtansine (T-DM1) versus any other pharmacological intervention resulted in an indirect comparison of trastuzumab emtansine versus trastuzumab capecitabine, for both overall survival and progression-free survival in patients with HER2-positive metastatic breast cancer. Statistically significant differences were found between these treatments in the indirect comparison. Limitations surrounding the quality of two of the three trials included in the indirect comparison are a cause for concern, and any conclusions drawn from this indirect comparison should be interpreted with caution.

See section 7.1 for more information.

2.1.6 Other Considerations

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

Patient Advocacy Group Input

From a patient perspective, access to additional therapies that will stop progression of the disease, even if only for a short amount of time, is an important aspect when consideration is given to treatment. Because there is no cure for metastatic breast cancer,

patients are looking for treatments with manageable side effect profiles that will extend life expectancy while offering an acceptable quality of life. Patient advocacy group input also indicated that many patients would be willing to tolerate the potential adverse effects of a treatment if it was found to prolong their survival, even for a short period of time.

PAG Input

From a PAG perspective, lapatinib + capecitabine is currently the standard of care for second line MBC and was considered to be an appropriate comparator. However, PAG indicated that in some jurisdictions trastuzumab or trastuzumab + chemotherapy (eg. vinorelabine) are other standards of care and a comparison to it would have been appropriate.

PAG identified several barriers to implementation. Pending a pERC recommendation on pertuzumab, the current standard of care in the first line setting is expected to change; however, PAG noted that clinical evidence is not available to support the use of T-DM1 following this drug. PAG is also unclear as to whether patients that have already received anti-HER2+ therapy with the current standard of care will be eligible to receive T-DM1. In addition, if implemented, T-DM1 will be one of several options available in the metastatic setting. As such, PAG expects that a consideration will be required on the eligibility criteria of patients to receive sequenced treatments.

Due to similarities in the name, PAG noted a potential hazard if the dosing of T-DM1 if confused with that of trastuzumab. PAG suggested that precautions such as the use of trade names on labels, warning information on pre-printed orders, safety notice in storage areas and separate storage areas as some ways to avoid drug mix-ups.

PAG indicated that wastage is a potential issue as T-DM1 comes in two single use vial sizes (100mg and 160mg) and dosing is weight based.

Other

The product monograph provided by the manufacturer (Hoffman-La Roche Limited) provides the following additional warnings:[1]

Cardiovascular – Left Ventricular Dysfunction

Patients treated with Kadcyla are at increased risk of developing left ventricular dysfunction. Left ventricular ejection fraction (LVEF) < 40% has been observed in patients treated with Kadcyla, and therefore symptomatic congestive heart failure (CHF) is a potential risk. In the pivotal study, TDM4370g/BO21977 (EMILIA) long term follow-up assessment of cardiac status was not conducted and therefore the long term effect of Kadcyla on cardiotoxicity is unknown.

Standard cardiac function testing (echocardiogram or multigated acquisition (MUGA) scanning) should be performed prior to initiation and at regular intervals (e.g. every three months) during treatment with KADCYLA. The long term cardiac effects of Kadcyla are not known. Evaluation of cardiac function following treatment discontinuation, in particular for patients with pre-existing cardiac dysfunction or with LVEF decline, should be considered and ordered based upon clinician judgment. If, at routine monitoring, LVEF is < 40%, or is 40% to 45% with a 10% or greater absolute decreased below the pre-treatment value, withhold Kadcyla and repeat LVEF assessment within approximately 3 weeks. Permanently discontinue Kadcyla if the LVEF has not improved or has declined further (see Product Monography for dose

adjustments). Treatment with Kadcyla has not been studied in patients with LVEF <50% prior to initiation of treatment.

Immune—Infusion-Related Reactions

Treatment with Kadcyla has not been studied in patients who had trastuzumab permanently discontinued due to infusion-related reactions; treatment with Kadcyla is not recommended for these patients.

Infusion-related reactions, characterized by one or more of the following symptoms - flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia have been reported in clinical trials of Kadcyla. In the pivotal study TDM4370g/BO21977 (EMILIA) the overall frequency of infusion-related reactions was 1.4% in patients treated with Kadcyla and 0.2% in patients treated with lapatinib plus capecitabine. In most patients, these reactions were ≤2 and resolved over the course of several hours to a day after the infusion was terminated. Patients should be observed closely for infusion-related reactions, especially during the first infusion. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Kadcyla treatment should be interrupted in patients with severe infusion-related reaction (≥Grade 3). Kadcyla treatment should be permanently discontinued in the event of a life threatening infusion-related reaction.

Special Populations

Pregnant Women

Kadcyla can cause fetal harm or death when administered to a pregnant woman. There are no studies of Kadcyla in pregnant women. No reproductive and developmental toxicology studies have been conducted with Kadcyla.

However, in the post-marketing setting, pregnant women receiving trastuzumab, the antibody component of Kadcyla resulted in cases of oligohydramnios, some associated with fatal pulmonary hypoplasia, skeletal abnormalities and neonatal death. The mechanism of action of DM1, the microtubule inhibiting cytotoxic drug component of Kadcyla, suggest that DM1 can cause teratogenicity and embryotoxicity.

Kadcyla should not be administered to pregnant women. Women who become pregnant must contact their doctor and should be advised of the possibility of harm to the fetus. If a pregnant woman is treated with Kadcyla, close monitoring by a multidisciplinary team is recommended.

Women of childbearing potential

Precautions should be undertaken to avoid pregnancy and at least two contraceptive methods should be used while taking Kadcyla and for at least 6 months after treatment has concluded. If pregnancy occurs, the physician should be immediately informed.

Nursing Women

It is not known whether Kadcyla is excreted in human milk. A study conducted in lactating cynomolgus monkeys demonstrated that trastuzumab was secreted in the

milk. As human IgG is excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Kadcyla, women should discontinue nursing prior to initiating treatment with Kadcyla. Women may begin nursing 6 months after concluding treatment.

2.2 Interpretation and Guidance

Burden of Metastatic Breast Cancer

Breast cancer is the most commonly diagnosed malignancy in Canadian women, with an estimated incidence of 23,600 new cases in Canada in 2011.[3] Deaths from breast cancer account for 14.4% of all annual cancer deaths (second leading cause of cancer deaths in women) with an estimated 5,100 Canadian women dying from breast cancer in 2011. Though many clinical end-points are relevant in the treatment of individuals with metastatic breast cancer, improvement in overall survival is considered to be one of the most important clinical outcomes by patients, health care professionals and regulatory bodies.

Effectiveness of T-DM1

EMILIA is a phase III, randomized, open-label International study in patients (n=991) with HER2-positive, unresectable, locally advanced or metastatic breast cancer who had previously been treated with trastuzumab and a taxane. Patients were randomized 1:1 to receive T-DM1 (3.6 mg/kg IV) every 21 days or a combination of lapatinib (1250 mg daily) and capecitabine (2000 mg/m2 days 1-14 every 21 days) . Treatment with T-DM1 significantly improved progression – free survival (median 9.6 vs 6.4 months: HR 0.65 $p < 0.001$) as determined by independent review and overall survival (30.9 months vs 25.1 months: HR = 0.68; $p =<0.001$; 2nd interim analysis at 331 events), both co-primary endpoints of this study.[2] With an absolute improvement of 3.2 months in progression free survival (independent review) and 5.8 months in overall survival, the magnitude of benefit is clinically meaningful. Improvement in progression free survival was observed across all subgroups with less benefit seen in patients 75 years of age and older and those with nonvisceral and nonmeasurable disease. Final analysis for overall survival is planned after 632 events.

This study was conducted in the appropriate population (HER2-positive with exposure to prior anthracyclines and taxanes) with an appropriate comparator arm. The open label manner of the study is reasonable given the different formulations of each drug.

Safety of T-DM1

Safety was considered one of the endpoints. Serious adverse events were reported in 18 % of patients receiving lapatinib and capecitabine compared to 15.5 % in the T-DM1 group. Adverse events of all grades occurred in 97.7 % of patients receiving lapatinib plus capecitabine vs. 95.9 % of those receiving T-DM1. Overall, there was a higher incidence of significant side effects (grade 3 or higher) in the lapatinib plus capecitabine arm (57 %) compared to the T-DM1 arm (40.8 %). Grade 3 or above diarrhea occurred in 20.7 % of patients receiving lapatinib plus capecitabine vs 1.6 % of those receiving T-DM1. Grade 3 or above Palmar-plantar erythrodysesthesia occurred in 16.4 % of patients receiving lapatinib plus capecitabine vs 0 % or T-DM1. Grade 3 or above thrombocytopenia was more common in patients receiving T-DM1 (12.9 %) compared to those receiving lapatinib and capecitabine (0.2 %). Thrombocytopenia was most commonly reported in the first 2 cycles of T-DM1; with does modifications the majority (98 %) of patients were able to continue treatment. The overall incidence of bleeding events was higher with T-DM1 (29.8 %) vs 15.8% with lapatinib plus capecitabine.

The majority of patients were able to maintain an LVEF of 45 % or greater throughout their treatment. Three patients in each group had drops in LVEF from baseline to < 40 %. To date, grade 3 left ventricular systolic dysfunction has developed in one patient in the T-DM1 group and no patients in the lapatinib/capecitabine group. There have been no cardiac specific deaths.

In terms of the toxicity spectrum, the number of serious adverse events, and adverse events of all grades were similar between treatment arms however more patients in the lapatinib plus capecitabine experienced greater 3 or greater toxicity (57 vs 40.8 %) and more patients in the lapatinib plus capecitabine arm required a dose reduction (lapatinib 27 %; capecitabine 53,4 %) compared to patients on the T-DM1 arm(16.3 %). More patients discontinued treatment with lapatinib (7.6 %) and capecitabine (9.4 %) compared to T-DM1 (5.9 %) because of toxicity. There were 5 deaths (4 in lapatinib plus capecitabine; 1 in T-DM1 arm) none of which were attributable to study treatment.

Limitations of Evidence

The limitations are: there is only one study (EMILIA) evaluating the role of T-DM1 in patients with MBC who have previously been exposed to HER2 targeted therapy. This study is limited to patients exposed to one line of HER2 targeted therapy (the majority (84 %) of patients had received HER2 targeted therapy in the metastatic setting). The EMILIA study did not blind study participants, treating physicians, or investigators to treatment assignment. Given that T-DM1 is an intravenous medication and that lapatinib and capecitabine are both oral agents, implementing blinding in this study may have been difficult. The lack of blinding would not have had a significant impact on the co-primary endpoints of this study which were progression –free survival (determined by independent review) and overall survival. Patients were excluded if they had cardiac dysfunction or a history of symptomatic congestive heart failure, serious cardiac arrhythmia requiring treatment, history of myocardial function or unstable angina within 6 months. As there is no safety data on the treatment of patients with cardiac dysfunction, only patients with normal cardiac status should be considered for treatment with T-DM1. Patients with symptomatic brain metastases, or treatment for brain metastases within 2 months were excluded and should not be considered for treatment with T-DM1.

Need and Therapeutic Options

The strength of T-DM1 include: an improvement of progression-free survival and overall survival in patients with HER2 positive disease who have been exposed to trastuzumab and a taxane. In general the toxicity of this drug is favourable with the most common grade 3 or higher toxicities reported as thrombocytopenia, and elevated transaminases (AST, ALT). After a median of 19 months follow-up there have been no significant cardiac toxicities reported with T-DM1. The OS advantage reported with T-DM1 is reflective of the 2nd interim analysis (after 331 deaths) however it is unlikely that this advantage will diminish with the final analysis (after 632 deaths). Based on the currently available data, T-DM1 should be considered a standard of care in the treatment of women with HER2 positive, unresectable, locally advanced or metastatic disease that have previously been exposed to trastuzumab and a taxane. This includes patients who have received trastuzumab and taxane in the adjuvant setting but whom have relapsed within 6 months of therapy. In the EMILIA study, the effect of T-DM1 was consistent across all 16 pre-specified subgroups with the exception of patients aged 75 years or older. Pre-specified sensitivity analysis by line of therapy demonstrated that in a subgroup of patients receiving third line therapy or later (n=512) there was statistically significant difference in investigator assessed PFS in favor of TDM-1 compared to lapatinib plus capecitabine (HR 0.69; 95% CI 0.55 to 0.86).[2] In addition, interim analysis from the TH3RESA study, a randomized controlled trial of T-DM1 vs. physicians' choice of treatment in patients with HER 2 positive MBC who have received at least 2 lines of HER2 targeted

therapy, has shown third-line patients receiving TDM-1 had improved PFS compared to physician's treatment of choice (HR 0.52).[20] Overall survival data for the TH3RESA study is not yet mature, but a trend towards improved OS with TDM-1 is seen.

Recently the combination of trastuzumab, pertuzumab and docetaxel (Cleopatra study) has been approved for 1st line therapy in patients with HER2 positive MBC. There is currently no clinical data available on the role of T-DM1 in the HER2 positive MBC population following treatment with trastuzumab, pertuzumab and docetaxel. The uptake of this 1st line regimen in Canada is currently limited by the lack of public funding in the majority of provinces. Patients with third party coverage may have access to this regimen in a limited number of settings. It is unlikely that further studies will be conducted directly comparing T-DM1 to dual blockade with trastuzumab and pertuzumab in the metastatic setting. Thus for patients treated with trastuzumab, pertuzumab and docetaxel in the first line setting, it may be reasonable to consider treatment with T-DM1 at the time of disease progression. Along with the TH3RESA study there is currently one other study which has recently completed enrollment that will impact how T-DM1 is used in the HER2 positive metastatic population. MARIANNE is a randomized 3 arm multicenter phase III study comparing T-DM1 and pertuzumab vs. T-DM1 and placebo vs. trastuzumab and a taxane in the first line setting.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to T-DM1 in women with HER2 positive, unresectable, locally advanced or metastatic breast cancer that have previously been treated with trastuzumab and a taxane. This recommendation is based on a single high-quality randomized controlled trial (EMILIA) that demonstrated a clinically and statistically significant benefit in progression-free and overall survival for women treated with T-DM1 compared to lapatinib plus capecitabine. While there were a similar percent of patients reporting serious adverse events in both treatment arms, more patients receiving lapatinib plus capecitabine discontinued treatment due to toxicity.

The Clinical Guidance Panel also considered that from a clinical perspective:

- Metastatic breast cancer is the second leading cause of cancer death in women and there is a need for new and improved systemic therapies, both in terms of efficacy and tolerability
- T-DM1 demonstrated an improvement in progression-free and overall survival in patients previously exposed to trastuzumab and a taxane
- Based on results seen in a subgroup of 3rd line patients in the EMILIA study and preliminary results from the ongoing study TH3RESA, there is evidence for clinical benefit in patients receiving TDM-1 in the third-line or later setting. Therefore, the use of TDM-1 can be considered for patients as a third line treatment of HER-2 positive metastatic breast cancer, whose disease has progressed on a taxane and trastuzumab in one of their previous therapeutic lines. However, these data did not specify how many patients received T-DM1 in the third line setting as compared to 4th line or beyond.
- T-DM1 has a favourable toxicity profile compared to other systemic treatments used in the management of metastatic breast cancer and was better tolerated than lapatinib plus capecitabine
- T-DM1 should be used cautiously in patients with borderline cardiac function (LVEF 50 % at baseline). There is no evidence to support the role of T-DM1 in patients with cardiac

dysfunction (LVEF < 50 %). Consideration may be given to the administration of T-DM1 in patients, who with medical management, experience improvement in their cardiac status.

- Dual HER2 blockade with trastuzumab and pertuzumab in combination with docetaxel has been approved for the treatment of women with HER2+ MBC in the first line setting. There is currently no clinical evidence supporting the administration of T-DM1 in women who have progressed after treatment with this regimen (trastuzumab, pertuzumab and docetaxel), however this may be a reasonable treatment option for this small population of patients. The results of two ongoing Phase III randomized controlled trials, with T-DM1 in the first (MARIANNE) and 3rd (TH3RESA) line MBC setting, will provide further information that will help determine the optimal HER2 targeted treatment strategy for this patient population.

3 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.

3.1 Description of the Condition

Breast cancer is the most commonly diagnosed malignancy in Canadian women, with an estimated incidence of 23,600 new cases in Canada in 2011.[3] Deaths from breast cancer account for 14.4% of all annual cancer deaths (second leading cause of cancer deaths in women) with an estimated 5,100 Canadian women dying from breast cancer in 2011. Deaths from breast cancer are attributable to either distant relapsed or *de novo* presentation of metastatic breast cancer. In general, women with metastatic breast cancer (MBC) have a 5-year survival rate of 15%, though it is recognized there is a wide variability between patients and between biological subtypes of breast cancer.[4]

The goals of systemic therapy in the treatment of MBC are to improve overall survival and to maintain and/or improve quality of life. In the past 10-15 years, a number of novel systemic therapies have been approved for the treatment of MBC based on improvement in clinical outcomes. The use of sequential single agent chemotherapy has been favoured over concurrent therapy (treatment with multiple agents) primarily in order to limit treatment related toxicities. More recently, this approach has been challenged by the introduction of new targeted agents. Targeted therapies are designed to block critical pathways involved in cancer cell growth and metastases. The introduction of targeted therapies has led to major clinical advances in the treatment of MBC, especially HER2-positive MBC.

The human epidermal growth factor receptor (HER) family is composed of tyrosine kinase receptors that are involved in the regulation of proliferation and survival of epithelial cells. The family includes four receptors: HER1 (epidermal growth factor receptor (EGFR), HER2 (neu, C-erbB2), HER3 and HER4. The HER2 has emerged as one of the most important targets for the treatment of breast cancer. HER2 is involved in regulating cell growth, survival, and differentiation.[23] Approximately 15-20% of all breast cancers have gene amplification or over-expression (or both) of human epidermal growth factor receptor 2 (HER2), a tyrosine kinase transmembrane receptor, resulting in a more aggressive phenotype of breast cancer and a poor prognosis.[5-7] In women with HER2-positive MBC, the use of the anti-HER2 humanized monoclonal antibody trastuzumab, in addition to cytotoxic chemotherapy, as compared to cytotoxic chemotherapy alone, has been found to significantly improve PFS and OS.[8] Thus anti-HER2 treatment is considered a standard approach for HER2-positive MBC.[9] Despite such therapy, the majority of patients with MBC who initially respond to trastuzumab demonstrate disease progression within 1 year of treatment initiation.[8] As such, there remains the need for new and improved targeted therapies both in terms of efficacy and tolerability.

3.2 Accepted Clinical Practice

The treatment of incurable locally advanced or MBC generally involves systemic anti-cancer therapies (e.g. hormonal therapy, chemotherapy, and targeted therapy), supportive systemic therapies (e.g. analgesics, anti-nausea agents, anti-bone resorptive agents, and steroids), radiation therapy, surgery (e.g. spinal cord compression, hip fractures, limited brain metastases) and the services of the palliative care allied health care team. The use of these various therapeutic modalities clearly vary by patient based on disease characteristics, co-

morbid conditions, and patient treatment preferences, as well as physician recommendations and availability of treatment options.

An improvement in overall survival is still considered the gold standard as evidence of a therapeutic benefit from any systemic agent in the treatment of breast cancer. In a recent review of randomized trials in MBC published between 1998-2007, 76 phase III trials were identified.[24] Of these 76 trials, only 15 (19.7%) demonstrated a statistical improvement in overall survival. Thus the ability to demonstrate an actual improvement in overall survival is challenging in the setting of MBC given the disease heterogeneity, cross-over to the experimental arm (in some trials) and the ability to receive standard treatment post progression.

First line therapy for HER2-positive MBC

Trastuzumab (Herceptin) is the first agent developed to target the HER2 pathway.[25] Trastuzumab is a recombinant, humanized monoclonal antibody that binds to domain IV on the juxtamembrane region of the extracellular domain of HER2 and inhibits tumor cell growth in vitro and in vivo via several mechanisms.[26] In women with HER2-positive MBC, the use of trastuzumab in the fist-line setting has been shown to improve progression-free and overall survival when administered in combination with chemotherapy (taxane) versus chemotherapy alone (taxane). In the pivotal trial by Slamon et al., the addition of trastuzumab to chemotherapy in women with HER2-positive MBC, significantly increased RR (32 versus 50%) median duration of response (6 versus 9 months), and overall survival (OS) (20 versus 25 months, P<0.01).[8] Based on this evidence and confirmatory trials, trastuzumab in combination with a taxane is now recommended as first-line therapy for women with HER2/neu-overexpressing MBC. Trastuzumab combination therapy is most effective in women with the highest level of HER2/neu protein overexpression, as indicated by an immunohistochemistry score of 3+ (moderate/strong membrane staining in at least 10% of tumour cells) or by HER2/neu gene amplification (defined as HER2/CEP17$\geq$ 2 by fluorescence in situ hybridization – FISH).

In the CLEOPATRA study, the effectiveness and safety of the combination of pertuzumab (a recombinant humanized monoclonal antibody) and trastuzumab with docetaxel was shown to have a significant overall survival benefit (HR 0.66 p = 0.0008) compared to trastuzumab and docetaxel alone in the treatment of women with HER2+ MBC in the first line setting.[27]

Second line therapy for HER2-positive MBC

The majority of patients with MBC who initially respond to trastuzumab and chemotherapy will demonstrate disease progression within 1 year of treatment initiation[8] thus necessitating the consideration of different approaches to block HER 2 signalling.

Lapatinib (Tykerb) is an oral active small molecule that inhibits the tyrosine kinases of HER2 and the epidermal growth factor receptor type 1 (EGFR). In pre-clinical studies lapatinib was found to be not cross-resistant with trastuzumab.[15,16] A phase III randomized open label study compared lapatinib in combination with capecitabine vs. capecitabine alone in women with HER2 + MBC or locally advanced breast cancer who had progressive disease after receiving an anthracycline, a taxane and trastuzumab.[17] The median time to progression , the primary endpoint of the study, was 8.4 months in the combination arm vs 4.4 months in the monotherapy arm (HR 0.47; p <0.001). Based on superior efficacy and reasonable toxicity, the combination of lapatinib and capecitabine was approved and funded for women with HER2 + MBC in the second line setting.

T-DM1 (trastuzumab emtansine) is an antibody-drug conjugate that incorporates the HER2-targeted antitumor antibody properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1 (derivative of maytansine). The antibody (T) and the cytotoxic agent (DM1) are conjugated by a stable linker.[10,11] T-DM1 allows drug delivery to

those cells which specifically overexpress HER-2, thereby improving the efficacy while minimizing exposure of the drug to normal tissues (lower toxicity). Phase II studies have demonstrated the clinical activity of T-DM1 in patients with HER2 + MBC.[12-14] In the Emilia study, women with HE2 + MBC who had progressed on a taxane and trastuzumab were randomized 1:1 to receive T-DM1 or lapatinib and capecitabine. Treatment with T-DM1 significantly improved progression – free survival (median 9.6 vs 6.4 months: HR 0.65 p < 0.001) as determined by independent review and overall survival (30.9 months vs 25.1 months: HR = 0.68; p =<0.001), both co-primary endpoints of this study.[2] There was a higher incidence of significant side effects (grade 3 or higher) in the lapatinib and capecitabine arm (57 %; diarrhea and hand-foot syndrome) compared to the T-DM1 arm (40.8 %; low platelets and elevated liver enzymes). More patients in the lapatinib-capecitabine group required a dose reduction (lapatinib 27 %; capecitabine 53.4 %) compared to patients on the T-DM1 arm (16.3 %). More patients discontinued treatment with lapatinib (7.6 %) and capecitabine (9.4 %) compared to T-DM1 (5.9 %) because of toxicity. There was no significant cardiac toxicity observed in either treatment arm.

3.3 Evidence-Based Considerations for a Funding Population

The evidence based population suitable for consideration of T-DM1 for the treatment of HER2-positive MBC would be the same patient population included in the clinical trial EMILIA.[2]

These would be women with HER 2 + metastatic or unresectable, locally advanced breast cancer that were previously treated with trastuzumab and a taxane. Patients must have progressed during or after the most recent treatment or within 6 months after treatment for early stage disease. All patients must have HER 2 + disease as defined by immunohistochemical analysis (3+ indicating positive status), fluorescence in situ hybridization (with an amplification ratio of $\geq$ 2.0) or both. Patients with both measurable and non-measurable disease were included. Patients should have a good performance status (ECOG score of 0-1), and have adequate left ventricular ejection fraction of 50% or more at baseline (determined by echocardiography or multiple-gated acquisition scanning).

Patients were excluded if they had previously been treated with T-DM1, lapatinib or capecitabine; had grade ≥3 sensory peripheral neuropathy, symptomatic brain metastases (or treatment for brain metastases within 2 months of study treatment), history of congestive heart failure or other serious cardiac problems (e.g. unstable angina).

Treatment with T-DM1 would continue until disease progression, unacceptable toxicity, or patient or physician recommendation

3.4 Other Patient Populations in Whom the Drug May Be Used

Pertuzumab/trastuzumab and docetaxel has been approved by Health Canada and is a treatment option for women with HER2 + MBC in the first line setting. Women who are treated with trastuzumab, pertuzumab and docetaxel in the first line setting will eventually experience disease progression. It may not be unreasonable to consider this population of women for treatment with T-DM1, although this group of women was not included in the EMILIA study population.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Two patient advocacy groups, Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer (Rethink) collaborated and provided joint input on trastuzumab emtansine (T-DM1; Kadcyla) for the treatment of metastatic breast cancer patients and their input is summarized below.

CBCN and Rethink conducted an online survey and key informant interviews to gather information from patients and caregivers about the impact of metastatic breast cancer on their lives and the effect of treatments on their disease. Patients were contacted through the membership databases of CBCN and Rethink. Survey questions comprised of a combination of scoring options and free form commentary. Survey participants were contacted through the membership databases of CBCN and Rethink. A total of 71 patients with metastatic breast cancer and 16 caregivers completed the survey. Cited responses are included verbatim to provide a deeper insight of the patient and caregiver perspective; cited responses are not corrected for spelling or grammar. No patients surveyed had direct experience with the drug under review. However, an online interview was conducted with two patients that did have experience with T-DM1. A review of current studies and grey literature was also conducted to identify issues and experiences that are commonly shared among breast cancer patients.

From a patient perspective, access to additional therapies that will stop progression of the disease, even if only for a short amount of time, is an important aspect when consideration is given to treatment. Because there is no cure for metastatic breast cancer, patients are looking for treatments with manageable side effect profiles that will extend life expectancy while offering an acceptable quality of life. Patient advocacy group input also indicated that many patients would be willing to tolerate the potential adverse effects of a treatment if it was found to prolong their survival, even for a short period of time.

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

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Metastatic Breast Cancer

Metastatic breast cancer is the spread of cancerous cell growth from the place where it first started to another place in the body. The most common site of breast cancer metastasis is to the bones, but can also spread to the lungs, liver, brain and skin. Current treatment options for HER2+ metastatic breast cancer are effective at prolonging progression-free disease, but most cases of advanced disease will progress and symptoms will worsen.

From a patient perspective, quality of life while living with metastatic breast cancer is an important consideration. Patients with metastatic breast cancer understand the limitations of current treatment options, and seek to live their remaining months and years with the best possible quality of life that they can achieve. The 71 patients who participated in the survey provided an answer to the question *How have the symptoms of metastatic cancer affected their quality of life?* Fatigue, insomnia, pain, problems concentrating and depression were the most frequently reported symptoms of the disease that impact a patient's quality of life. Other physical symptoms that were identified by patients included: early menopause, mood swings, loss of appetite, neuropathy, loss of balance, incontinence and skin bruising.

Metastatic breast cancer also impacts many social aspects of a patient's life, including restricting an individual's ability to work, to care for children and dependents, and to be social and meaningfully participate in their community. The survey asked *what kind of impact living with metastatic breast cancer has had on their quality of life*. Other experiences identified by patients: guilt, the feeling of being a burden on caregivers, fear of death, poor body image, not knowing what functionality will be lost, fear of impact of the cancer and the loss of a parent on children, not knowing what will happen to children, the loss of support of loved ones, martial stress/loss of fidelity and affection from husband. The responses to both survey questions are summarized in the table below.

Affect on Quality of Life		**Significant or Debilitating Impact (N = 71 patients)**	**Moderate Impact (N = 71 patients)**
How have the symptoms of metastatic cancer affected your quality of life?	Fatigue	54%	40%
	Insomnia	39%	46%
	Pain	37%	44%
	Problems Concentrating	31%	59%
	Depression	26%	53%
How has living with metastatic cancer restricted your ability to participate in the following areas?	Work	71% of those employed	-
	Provide Care giving Responsibilities	21% of those with children or dependents	53% of those with children or dependents
	Exercise	49%	38%
	Pursue Hobbies and Personal Interests	42%	42%
	Participate in Social Events and Activities	41%	41%
	Volunteer	31%	46%
	Self-Manage Other Chronic Diseases on Health Issues	25%	43%
	Spend Time with Loves Ones	22%	52%

4.1.2 Patients' Experiences with Current Therapy for Metastatic Breast Cancer

Patient groups identified their goals of current treatment options for metastatic breast cancer include controlling the progression of the disease (extending their life), and reducing cancer-related symptoms (extending or stabilising quality of life). Treatment options and their effectiveness vary among type of cancer, location of cancer, and how symptoms are experienced by patients.

Patients report that the financial burden associated with living with breast cancer extends far beyond any loss of income during a temporary or permanent absence from

employment. In addition to the loss of income during illness, breast cancer patients can incur substantial costs associated with treatment and disease management.

Literature published by the Canadian Breast Cancer Network about the financial impact of breast cancer on patients identified the following:

- 80% of breast cancer patients report a financial impact due to their illness. Patients who are self-employed frequently do not have health care coverage that will cover the cost of treatment for the breast cancer, nor medication and alternative treatments such as massage, acupuncture and nutritional counselling to manage side effects.
- Many patients are not eligible for their corporate health care plan, or face confusing and time-consuming application processes to access corporate or government assistance plans.
- 44% of patients have used their savings, and 27% have taken on debt to cover costs.
- Breast cancer results in high out of pocket expenses related to devices and family care costs. Examples of common costs include:
    - childcare when ill, when receiving clinic-based clinics, and when travelling to receive treatment in another community or region
    - parking costs during treatment and medical appointments; and
    - transportation and accommodation costs when patients must travel to receive.

These findings were consistent with the responses to the survey of CBCN and Rethink:

- Nearly one third of patients indicated that the cost of medication, the cost of alternative treatments (i.e. massage, physiotherapy, etc.) to manage symptoms and side effects, and the time required to travel to treatment had a significant or debilitating impact on their quality of life.
- 24% of patients indicated that the costs associated with travel had a significant or debilitating impact on their quality of life, and 41% of patients indicated that it had some or moderate impact on their quality of life.

Other barriers that were included in the survey responses were: not qualifying for insurance at work, inability to change employers due to loss of insurance, and the prohibitive cost of new treatment options.

"Many of the next step treatments are very expensive and not covered by government programs and it is a HUGE struggle to get coverage. … When dealing with an incurable disease the last thing you want to have to do is spend time on a letter writing campaign to argue about whether or not you should receive the drugs recommended by your physician. At about $1500.00 a week, I don't know many who can afford that."

In response to questions on the survey relating to the availability of support services such as childcare, transportation, and alternative treatments in their community:

- 53% of respondents with children or other dependents indicated there is minimal or no access to appropriate care for their loved ones when they are experiencing debilitating symptoms to their cancer, and 40% identified barriers to accessing quality care during cancer treatment.
- 26% of patients indicated there are minimal or no transportation options in their community when they seek treatment and support for symptoms, and 18% indicated a lack of adequate transportation options to access cancer treatment.

One patient indicated that in a rural community, it is difficult to get to the hospital in the winter months.

When asked *what level of side effects and how much impact on one's quality of life would be worth extending progression-free disease by six months*, the responses clearly indicated that this assessment can only be determined by an individual patient in this circumstance.

When asked to rate *how much impact different symptoms of cancer and cancer treatment would be considered tolerable*:

- Almost two-thirds of patients indicated that fatigue, nausea, depression, problems with concentration, memory loss, diarrhea and insomnia, some or a moderate impact on one's quality of life would be considered acceptable, and approximately one quarter of patients indicated that a strong or debilitating impact would be considered acceptable.
- 70% of patients indicated that some or moderate pain would be considered acceptable, and 27% of patients indicated that strong or debilitating pain would be considered acceptable.

One patient indicated that for her, side-effects were not a big factor in assessing whether she would begin a new treatment. Other than hair loss, she was able to work with her physician to identify and receive medication to adequately manage and in some cases, eliminate side-effects.

Based on comments provided in the open-ended portion of the survey, patients made two observations:

- Some patients felt they did not understand the wording of the question.
- Some patients did not feel that they had the capacity to respond to a hypothetical question of this nature.

"My preference is for access to lots of treatments so I can live for long time. Less side effects are preferable, but if there is no option I will put up with symptoms of treatment in order to live longer."

"Not all patients suffer the same way. […] It was a difficult task to answer that question."

When asked in the survey about their willingness to tolerate risk with a new treatment:

- 34% were willing to accept serious risk with treatment if it would control the disease
- 45% were willing to accept some risk with treatment
- 21% were very concerned and felt less comfortable with serious risks with treatment.

The responses to the open ended question in the key informant interviews confirmed that the decision to determine what risks and side effects are tolerable must rest in the hands of each individual patient. While a side-effect such as hair loss, nausea and fatigue for a medication may be common across patients, each patient will assess its impact on their quality of life differently.

"I think patients (ESPECIALLY young patients) should be given more decision making power in terms of access to radical treatments to control disease. […] With two small children, I

am determined to access any treatment that can extend my life and I hate struggling with doctors for this access."

"It has been very frustrating that doctors do not address the more subjective symptoms such as pain related to chemotherapy (muscle and joint), which persists after chemotherapy"

"I believe that I would prefer to tolerate severe restrictions in the quality of my life, if it meant that I would be able to have a longer period without progression."

"Had you asked me some of these questions four years ago, the answers would have been different. My oncologist tells me that I am running out of treatment options. […] It is very scary to face the day (soon) when I will have no treatment and the cancer will be allowed to run its course."

4.1.3 Impact of Metastatic Breast Cancer and Current Therapy on Caregivers

While caregivers provide loving support, they experience a significant negative impact on their quality of life. Caregiver respondents reported experiencing a number of symptoms of stress, as well as a negative impact on their ability to continue their daily routines, responsibilities, and self-care for personal health issues.

- 77% of caregivers indicated that anxiety, fatigue, and problems with concentration had a negative impact on their quality of life
- 67% of caregivers indicated that depression and insomnia had a negative impact on their quality of life, and
- 55% of caregivers indicated that memory loss and physical pain such as muscle tension had a negative impact on their quality of life.

All caregivers reported that their role has resulted in a negative impact on their personal, social, and professional lives. 100% of caregivers identified restrictions to their employment, their ability to pursue personal interests and hobbies, their ability to travel, and their ability to exercise. One respondent indicated that there was a clear impact on his or her ability to fulfill his job responsibilities and negatively impacted on his or her career progression.

- 89% of caregivers identified restrictions to their ability to participate in social events and activities
- 75% of caregivers identified restrictions to their ability to volunteer
- 67% of caregivers identified restrictions to their ability to spend time with loved ones, and
- 44% of caregivers identified restrictions to their ability to care for children and dependents.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences to Date with T-DM1

Patient group input states that the following results are based on a phase III clinical trial that compared T-DM1with capecitabine plus lapatinib. Results showed the risk of death was reduced by 32 percent for people who received T-DM1 compared to those who received lapatinib plus capecitabine. The most common side effects reported by patients in the clinical trial were thrombocytopenia and increased AST levels e. However, both patients interviewed by CBCN/Rethink indicated these side effects were minimal to non-existent.

By delaying the progression of the disease, T-DM1can relieve cancer-related symptoms, and improve a patient's quality of life. When living with no or with minimal cancer-related symptoms, and with minimal side effects from the treatment, patients are able to reduce the impact of cancer on their ability to care for children and dependents, continue with their employment and earn income, spend time with loved ones and participate in their life in a meaningful way by engaging in social activities, travelling, maintaining friendships, and pursuing personal interests.

Patients living with metastatic breast cancer are aware that their advanced disease will progress with worsening symptoms until death, and embrace opportunities to try new treatment, even if benefits may be as little as a six month extension of progression-free disease. It is also very important for patients to have quality of life when receiving treatment for metastatic disease to have the energy to attend children's activities and spend time with family and friends. A number of patients expressed concern over the costs of the treatment, indicating that new treatments often come with high costs which must be covered by patients out of pocket, or which require lengthy processes for public and private insurance to secure approval for the expense.

Two Canadian patients living with HER2+ metastatic breast cancer participated in the EMILLA trial (enrolled in 2010 & 2013). One (1) patient stated that when the cancer recurred in 2010, she had 2 lumps under her armpit. After the first infusion of T-DM1, she could feel the tumours getting smaller, and shortly after, one of the lumps disappeared completely, and the larger one kept getting smaller. Currently there are no lumps in this area. The patient expressed that her quality of life while taking this meditation is excellent.

The other patient (1) is only in the 2nd cycle of treatment, within two weeks of beginning the treatment her physical symptoms have subsided.

> *"Wonderfully effective! I have excellent quality of life on this treatment. I am able to be involved in my children's daily lives, with no limitations due to side effects. I am able to go to the gym, a couple times a week, volunteer at my children's school, be involved in our church, and I also work as a supply Educational Assistant."*
>
> *"I would give this treatment 10 out of 10 in terms of quality of life. Within six weeks of starting treatment I started running again, returned to work and feel physically and mentally stronger than ever."*

The patients (2) are well aware of the possible risks of this treatment and were made aware that all patients can respond differently to side effects. One (1) patient stated that

she feels very fortunate to have experienced very minimal side effects because she knows that this is not the case for all women.

The first patient (1) said if she was unable to access this treatment she believes she would likely be taking lapatinib and capecitabine**, which she has heard have more gastrointestinal side effects (eg. diarrhea, nausea, etc.). Her oncologist also mentioned doxorubicin which can cause nausea, fatigue, hair loss, and lowered immunity.**

The other patient's (1) only option would be more traditional chemotherapy because of the side effects she would not be able to work, or be physically active which is very important to her.

One patient (1) could only identify one side effect to this line of therapy which was dry mouth. It should be noted that for this patient at the beginning of the treatment she had elevated liver enzymes and had to have her dose lowered. This later subsided. The second patient (1) had a 5-day fever after the first treatment and no side effects since.

One (1) of the patients expressed that this therapy allowed her to experience a very good quality of life. She was diagnosed at stage IV and since beginning this line of treatment she has been able to participate in daily activities at home and in her community. She did not discuss the financial impact of the drug however the other patient that has just begun this treatment expressed a concern with the high price. She has private health insurance but even with that she will be expected pay for the remainder which could be around $2000 a month.

Neither patient commented on the administration of this drug.

4.3 Additional Information

No information was provided in this section by CBCN and Rethink.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for trastuzumab emtansine (Kadcyla) for metastatic breast cancer. 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.pcodr.ca).

Overall Summary

Input on the trastuzumab emtansine (T-DM1) review was obtained from nine of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, lapatinib + capecitabine is currently the standard of care for second line MBC and was considered to be an appropriate comparator. However, PAG indicated that in some jurisdictions trastuzumab or trastuzumab + chemotherapy (eg. vinorelabine) are other standards of care and a comparison to it would have been appropriate.

PAG identified several barriers to implementation. Pending a pERC recommendation on pertuzumab, the current standard of care in the first line setting is expected to change; however, PAG noted that clinical evidence is not available to support the use of T-DM1 following this drug. PAG is also unclear as to whether patients that have already received anti-HER2+ therapy with the current standard of care will be eligible to receive T-DM1. In addition, if implemented, T-DM1 will be one of several options available in the metastatic setting. As such, PAG expects that a consideration will be required on the eligibility criteria of patients to receive sequenced treatments.

Due to similarities in the name, PAG noted a potential hazard if the dosing of T-DM1 if confused with that of trastuzumab. PAG suggested that precautions such as the use of trade names on labels, warning information on pre-printed orders, safety notice in storage areas and separate storage areas as some ways to avoid drug mix-ups.

PAG indicated that wastage is a potential issue as T-DM1 comes in two single use vial sizes (100mg and 160mg) and dosing is weight based.

Please see below for more detailed PAG input on individual parameters.

5.1 Factors Related to Comparators

The comparison of T-DM1 with lapatinib + capecitabine in the pivotal study reflects the current standard of care in many jurisdictions. However, PAG indicated that this comparison may not be appropriate for all jurisdictions as uptake of 2nd line lapatinib + capecitabine is limited. PAG noted that in some jurisdictions trastuzumab + chemotherapy is currently an alternative 2nd line treatment and considered it as a more relevant comparator. PAG did however note that the economic evaluation will be making a comparison with lapatinib + capecitabine and trastuzumab + chemotherapy.

PAG indicated that the use of first line pertuzumab is expected to be available in Canada prior to T-DM1. This will likely be a barrier to implementation as there is no clinical evidence to support the use of T-DM1 following first line pertuzumab.

5.2 Factors Related to Patient Population

Patients who had received previous treatment with lapatinib + capecitabine were excluded from the pivotal study. If implemented, as the majority of HER2+ patients will likely be eligible to receive T-DM1, PAG is unclear as to whether patients that have already received anti-HER2+ therapy will be eligible to receive T-DM1. In addition, PAG noted that if implemented T-DM1 will be one of several options available in the metastatic setting. As such, PAG expects that guidance will be required on the eligibility criteria of patients to receive sequenced treatments.

5.3 Factors Related to Accessibility

PAG noted the availability of well established HER2+ testing as an enabler to implementation. PAG also noted that the unlike the current standard of care T-DM1 is an IV drug and will bypass accessibility issues related to oral drugs.

PAG noted several barriers to accessibility to patients in less centralised settings. Access of treatment in rural outreach setting will likely be limited as there may be a potential for use of trastuzumab in place of T-DM1 or vice-versa. Likewise, PAG also noted that availability of T-DM1 in the rural setting may increase the possibility of drug wastage. Lastly, in some jurisdictions trastuzumab is funded centrally but PAG is unclear about the availability of T-DM1 through this centralised funding mechanism.

5.4 Factors Related to Dosing

PAG noted that depending on the treatment regimen that T-DM1 may replace, it may require more or less chemotherapy chair time. If T-DM1 is replacing trastuzumab + chemotherapy there would be less chemo chair time as T-DM1 has only one IV drug administered as opposed to two for the comparator. If replacing lapatinib + capecitabine, both oral drugs, there will be additional chemotherapy chair time.

T-DM1 dosing is weight based and requires the administration of 3.6mg/kg. As a result, this presents a potential hazard if the dosing is confused with that of trastuzumab (6-8mg/kg). PAG noted that the Phase 1 dose escalation study for T-DM1 stopped at 4.2 mg/kg. As such, if T-DM1 is mixed at the wrong dose (6-8mg/kg) this will potentially double the dose for the patient which is a significant safety concern.

5.5 Factors Related to Implementation Costs

PAG noted that drug wastage is a potential barrier to implementation. Currently T-DM1 comes in two single use vial sizes (100mg and 160mg). As dosing is weight based, PAG indicated that wastage is a potential issue. Pharmacies may also accrue additional costs for larger amounts of refrigerated storage that will be required for T-DM1.

5.6 Other Factors

PAG noted the need for safety precautions to avoid pharmacy or administration confusion among trastuzumab and T-DM1. PAG suggested that precautions be systematically introduced such as the use of trade names on labels, warning information on pre-printed orders, safety notice in storage areas and separate storage areas as some ways to avoid drug mix-ups.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness of single-agent therapy with trastuzumab emtansine (T-DM1; Kadcyla) compared to an appropriate comparator, in patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who have received prior therapy with trastuzumab and a taxane for previous metastatic breast cancer or who developed disease recurrence during or within six months of completing adjuvant therapy with these agents for breast cancer.

See Table 3 in Section 6.2.1 for outcomes of interest and appropriate comparators.

Note: No Supplemental Questions relevant to the pCODR review or to the Provincial Advisory Group were identified.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel 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.

Table 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCT	Patients with unresectable locally advanced or metastatic breast cancer who have received prior treatment with trastuzumab and a taxane for previous metastatic breast cancer or who have developed disease recurrence during or within six months of completing adjuvant therapy with trastuzumab and a taxane for breast cancer.	Trastuzumab emtansine 3.6 mg/kg i.v. every 3 weeks (i.e., 21-day cycle) until disease progression or unacceptable toxicity.	Lapatinib + capecitabine OR Trastuzumab + vinorelbine OR Trastuzumab + capecitabine	**OS** PFS Response† Time to symptom progression **QOL** Adverse events/ toxicity
Abbreviations: i.v.=intravenous infusion; OS=overall survival; PFS=progression-free survival; QOL=quality of life; RCT=randomized controlled trial.				

**Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions.*
†Response includes the complete response rate as well as the objective response rate (complete + partial responses).

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; EMBASE (1980-) via Ovid; The Cochrane Central Register of Controlled Trials (2013, Issue 9) via Wiley; 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 concepts were trastuzumab emtansine (T-DM1) and Kadcyla, and breast cancer.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year. Retrieval was limited to the English language.

The search is considered up to date as of October 2, 2013.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicatrials.gov and Ontario Institute for Cancer Research – Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the San Antonio Breast Cancer Symposium (SABCS) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for information as required by the pCODR Review Team.

6.2.3 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.

6.2.4 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.

6.2.5 Data Analysis

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

6.2.6 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.

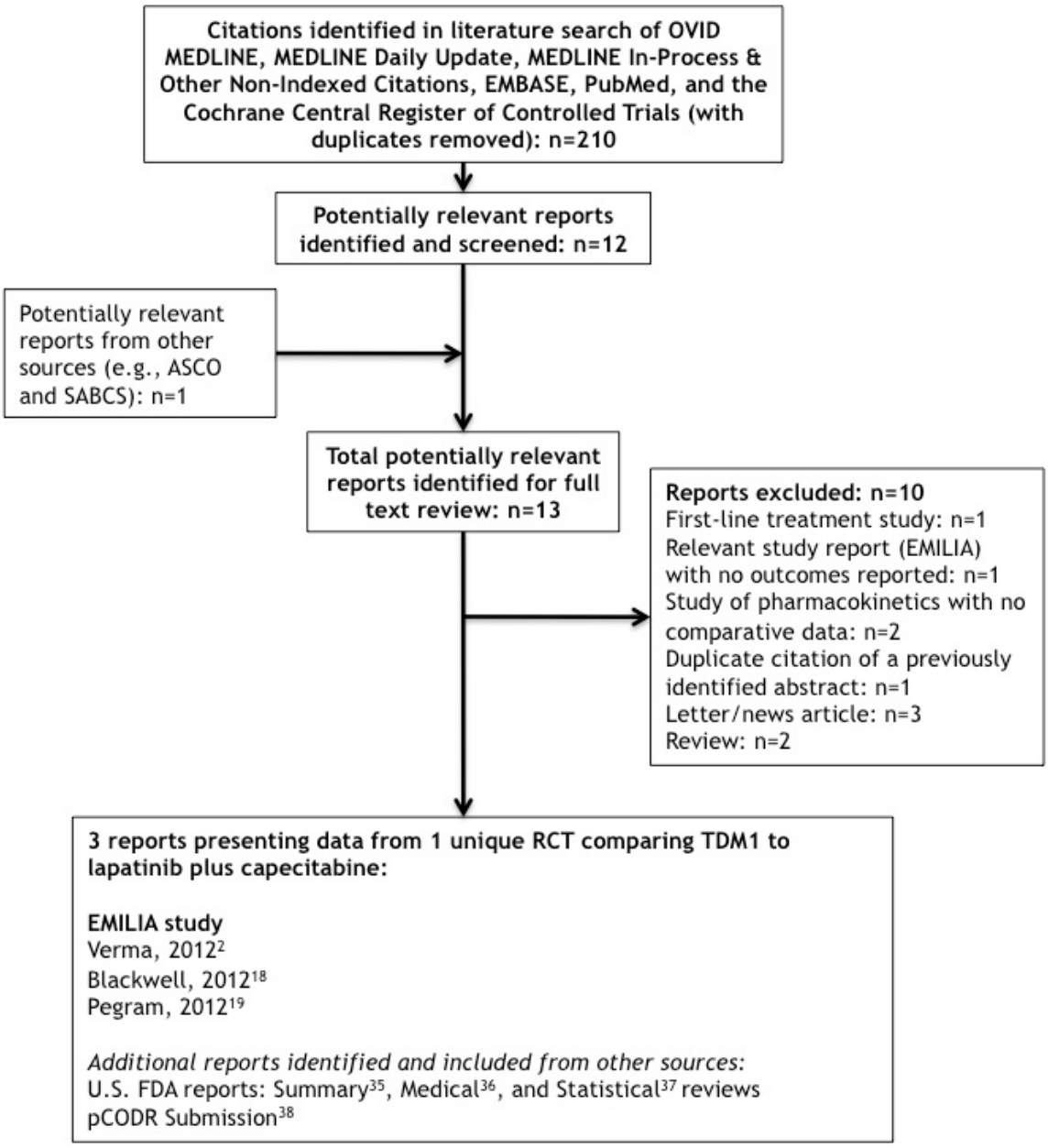
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided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

6.3 Results

6.3.1 Literature Search Results

Of the 211 citations identified in bibliographic databases and other sources, 13 potentially relevant reports were identified for full text review. Of those, three reports, representing one RCT, were included in the pCODR systematic review[2,18,19] and 10 studies were excluded (see Figure 1). Studies were excluded because they were a study of first-line treatment with T-DM1 [28], a report of an eligible study with no outcomes of interest reported[29], pharmacokinetic studies with no comparative data[30,31], a letter or news article[32-34], a review[35,36], or a duplicate citation of a previously identified abstract.[37] In addition, the United States Food and Drug Administration's (U.S. FDA) Summary[38], Medical[39], and Statistical[40] Reviews were included, as was the submission by the manufacturer to pCODR.[41]

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of Studies.



6.3.2 Summary of Included Studies

Provide a brief statement summarizing the number and type of included studies.

6.3.2.1 Detailed Trial Characteristics

a) Trials

Only one study, the EMILIA study,[2] met the eligibility criteria for this systematic review (Table 1). The trial was an open-label randomized controlled superiority trial comparing T-DM1 to lapatinib plus capecitabine in patients with HER2-positive unresectable, locally advanced or metastatic breast cancer who had received previous treatment with trastuzumab and a taxane. The study was conducted at more than 213 sites[2] in 26 countries[39] and was funded by F. Hoffmann-La Roche and Genentech.

An appropriate method of randomization was used and was stratified by region (U.S., Western Europe, or other), number of prior chemotherapy regimens for unresectable locally advanced or metastatic disease (0 or 1 vs. >1), and by disease involvement (visceral vs. nonvisceral).

The trial had multiple primary outcomes including progression-free survival (as assessed by independent review; original study protocol), overall survival (protocol amendment in October 2010 with data still masked to investigators), and safety (original study protocol). Secondary outcomes included progression-free survival (as assessed by investigator), objective response rate (complete response plus partial response; as assessed by both investigator and independent review), duration of objective response, time to treatment failure, and time to symptom progression.[2] Response was assessed by both the investigators and by an independent review committee using modified RECIST criteria at baseline and every six weeks thereafter until investigator-assessed disease progression. A final assessment was also required six weeks after progression. Progression-free survival was defined as the time from randomization to first occurrence of progression or death from any cause. Overall survival was defined as the time from randomization to death from any cause. Time to symptom progression was defined as the time from randomization to the first documentation of 5-point or more decrease from baseline in the scoring of responses as measured by the Functional Assessment of Cancer Therapy-Breast (FACT-B) instrument using the Trial Outcome Index (TOI) subscale which includes the physical, functional, and breast subscales.[2]

The original trial protocol, with progression-free survival as the primary endpoint, required a sample size of 580 patients.[2] The amended protocol (October 2010), with overall survival as a co-primary endpoint, required a sample size of 980 patients.[2] This sample size provided 90% power to detect a hazard ratio (HR) of 0.75 for progression or death from any cause and 80% power to detect a HR of 0.80 for death from any cause, with T-DM1 as compared with lapatinib plus capecitabine with a two-sided alpha of 0.05. The primary analysis for progression-free survival was to be performed after 508 independently assessed events.[2] The final analysis for overall survival was to be performed after 632 deaths, with a planned interim analysis at the time of the primary analysis for progression-free survival.[2] Following the first interim analysis, a second interim analysis was added to the statistical plan for the trial and was to be conducted after 50% of the required number of deaths occurred (316 events). Stopping boundaries were determined using a Lan-De Mets alpha-spending function, with an O'Brien-Fleming boundary. The Kaplan-Meier method was used to estimate the median, 1- and 2-year survival rates and 95% confidence intervals (95% CI) for progression-free survival and overall survival. A Cox proportional hazards model, with the stratification factors used for randomization, was used to estimate the hazard ratios and 95% CI's. Objective response rates were compared

between the intervention and control arms using the Mantel-Haenszel chi-square test with stratification by the factors used for randomization.

b) Populations

A total of 991 patients were enrolled and randomized in a 1:1 ratio to either T-DM1 (n=495) or to lapatinib plus capecitabine (n=496). The baseline characteristics for each of the two treatment groups were similar (Table 4).

Table 4. Baseline Patient Characteristics in the EMILIA study.[2,39]

Characteristic	T-DM1	Lapatinib+ Capecitabine
n	495	496
Age (years)		
Median	53	53
Range	25-84	24-83
Race (%)		
White	358 (72)	374 (75)
Asian	94 (19)	86 (17)
Black	29 (6)	21 (4)
Other	7 (1)	10 (2)
Not available	7 (1)	5 (1)
Region (%)		
United States	134 (27)	136 (27)
Western Europe	157 (32)	160 (32)
Asia	82 (17)	76 (15)
Other	122 (25)	124 (25)
ECOG PS (%)		
0	299 (60)	312 (63)
1	194 (39)	176 (35)
Not available	2 (<1)	8 (2)
Site of disease involvement (%)		
Visceral	334 (67)	335 (68)
Nonvisceral	161 (33)	161 (32)
Hormone-receptor status (%)		
ER-positive, PgR-positive, or both	282 (57)	263 (53)
ER-negative and PgR-negative	202 (41)	224 (45)
Unknown	11 (2)	9 (2)
Prior systemic therapy (%)		
Anthracycline	303 (61)	302 (61)
Other chemotherapy	385 (78)	382 (77)
Biologic agent other than trastuzumab or pertuzumab	13 (3)	21 (4)
Endocrine therapy	205 (41)	204 (41)
Prior chemotherapy regimens for locally advanced or metastatic disease (%)		
0 or 1	304 (61)	305 (61)
>1	191 (39)	191 (39)
Prior trastuzumab treatment (%)		
For metastatic breast cancer only, early breast cancer only, or both	417 (84)	419 (84)
For early breast cancer only	78 (16)	77 (16)
Duration of trastuzumab treatment (%)		

Table 4. Baseline Patient Characteristics in the EMILIA study.[2,39]		
Characteristic	**T-DM1**	**Lapatinib+ Capecitabine**
<1 year	210 (42)	212 (43)
≥1 year	285 (58)	284 (57)
Time since last trastuzumab treatment (months)		
Median	1.5	1.5
Range	0-63	0-98
Stage of disease (%)		
I	44 (9)	43 (9)
II	127 (26)	139 (28)
III	155 (31)	138 (28)
IV	114 (23)	131 (26)
Unknown	55 (11)	45 (9)
Number of metastatic sites (%)		
<3	298 (60)	307 (62)
≥3	189 (38)	175 (35)
Unknown	8 (2)	14 (3)
Measurable disease (%)	397 (80)	389 (78)
Notes: ECOG PS=Eastern Cooperative Oncology Group performance status; **ER**=estrogen receptor; **n**=number of patients randomized; **PgR**=progesterone receptor.		

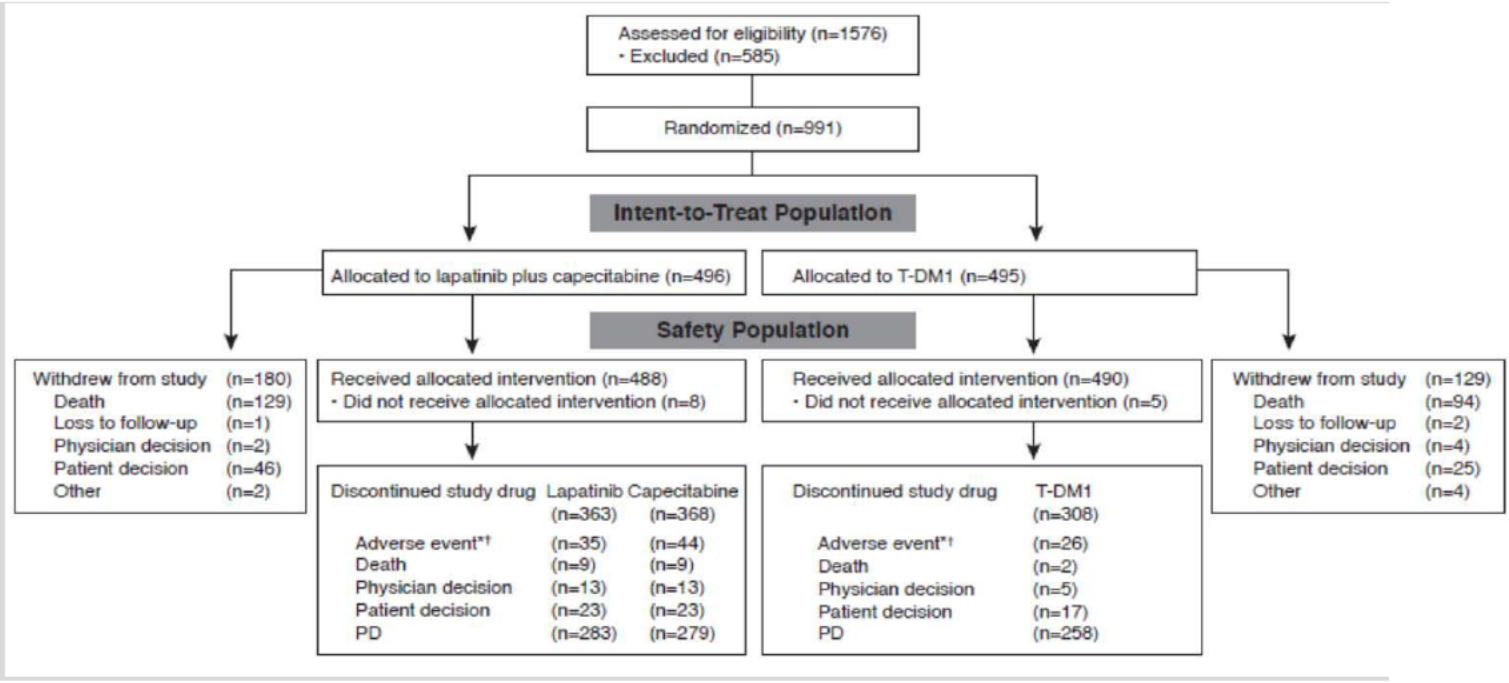
c) Interventions

Patients in the T-DM1 arm (n=495) were to receive T-DM1 at a dose of 3.6 mg/kg intravenously every 21 days until disease progression or unmanageable toxic effects.[2] Patients in the combination lapatinib/capecitabine control arm were to receive lapatinib at a dose of 1250 mg orally, daily plus capecitabine 1000 mg/m^2 every 12 hours on days 1-14 every 21 days. Information on how dose reductions and treatment discontinuation for each study and drug were handled can be found in Table 1. Dose reductions for lapatinib and capecitabine occurred in 27.3% and 53.4% of patients, respectively. The median daily dose received for lapatinib was 1250.0 mg per day (range, 250.0 to 1332.3 mg per day) and for capecitabine was 1729.8 mg/m^2 per day (range, 781.6 to 2338.4 mg/m^2 per day). Dose reductions for T-DM1 occurred in 16.3% of patients. The median daily dose received for T-DM1 was 3.5 mg/kg every 21 days (range 2.7 to 4.0 mg/kg every 21 days).

d) Patient Disposition

The disposition of the patients at the time of the primary analysis for progression-free survival (data cut off: January 14, 2012), for both the intent-to-treat population and the safety population can be found in Figure 2. The intent-to-treat population included all 991 randomized patients with 495 randomized to receive T-DM1 and 496 patients to receive lapatinib plus capecitabine.[2] The safety population included 490 patients allocated to receive T-DM1 and 488 patients allocated to receive lapatinib plus capecitabine. Of the 495 patients randomized to the T-DM1 arm, 129 (26.1%) patients withdrew from the study. Of those, two were lost to follow-up, four withdrew due to physician's decision, 25 due to patient decision and four were due to 'other' reasons. Of the 496 patients randomized to the lapatinib plus capecitabine arm, 180 patients withdrew from the study. Of those, one was lost to follow-up, two were due to physician's decision, 46 were due to patient decision, and two were due to 'other' reasons.

Figure 2. Intent-to-treat and safety populations and patient disposition in the EMILIA study at the time of the progression-free survival analysis.[2]



*Two patients in the lapatinib plus capecitabine arm and three patients in the T-DM1 arm had both an adverse event and progressive disease at the time of treatment discontinuation, with progressive disease attributed as the primary reason for discontinuation.
†The most common adverse events leading to lapatinib or capecitabine discontinuation were diarrhea (n=12) and vomiting (n=11), and diarrhea (n=14), respectively. The most common adverse event leading to T-DM1 discontinuation was thrombocytopenia (n=10).
Source: Verma et al, 2012.[2]

e) Limitations/Sources of Bias

The EMILIA study[2] was an open-label randomized controlled trial. Given the fact that T-DM1 is an intravenous agent and lapatinib and capecitabine are oral agents, implementing blinding in this study would have been difficult. It should be noted that the lack of blinding of study treatment personnel and patients may have had an impact on the results of the trial. For instance, almost twice as many patients in the lapatinib plus capecitabine arm (n=46) withdrew from the study due to patient decision than in the T-DM1 arm (n=25). This difference may be due to the patients knowing what treatment they were receiving and their perception of whether that agent was working or not.

Although the study participants, investigators, and physicians were not blinded to treatment allocation, the study used an independent review committee, blinded to treatment allocation, to assess tumour response, thus limiting the potential for bias in tumour assessments. In addition, the study protocol was amended during the recruitment phase to include overall survival (an objective outcome) as a co-primary outcome. The subsequent increase to the required sample size and amendment to the analysis plan was carried out in an appropriate manner, while the investigators were still blinded to treatment allocation.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

The primary efficacy analysis was based on the intent-to-treat population, which was comprised of all randomized study subjects (T-DM1 arm, n=495; lapatinib plus capecitabine arm, n=496).[2] The safety population consisted of patients who receive the treatment to which they were allocated (T-DM1 arm, n=490; lapatinib plus capecitabine, n=488). Key efficacy and harms outcomes can be found in Table 2.

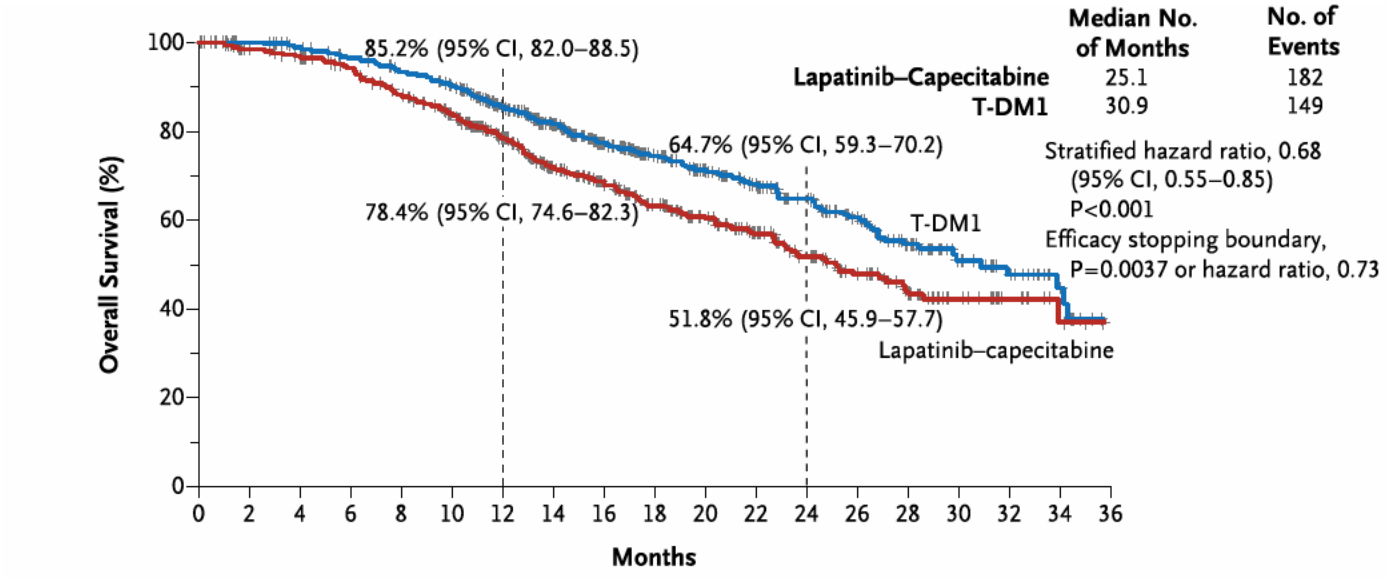
Efficacy Outcomes

Overall Survival

Overall survival was a co-primary outcome of the EMILIA study.[2] The analysis was stratified by world region (U.S., Western Europe, or other), number of prior chemotherapy regimens for unresectable locally advanced or metastatic disease (0 or 1 vs. >1) and disease involvement (visceral vs. non-visceral) using a Cox proportional hazards model to estimate the hazard ratios and 95% CI's.

The final analysis of overall survival, using the intent-to-treat population with a data cut-off of July 31, 2012, demonstrated a statistically significant difference in overall survival for T-DM1 (median 30.9 months) compared to lapatinib plus capecitabine (median 25.1 months), with HR 0.68, 95% confidence interval (CI) 0.55-0.85, p<0.001 (Table 2 and Figure 3). There were 331 deaths with a median follow-up of 18.6 months. One-year survival rates were 85.2% (95% CI 82.0% to 88.5%) in the T-DM1 arm and 78.4% (95% CI 74.6% to 82.3%) in the lapatinib plus capecitabine arm. Two-year survival rates were 64.7% (95% CI 59.3% to 70.2%) in the T-DM1 arm and 51.8% (95% CI 45.9% to 57.7%) in the lapatinib plus capecitabine arm.[2]

Figure 3. Kaplan-Meier survival curves for the final overall survival analysis in the EMILIA study.[2]



No. at Risk

Lapatinib–capecitabine	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

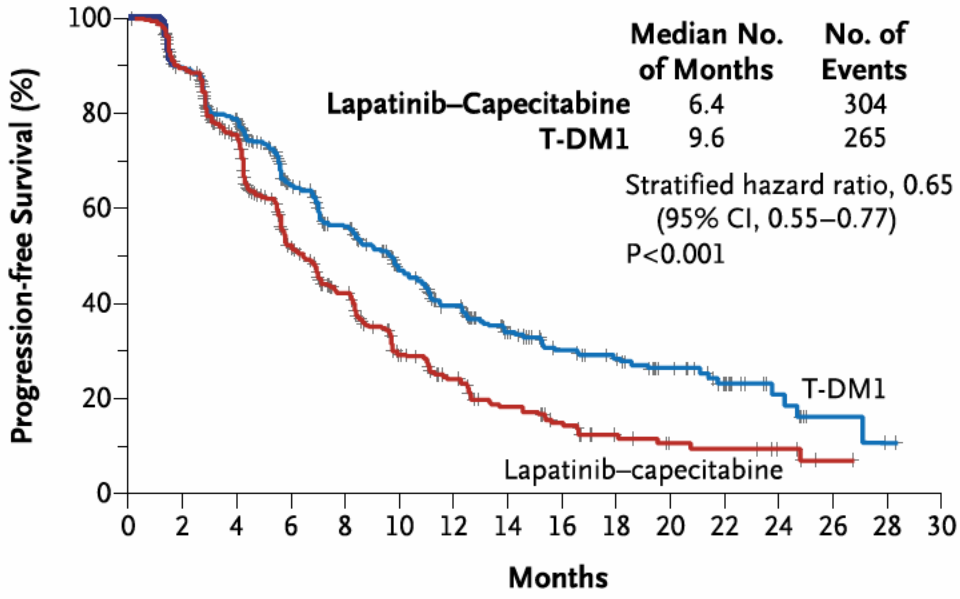
Source: Verma et al, 2012.[2]

Progression-Free Survival

Progression-free survival as assessed by an independent review committee (independent PFS), was a co-primary endpoint of the EMILIA study.[2]

The final analysis of independent PFS, using the intent-to-treat population with a data cut-off of January 14, 2012, demonstrated a statistically significant difference in PFS for T-DM1 (median 9.6 months) compared to lapatinib plus capecitabine (median 6.4 months) with HR 0.65, 95% CI 0.55 to 0.77, p<0.001 (Table 2 and Figure 4). There were a total of 569 events after a median follow-up of 13 months.

Figure 4. Kaplan-Meier survival curves for the final independent PFS analysis in the EMILIA study.[2]



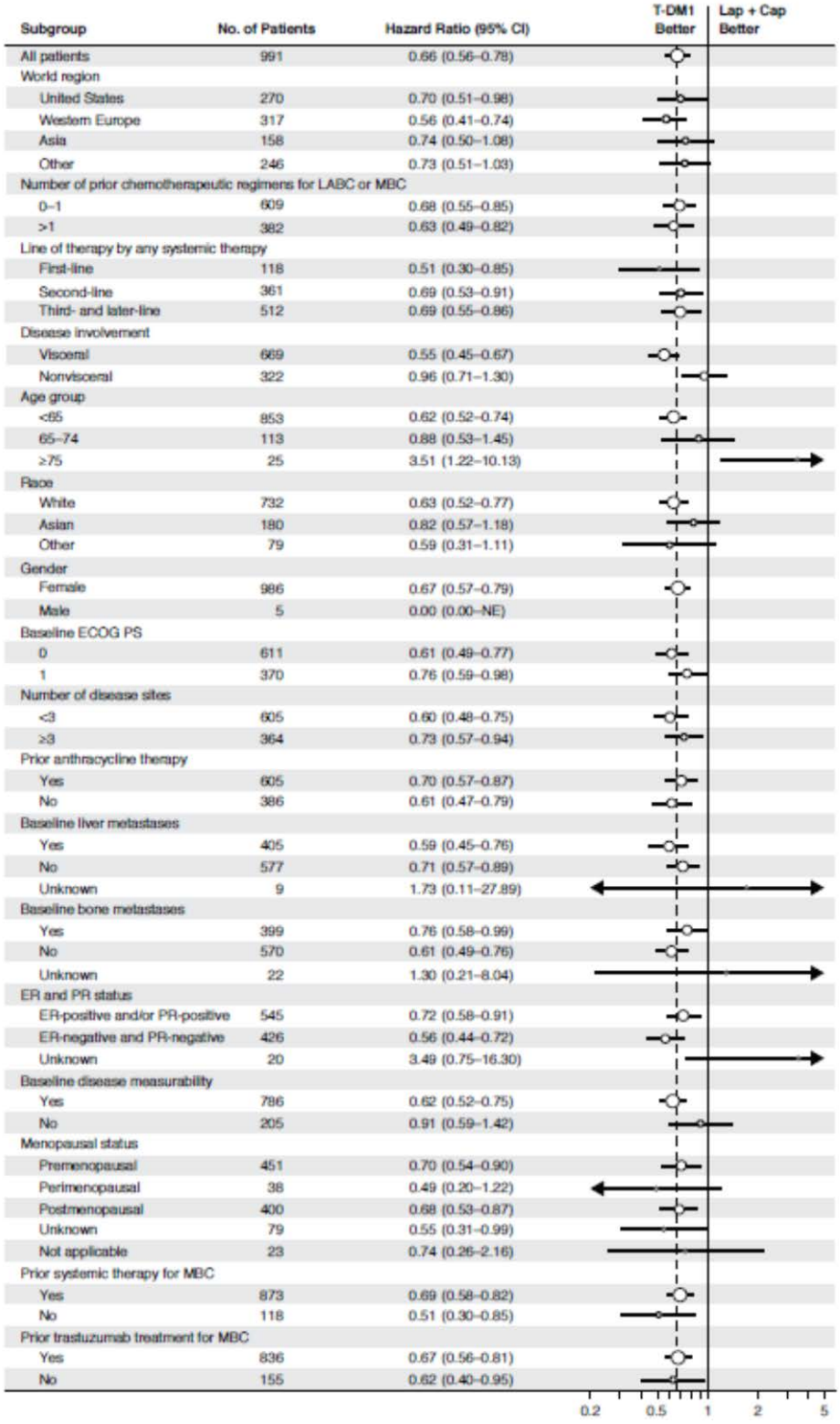
No. at Risk

Lapatinib–capecitabine	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

Source: Verma et al, 2012.[2]

Pre-specified sensitivity analyses using 16 subgroups were also conducted for independent PFS. Figure 5 shows the results of those analyses, with censoring for non-protocol therapy. Of note, the effect was consistent across subgroups with the exception of patients aged 75 years or older (Figure 5).

Figure 5. Sensitivity Analyses for Independent PFS in 16 Patient Subgroups in the EMILIA Study.[2]



Subgroup	No. of Patients	Hazard Ratio (95% CI)
All patients	991	0.66 (0.56–0.78)
World region		
United States	270	0.70 (0.51–0.98)
Western Europe	317	0.56 (0.41–0.74)
Asia	158	0.74 (0.50–1.08)
Other	246	0.73 (0.51–1.03)
Number of prior chemotherapeutic regimens for LABC or MBC		
0–1	609	0.68 (0.55–0.85)
>1	382	0.63 (0.49–0.82)
Line of therapy by any systemic therapy		
First-line	118	0.51 (0.30–0.85)
Second-line	361	0.69 (0.53–0.91)
Third- and later-line	512	0.69 (0.55–0.86)
Disease involvement		
Visceral	669	0.55 (0.45–0.67)
Nonvisceral	322	0.96 (0.71–1.30)
Age group		
<65	853	0.62 (0.52–0.74)
65–74	113	0.88 (0.53–1.45)
≥75	25	3.51 (1.22–10.13)
Race		
White	732	0.63 (0.52–0.77)
Asian	180	0.82 (0.57–1.18)
Other	79	0.59 (0.31–1.11)
Gender		
Female	986	0.67 (0.57–0.79)
Male	5	0.00 (0.00–NE)
Baseline ECOG PS		
0	611	0.61 (0.49–0.77)
1	370	0.76 (0.59–0.98)
Number of disease sites		
<3	605	0.60 (0.48–0.75)
≥3	364	0.73 (0.57–0.94)
Prior anthracycline therapy		
Yes	605	0.70 (0.57–0.87)
No	386	0.61 (0.47–0.79)
Baseline liver metastases		
Yes	405	0.59 (0.45–0.76)
No	577	0.71 (0.57–0.89)
Unknown	9	1.73 (0.11–27.89)
Baseline bone metastases		
Yes	399	0.76 (0.58–0.99)
No	570	0.61 (0.49–0.76)
Unknown	22	1.30 (0.21–8.04)
ER and PR status		
ER-positive and/or PR-positive	545	0.72 (0.58–0.91)
ER-negative and PR-negative	426	0.56 (0.44–0.72)
Unknown	20	3.49 (0.75–16.30)
Baseline disease measurability		
Yes	786	0.62 (0.52–0.75)
No	205	0.91 (0.59–1.42)
Menopausal status		
Premenopausal	451	0.70 (0.54–0.90)
Perimenopausal	38	0.49 (0.20–1.22)
Postmenopausal	400	0.68 (0.53–0.87)
Unknown	79	0.55 (0.31–0.99)
Not applicable	23	0.74 (0.26–2.16)
Prior systemic therapy for MBC		
Yes	873	0.69 (0.58–0.82)
No	118	0.51 (0.30–0.85)
Prior trastuzumab treatment for MBC		
Yes	836	0.67 (0.56–0.81)
No	155	0.62 (0.40–0.95)

Source: Verma et al, 2012.[2]

The authors also reported similar results for investigator-assessed PFS: T-DM1 (median 9.4 months) compared to lapatinib plus capecitabine (median 5.8 months; HR 0.66, 95% CI 0.56-0.77, p<0.001).[2]

Response

Data for objective, complete and partial response, as assessed by the independent review committee, can be found in Table 5. The rate of objective response (complete plus partial responses) was statistically significantly higher in the T-DM1 arm (43.6% of 397 evaluable patients) compared to the lapatinib plus capecitabine arm (30.8% of 389 evaluable patients; p<0.001).[2]

Table 5. Response Outcomes as Assessed by Independent Review Committee in the EMILIA Study.[2]

Response outcome	T-DM1 (N=397)	Lapatinib plus Capecitabine (N=389)	p-value
Objective response n % (95% CI) p-value	 173 43.6 (38.6-48.6) p<0.001	 120 30.8 (26.3-35.7)	p<0.001
Complete response, n (%)	4 (1.0)	2 (0.5)	NR
Partial response, n (%)	169 (42.6)	118 (30.3)	NR

Notes: n=number of patients with response; **N**=number of patients evaluable for response; **T-DM1**=trastuzumab emtansine.

Quality of Life

Time-to-symptom progression was a secondary outcome in the EMILIA study and was defined as the time from randomization to the first documentation of a 5-point or more decrease from baseline in the scoring of responses as measured by the Functional Assessment of Cancer Therapy-Breast (FACT-B) instrument using the Trial Outcome Index (TOI) subscale which includes the physical, functional, and breast subscales. Scores on the FACT-B TOI range from 0 to 92, with higher scores indicating better quality of life.

The median time to a decrease of 5 points or more in the FACT-B TOI score was longer in the T-DM1 arm (median 7.1 months) compared to the lapatinib plus capecitabine arm (median 4.6 months), with HR 0.80, 95% CI 0.67 to 0.95, p=0.012.[2]

No further quality of life assessments were reported.

Harms Outcomes

Adverse events that occurred in 2% or more of patients in either arm of the EMILIA study can be found in Table 6. Grade 3 or above adverse events occurred in higher proportion of patients in the lapatinib plus capecitabine arm (57.0% of 488 patients) than occurred in the T-DM1 arm (40.8% of 490 patients). Both any grade and grade 3 or above diarrhea and palmar-planar erythrodysesthesia occurred in more patients in the lapatinib plus capecitabine arm than in the T-DM1 arm (Table 6). Higher incidences of any grade and grade 3 or above thrombocytopenia, elevated aspartate aminotransferase and elevated alanine aminotransferase were reported in the T-DM1 arm than in the lapatinib plus capecitabine arm (Table 6).

Left ventricular ejection fraction of 45% or more was maintained in 97.1% of patients in the T-DM1 arm and in 93.0% of patients in the lapatinib plus capecitabine arm. Of the 481 patients in the T-DM1 arm and the 445 patients in the lapatinib plus capecitabine arm who could be evaluated, 8 patients (1.7%) and 7 patients (1.6%), respectively, had an ejection fraction less than 50% and at least 15 percentage points below the baseline value. Grade 3 left ventricular systolic dysfunction developed in one patient in the T-DM1 arm and in no patients in the lapatinib plus capecitabine arm. The incidence of any Grade of bleeding events was 29.8% in the T-DM1 arm compared to 15.8% in the lapatinib plus capecitabine arm.[2] The rate of Grade 3 or above bleeding events was 1.4% and 0.8% in the T-DM1 and lapatinib plus capecitabine arms, respectively.[2]

Five deaths were attributed to adverse events that occurred within 30 days after the last dose of a study drug: four in the lapatinib plus capecitabine arm and one in the T-DM1 arm. A total of 29 (5.9%) of 490 patients in the T-DM1 arm discontinued T-DM1 due to an adverse event.[39] A total of 37 patients (7.6%) discontinued lapatinib and 46 patients (9.4%) discontinued capecitabine due to an adverse event out of 488 patients in the lapatinib plus capecitabine arm.[39]

Dose reductions for lapatinib and capecitabine occurred in 27.3% and 53.4% of patients, respectively.[2] Dose reductions for T-DM1 occurred in 16.3% of patients.[2]

Table 6. Adverse Events that Occurred in 2% or More of Study Subjects in Either Group in the EMILIA Study.[2]

Adverse Event	T-DM1 (n=490)		Lapatinib plus Capecitabine (n=488)	
	Any grade AE (%)	Grade 3 or above AE (%)	Any grade AE (%)	Grade 3 or above AE (%)
Any event	95.9	40.8	97.7	57.0
Diarrhea	23.3	1.6	79.7	20.7
Palmar-plantar erythrodysesthesia	1.2	0	58.0	16.4
Vomiting	19.0	0.8	29.3	4.5
Neutropenia	5.9	2.0	8.6	4.3
Hypokalemia	8.6	2.2	8.6	4.1
Fatigue	35.1	2.4	27.9	3.5
Nausea	39.2	0.8	44.7	2.5
Mucosal inflammation	6.7	0.2	19.1	2.3
Anemia	10.4	2.7	8.0	1.6
Elevated ALT	16.9	2.9	8.8	1.4
Elevated AST	22.4	4.3	9.4	0.8
Thrombocytopenia	28.0	12.9	2.5	0.2

Notes: AE=adverse event; **ALT**=alanine aminotransferase; **AST**=aspartate aminotransferase; **T-DM1**-trastuzumab emtansine; **n**=number of patients.
Source: Verma et al, 2012.[2]

6.4 Ongoing Trials

One ongoing RCT was identified investigating the use of T-DM1 in patients with HER2-positive unresectable locally advanced or metastatic breast cancer who have received at least two prior treatments with HER2-directed therapy (trastuzumab and a taxane, lapatinib) for previous metastatic breast cancer or who have developed disease recurrence during or within six months of completing adjuvant therapy with trastuzumab: NCT01419197.[22] Details of this trial can be found in Table 7. In addition, one RCT that was identified as important to this CGR was also identified that investigated the use of T-DM1 plus pertuzumab compared to T-DM1 plus placebo compared to trastuzumab plus a taxane in patients with previously untreated metastatic or recurrent locally advanced breast cancer: NCT01120184.[42] Details of this trial can be found in Table 8.

Table 7. Study NCT01419197: A phase III randomized, multicentre, two-arm, open-label trial to evaluate the efficacy of trastuzumab emtansine compared with treatment of physician's choice in patients with HER2 positive metastatic breast cancer who have received at least two prior regimens of HER2 directed therapy (TH3RESA).[22]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT01419197 **TH3RESA** Active control, multicentre, open-label randomized phase III trial. Start date: September 2011 Expected completion date: June 2015 Estimated enrolment: 606 Sponsor: Hoffmann-La Roche.	Histologically or cytologically confirmed breast cancer. HER2-positive disease by laboratory confirmation. Metastatic or unresectable locally advanced/recurrent breast cancer. Disease progression after at least two regimens of HER2-directed therapy in the metastatic or unresectable locally advanced/recurrent setting. Prior treatment with trastuzumab, a taxane, and lapatinib. Disease must be measurable or evaluable by RECIST criteria. ECOG PS 0-2 Age ≥18 years ***Excluded:***	**Trastuzumab emtansine** 3.6 mg/kg intravenously every 21 days. ***OR*** **Treatment of physician's choice** (chemotherapy, hormonal therapy, biologic drug and/or HER2-directed therapy)	<u>Primary outcomes:</u> Progression-free survival (independent tumour assessments) Overall survival <u>Secondary outcomes:</u> Objective response rate Duration of objective response Adverse events Time to pain symptom progression (EORTC QLQ BM22)

Table 7. Study NCT01419197: A phase III randomized, multicentre, two-arm, open-label trial to evaluate the efficacy of trastuzumab emtansine compared with treatment of physician's choice in patients with HER2 positive metastatic breast cancer who have received at least two prior regimens of HER2 directed therapy (TH3RESA).[22]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
	Patients with prior trastuzumab emtansine (T-DM1).		

Notes: **ECOG**=Eastern Cooperative Oncology Group; **EORTC**=European Organisation for Research and Treatment of Cancer; **PS**=performance status; **QLQ**=Quality of life Questionnaire.
Available from: http://clinicaltrials.gov/ct2/show/NCT01419197?term=nct01419197&rank=1.

Table 8. Study NCT01120184: A study of T-DM1 plus pertuzumab versus trastuzumab (Herceptin) plus a taxane in patients with metastatic breast cancer (MARIANNE).[42]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT01120184 **MARIANNE** Double-blind, multicentre, randomized phase III trial. Start date: July 2010 Expected completion date: April 2016 Estimated enrolment: 1095 Sponsor: Hoffmann-La Roche.	Histologically or cytologically confirmed adenocarcinoma of the breast with locally recurrent or metastatic disease. Patients with locally advanced disease must have recurrent or progressive disease, which must not be amenable to resection with curative intent. HER2-positive disease. ECOG PS 0 or 1. Age ≥18 years ***Excluded:*** Patients with prior chemotherapy for metastatic breast cancer or recurrent locally advanced disease. Less than 6 months since last dose of vinca-alkaloid or taxane	**T-DM1 + Pertuzumab** T-DM1 3.6 mg/kg iv every 21 days + pertuzumab 840 mg iv on day 1 of cycle 1 followed by 420 mg iv every 21 days in subsequent cycles. ***OR*** **T-DM1 + Placebo** T-DM1 3.6 mg/kg iv every 21 days + placebo administered on same schedule as for pertuzumab above. ***OR*** **Trastuzumab + Taxane** *With docetaxel:* Trastuzumab 8 mg/kg iv on cycle 1 followed by 6 mg/kg every 21 days in subsequent cycles + docetaxel 75 mg/m^2 or 100 mg/m^2 iv every 21 days for a minimum of 6 cycles.	<u>Primary outcomes:</u> Progression-free survival (independent tumour assessments) Safety <u>Secondary outcomes:</u> Overall survival Time-to-treatment failure Objective response rate Duration of objective response Clinical benefit rate

Table 8. Study NCT01120184: A study of T-DM1 plus pertuzumab versus trastuzumab (Herceptin) plus a taxane in patients with metastatic breast cancer (MARIANNE).[42]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
	cytotoxic chemotherapy until the time of metastatic diagnosis. Hormone therapy <7 days prior to randomization. Trastuzumab therapy and/or lapatinib (neo- or adjuvant setting) <21 days prior to randomization. Prior T-DM1 or pertuzumab therapy.	*With paclitaxel:* Trastuzumab 4 mg/kg iv on day 1 of cycle 1 followed by 2 mg/kg weekly starting on day 8 of cycle 1 + paclitaxel 80 mg/m^2 iv for a minimum of 18 weeks.	

Notes: ECOG=Eastern Cooperative Oncology Group; **PS**=performance status.
Available from: http://clinicaltrials.gov/ct2/show/NCT01120184?term=marianne&rank=2

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of trastuzumab emtansine (T-DM1) for the treatment of HER2-postivie unresectable locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane:

- Critical appraisal of an indirect comparison of trastuzumab emtansine (T-DM1) with capecitabine plus trastuzumab

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Critical Appraisal of an Indirect Comparison of Trastuzumab Emtansine (T-DM1) Versus All Available Pharmacological Interventions

7.1.1 Objective

To summarize and critically appraise the methods and findings of the manufacturer-submitted indirect comparison of trastuzumab emtansine (T-DM1) versus all available pharmacological interventions used for the treatment of HER2-positive unresectable locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane.

7.1.2 Findings

The manufacturer submitted an indirect comparison to estimate the efficacy of trastuzumab emtansine versus all available pharmacological interventions in order to inform their economic model to determine cost-utility and cost-effectiveness. The indirect comparison is highlighted in the following two network diagrams provided by the manufacturer for overall survival (Figure 6) and progression-free survival (Figure 7):

Figure 6. Network diagram of main indirect comparison of overall survival.
(Non-disclosable clinical information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed)

Figure 7. Network diagram of main indirect comparison of progression-free survival.
(Non-disclosable clinical information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed)

The main analysis for the indirect comparison submitted by the manufacturer was based on the results of three trials: the EMILIA[2] trial compared T-DM1 to capecitabine + lapatinib; the GBG26 trial[43] compared capecitabine + trastuzumab to capecitabine; and the EF100151 trial[44] that compared capecitabine + lapatinib to capecitabine. Two other studies[45,46] were identified through the systematic review as meeting the eligibility criteria, however, they were excluded from the main analysis due to their lack of comparability to the other three studies in patient population, prior treatment status and lack of detailed information on the study population.

The comparison between trastuzumab emtansine and capecitabine plus trastuzumab was obtained by a second-order indirect comparison through GBG26 and EGF100151.

A summary of the studies is presented in Table 8, taken from the indirect treatment comparison report submitted by the manufacturer.

Table 8. Studies included in the submitter's indirect treatment comparison report.

Study	EMILIA trial	GBG26 Trial	EGF100151 trial
Primary study reference	Verma, 2012 [15]	Von Minckwitz [17]	Cameron, 2008 [18]
Publication type	Journal article	Journal article	Journal article
Intervention	Capecitabine + Lapatinib (N=496)	Capecitabine + Trastuzumab (N= 78)	Capecitabine + Lapatinib (N=198)
Comparator (all active controlled)	Trastuzumab-DM1 (N=495)	Capecitabine (N= 78)	Capecitabine (N=201)
Location	USA and non-USA sites[2]	Non-USA sites	USA and non-USA sites
Design	RCT Phase III[2]	RCT Phase III[2]	RCT Phase III[2]
Method of randomisation	Adequate	Unclear	Unclear
Method of blinding (care provider, patient, and outcome assessor)	Open-label but assessor-blind (IRC)[3]	Open-label	Open-label, but assessor-blind (IRC)
Cross-over permitted	No	No	Yes

Primary outcome	PFS by IRC, OS, safety		TTP		TTP	
Secondary outcomes	PFS by INV, ORR, time to treatment failure, pharmacokinetics, DOR, patient-reported QoL, OS rate, TTP		OS, response rate, clinical benefit rate, DOR, safety, dose interruptions, withdrawal		PFS, OS, clinical benefit rate, withdrawal, safety, QoL, EQ-5D utilities, response rate, biomarker analysis	
Present line of therapy: First-line, n (%)	0 (0)		NR		88 (22)	
Present line of therapy: first-line fast relapser, n (%)	118 (12)		NR		0 (0)	
Present line of therapy: Second-line, n (%)	361 (36)		156 (100)		NR	
Present line of therapy: third-line, n (%)	512 (52)		NR		NR	
Advanced or metastatic sites in the brain, n (%)	NR		3 (2)		NR	
	Capecitabine + Lapatinib	T-DM1	Capecitabine+ Trastuzumab	Capecitabine	Capecitabine + Lapatinib	Capecitabine
Patients with ER+ and/or PR+, n (%)	263 (53)	282 (57)	41 (56) (N=73)	43 (62) (N=71)	96 (48)	93 (46)
Patients with Performance Status=1, n (%)	176 (36)	194 (39)	NR	NR	76 (38)	83 (41)
Study duration	Capecitabine + Lapatinib: 53.73 weeks (range: 0 weeks -151.67 weeks); T-DM1: 55.9 weeks (0 weeks - 147.33 weeks) – at first interim analysis Capecitabine + Lapatinib: 80.60 weeks (range: 0 weeks -177.67 weeks); T-DM1: 82.76 weeks (0 weeks - 173.33 weeks) – at second interim analysis[2]		89.70 weeks (20.7 months)		Capecitabine + Lapatinib: ~20 weeks; Capecitabine: ~15 weeks[2]	

Adjusted indirect treatment comparisons were performed according to the methodology of Bucher and colleagues. Bucher's method relies on the assumption of constant efficacy, which requires that all trials included in the analysis to be equivalent and attempting to measure the same treatment effect. For this assumption to be valid, the studies need to be treating the same indications in comparable populations and apply common treatment in the same manner, such as dosage and frequency. Both these assumptions appear to be met. Hazard ratios for individual trials and the indirect comparison for overall survival and progression-free survival are presented in Table 9.

Table 9. Hazard ratios and 95% CI for PFS and OS results of studies included in the submitter's indirect treatment comparison report.

Comparison			Hazard ratio			
Source	Treatment	Control	Point estimate	95% Lower CI	95% Upper CI	P value
PFS						
EMILIA [15]	T-DM1	C + L	0.65	0.55	0.77	-
[redacted]*	C + T	C	[redacted]	[redacted]	[redacted]	-
EGF100151 [18]	C + L	C	0.55	0.40	0.74	-
Indirect comparison (T-DM1 vs.)						
Capecitabine + Trastuzumab (second-order indirect)			[redacted]	[redacted]	[redacted]	[redacted]
OS						
EMILIA [15]	T-DM1	C + L	0.68	0.55	0.85	-
[redacted]*	C + T	C	[redacted]	[redacted]	[redacted]	-
EGF100151 [18]	C + L	C	0.78	0.62	0.97	-
Indirect comparison (T-DM1 vs.)						
Capecitabine + Trastuzumab (second-order indirect)			[redacted]	[redacted]	[redacted]	[redacted]

*: Data taken from CSR; CI: Confidence Interval; C; Capecitabine; HR: Hazard Ratio; L: Lapatinib; OS: Overall Survival; PFS: Progression Free Survival; T: Trastuzumab; HR<1 represents intervention has better efficacy than comparator

(Non-disclosable clinical information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed)

Limitations

The most significant limitation in this indirect comparison is the quality of the trials included. Further, given the limited number of trials (three), the issue of quality is much more dominant.

In the GBG26 trial, the risk of bias was not clear as the method of allocation concealment was not reported. It was an open-label trial with no centre assessment of response. Details for the handling of missing data were not reported. Not all patients in the trial (70%) were pre-treated with a taxane and trastuzumab; though the manufacturer considered this was still sufficient for inclusion in the indirect comparison.

In the EGF10051 trial, the risk of bias was high given that the method of randomisation and allocation concealment was not reported. The method of blinding to determine the outcomes was not clear. This trial also permitted cross-over between the treatment arms. The manufacturer analyzed the hazard ratio for overall survival for the indirect comparison with the exclusion of cross-over patients and also by censoring patients at the time of cross-over. Further, the follow-up was relatively short (15 – 20 weeks) compared to the other two trials.

The quality of the manufacturer-submitted indirect comparison was assessed according to the recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[47] Details and commentary for each of the relevant items identified by the ISPOR group are provided in Table 10.

Table 10. ISPOR checklist to evaluate a reported network meta-analysis and the scoring for the submitter's indirect treatment comparison report.[47]		
ISPOR Checklist Item		**Details and Comment**
1.	Are the rationale for the study and the study objectives stated clearly?	Yes the rationale and objectives are clearly stated.
2	Does the methods section include the following: Description of eligibility criteria? Information sources? Study selection process? Data extraction (validity/quality assessment of individual studies?	Yes, the information sources, search strategy, study selection and data extraction process are clearly stated.
3	Are the outcome measures described?	Background material justifies the need to prolong survival in this population.
4	Is there a description of methods for analysis/synthesis of evidence?	Yes, the methodology used is described.
5.	Do the methods described include the following: Description of analyses methods/models? Handling of potential bias/inconsistency? Analysis framework?	Yes, they use the Bucher method, which they describe. Determination of heterogeneity is described.
6.	Are sensitivity analyses presented?	Yes, they include one sensitivity analysis to examine the HR if the two excluded trials are included in the estimate.
7.	Do the results include a summary of the studies included in the network meta-analysis? Individual study data? Network of studies?	Yes, a description of the studies with baseline patient characteristics, as well as study design is provided. A flow chart detailing the review process is given, along with figures describing the network of studies.
8.	Does the study describe an assessment of model fit? Are competing models being compared?	Not applicable.
9.	Are the results of the evidence synthesis presented clearly?	Yes, a table summarizing the hazard ratios for individual trials and the indirect comparison are provided. The results of the sensitivity analysis are not presented in a table but a figure.
10.	Does the discussion include the following? Internal validity of analysis? External validity? Implications of results for target audience?	Yes, a description of the main findings is included. Both internal and external validity of the results are discussed. The implications of results for the target audience are discussed.

7.1.3 Summary

The indirect comparison of trastuzumab emtansine versus any other pharmacological intervention resulted in an indirect comparison of trastuzumab emtansine versus trastuzumab capecitabine, for both overall survival and progression-free survival in patients with HER2-positive metastatic breast cancer. Statistically significant differences were found between these treatments in the indirect comparison. Limitations surrounding the quality of two of the three trials included in the indirect comparison are a cause for concern, and any conclusions drawn from this indirect comparison should be interpreted with caution.

8 ABOUT THIS DOCUMENT

This Final 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 metastatic 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 pCODR website (www.pcodr.ca).

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. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information, therefore, this information was redacted from this publicly available Guidance Report.

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..

The Breast Clinical Guidance Panel is comprised three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

1. Literature Search via OVID Platform.

Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, and Ovid MEDLINE (R) Daily Update.

1. (trastuzumab: adj emtansine:).ti,ab,rn,nm,sh,hw,ot.
2. (ado-trastuzumab: adj emtansine:).ti,ab,rn,nm,sh,hw,ot.
3. Kadcyla:.ti,ab,rn,nm,sh,hw,ot.
4. (t-dm1 or t-dm-1 or tdm-1 or (trastuzumab: adj dm1)).ti,ab,rn,nm,sh,hw,ot.
5. Pro-132365.ti,ab,rn,nm,sh,hw,ot.
6. 1018448-65-1.rn,nm.
7. Or/1-6
8. Exp breast neoplasms/
9. ((breast: or mammar:) and (cancer: or carcinoma: or neoplasm: or tumo?r:)).ti,ab,sh,hw,ot.
10. 8 or 9
11. 7 and 10

Ovid EMBASE

1. *trastuzumab emtansine/
2. (trastuzumab: adj emtansine:).ti,ab.
3. (ado-trastuzumab: adj emtansine:).ti,ab.
4. Kadcyla:.ti,ab.
5. (t-dm1 or t-dm-1 or tdm-1 or (trastuzumab: adj dm1)).ti,ab.
6. Pro-132365.ti,ab.
7. Or/1-6
8. Exp *breast cancer/
9. ((breast: or mammar:) and (cancer: or carcinoma: or neoplasm: or tumo?r:)).ti,ab.
10. 8 or 9
11. 7 and 10

2. Literature Search via PubMed

PubMed

1. trastuzumab* emtansine* OR ado-trastuzumab* emtansine* OR kadcyla* OR t-dm1 OR tdm-1 OR trastuzumab* dm1*
2. publisher[sb]
3. 1 and 2

3. Literature Search via Cochrane Central Register of Controlled Trials (CENTRAL)

Search terms: (trastuzumab* emtansine* OR ado-trastuzumab* emtansine* OR kadcyla* OR t-dm1 OR tdm-1 OR trastuzumab* dm1*) in Cochrane Central Register of Controlled Trials.

4. Grey Literature Searches

Clinical Trial Registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: emtansine, trastuzumab-dm1, t-dm1, Kadcyla

Select International Agencies:

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

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

Search terms: trastuzumab emtansine, trastuzumab-dm1, t-dm1, Kadcyla

Conference Abstracts:

American Society of Clinical Oncology (ASCO)
via the *Journal of Clinical Oncology* search portal: http://jco.ascopubs.org/search

Search terms: Kadcyla, trastuzumab emtansine, trastuzumab-dm1, t-dm1

San Antonio Breast Cancer Symposium (SABCS)
via the *Cancer Research* search portal: http://cancerres.aacrjournals.org/search
The abstracts for each year of the SABCS are published in the following issues:
Cancer Research 2012;72(24 Suppl 3)
Cancer Research 2011;71(24 Suppl 3)
Cancer Research 2010:70(24 Suppl 2)
Cancer Research 2009:69(24 Suppl 1)
Cancer Research 2008:69(2 Suppl 1)
Poster presentations of identified abstracts, if available, were obtained from the SABCS website: http://www.sabcs.org/

Search terms: emtansine, trastuzumab-dm1, t-dm1, Kadcyla

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