pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Trastuzumab Emtansine (Kadcyla) **Submitted Funding Request:** The treatment of patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who have received prior treatment with trastuzumab and a taxane	
Submitted By: Hoffman-La Roche Ltd.	**Manufactured By:** Hoffman-La Roche Ltd.
NOC Date: September 11, 2013	**Submission Date:** March 15, 2013
Initial Recommendation: October 31, 2013	**Final Recommendation:** January 10, 2014

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding trastuzumab emtansine (T-DM1; Kadcyla) for patients with HER2-positive, unresectable locally advanced or metastatic breast cancer conditional on its cost-effectiveness being improved to an acceptable level. Funding should be for patients who have an ECOG performance status 0 or 1. Patients must have received prior treatment with trastuzumab plus chemotherapy in the metastatic setting or have disease recurrence during or within 6 months of completing adjuvant therapy with trastuzumab plus chemotherapy. pERC made this recommendation because it was satisfied that there is a net clinical benefit of T-DM1 based on improvements in overall survival and progression-free survival compared with lapatinib plus capecitabine. However, the Committee noted that T-DM1 could not be considered cost-effective at the confidential price and the resulting Economic Guidance Panel's estimates of the range of incremental cost-effectiveness ratios when compared with lapatinib plus capecitabine.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given pERC was satisfied that there is a net clinical benefit of T-DM1, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of T-DM1 to an acceptable level. **Optimal Sequencing of T-DM1 and Other Therapies** There is currently no evidence available on the effectiveness of T-DM1 in those patients who progress after receiving pertuzumab in the first-line setting. Therefore, pERC concluded that the optimal sequencing of T-DM1 and other treatments in this patient population is currently unknown. pERC was unable to make an informed recommendation on the use of T-DM1 following disease progression after receiving first-line pertuzumab. pERC noted that treatments for metastatic breast cancer are evolving more quickly than studies can be done to inform the optimal sequencing of these therapies.. In light of this, provinces may want to consider collecting data prospectively on patients who progress after receiving first line pertuzumab and subsequently receive T-DM1 in order to develop evidence on the efficacy of T-DM1 when used in this sequence.

SUMMARY OF pERC DELIBERATIONS

pERC noted that breast cancer is the second most common cause of cancer deaths in Canadian women. pERC also noted that standard therapies for 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 include lapatinib plus capecitabine and trastuzumab plus chemotherapy. pERC noted that although treatments are available to patients, there still remains a need for more effective treatment options that provide longer progression-free survival and overall survival. One randomized controlled trial (EMILIA, Verma 2012) was included in the pCODR systematic review, which compared trastuzumab emtansine (T-DM1; Kadcyla) to lapatinib plus capecitabine. pERC considered this to be an appropriate comparator as it is a standard treatment option.

pERC's Deliberative Framework for drug funding recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated on the results of the EMILIA study and determined that there was an overall net clinical benefit for T-DM1. This was based on a statistically significant and clinically meaningful improvement in both the progression-free survival and overall survival of patients treated with T-DM1 compared with the patients receiving lapatinib plus capecitabine. pERC considered the magnitude of the benefit to be very meaningful and also noted that observing an improvement in overall survival in patients who have previously been treated in the metastatic setting is an unusual and important outcome. pERC also noted that the EMILIA study provided evidence for the effectiveness of T-DM1 in patients who have disease recurrence during or within 6 months of completing adjuvant therapy with trastuzumab plus a taxane. After careful consideration, pERC noted that it would be reasonable to use T-DM1 for patients who have received trastuzumab in combination with chemotherapy other than a taxane. Alternative chemotherapies (other than a taxane) are available for use in combination with trastuzumab and may be reasonable options for some patients. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the Provincial Advisory Group regarding the efficacy of T-DM1 in the third line setting. pERC discussed subgroup data from the EMILIA study demonstrating an improvement in progression-free survival in patients who received TDM-1 in the third line setting or beyond. These findings were also supported by interim analyses from the TH3RESA study, which evaluated TDM-1 in patients who had received at least two prior lines of HER-2 targeted therapy. pERC therefore concluded that there is a net overall clinical benefit to the use of T-DM1 in patients who have received prior treatment with trastuzumab plus chemotherapy in the metastatic setting or have disease recurrence during or within 6 months of completing adjuvant therapy with trastuzumab plus chemotherapy.

pERC discussed the toxicity profile of T-DM1 based on the results of the EMILIA study. pERC noted that overall, there were fewer patients with grade 3 adverse events in the T-DM1 group compared with lapatinib plus capecitabine. Some adverse events such as elevated alanine aminotransferase and thrombocytopenia were more frequently observed in the T-DM1 group compared with the lapatinib plus capecitabine group. However, in the context of other systemic therapies, pERC considered the overall tolerability of T-DM1 to be acceptable.

pERC deliberated upon the alignment of T-DM1 with patient values. Patient advocacy group input indicated that patients with HER2 positive unresectable locally advanced or metastatic breast cancer valued extending life and prolonging progression-free survival. Therefore, based on the improvement in overall survival and progression-free survival demonstrated in the EMILIA study, pERC considered that T-DM1 aligned with these patient values. Patient input also indicated that patients valued treatments that maintained quality of life. pERC noted that T-DM1 was well-tolerated by patients. In addition, in the EMILIA study, the time to deterioration of quality of life was longer in the T-DM1 group compared to the lapatinib plus capecitabine group. Therefore, overall, pERC considered that access to T-DM1 aligns with patient values.

pERC deliberated on the cost-effectiveness of T-DM1. pERC noted that the submitted economic model had structural limitations that prevented the pCODR Economic Guidance Panel (EGP) from fully assessing the impact of some of the clinical assumptions. As a result, the EGP was unable to provide an upper limit to their cost-effectiveness estimate. pERC noted that as a result of these structural limitations in the submitted model, over half of the estimated clinical benefit came from assumptions made regarding post-progression survival and carryover benefit once the drug was discontinued. While pERC recognized that it is clinically plausible that there could be some carry-over benefit of T-DM1 once treatment is stopped, there is an absence of clinical evidence to justify this benefit. pERC also noted that the estimates of incremental cost-effectiveness were also impacted by how the PFS and OS benefit were extrapolated beyond the trial period. It was noted that in the manufacturer's submitted model, the majority of the clinical benefit is a result of post-progression survival, which is unrealistic from a clinical perspective. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the manufacturer regarding the plausibility of post-progression benefit in patients following treatment with T-DM1 and considered the submitters question as to whether T-DM1 provided significant post-progression survival benefit. pERC acknowledged that the data provided in the manufacturer's feedback suggests similar hazard ratios for pre and post progression survival (HR=0.68 and HR=0.71, respectively) in patients that had received T-DM1. However, pERC considered that although there appears to be benefit in the post-progression state, pERC was not able to establish why this benefit occurred and nor could it determine the magnitude of this benefit that can be attributed to T-DM1. pERC further noted that limitations in the economic model prevented the Economic Guidance Panel (EGP) from varying either progression-free survival or overall survival within the model and the EGP could not assess post-progression survival independent of pre-progression survival. pERC acknowledged that, as a result, the EGP was unable to estimate the amount of benefit attributed to the post-progression state. In addition, pERC noted that the costs of post-progression treatments were not incorporated into the model, therefore, the potential impact on cost-effectiveness of all the costs and benefits in the post-progression state is not fully understood at this time. Lastly, pERC noted that the manufacturer had previously had not made the hazard ratios for pre and post progression survival (HR=0.68 and HR=0.71, respectively) disclosable so this information was not provided to pERC. It was only after the Initial Economic Guidance Report was completed and the pERC Initial Recommendation was issued that the manufacturer made this information fully disclosable and pERC was able to transparently use it to inform a publicly available recommendation.

pERC also noted that the EGP made adjustments to the economic analysis by shortening the time horizon and accounting for potential drug wastage. Therefore, pERC concluded that T-DM1 was not cost-effective at the submitted price. Upon reconsideration of the pERC initial recommendation, pERC discussed feedback received from the manufacturer regarding the plausibility of the manufacturer's 7 year time horizon as opposed to the EGP's shortened 5 year time horizon. pERC considered input from the pCODR Clinical Guidance Panel and acknowledged that a time horizon of 5-10 years is within a clinically plausible range for this patient population and agreed with the EGP's re-adjusted estimates from a 5 to a 7 year time horizon. Upon consideration of the EGP's reanalysis, pERC considers that T-DM1 is still not cost effective at the submitted price and the EGP's reanalysis estimates.

pERC also noted that an economic analysis comparing T-DM1 with trastuzumab plus capecitabine was submitted using an indirect comparison. There was considerable uncertainty in the clinical estimates from the indirect comparison and the manufacturer did not provide any sensitivity analyses around these estimates. In general, pERC considered that there was insufficient evidence to draw conclusions on the comparative efficacy and cost-effectiveness of T-DM1 versus trastuzumab plus capecitabine. pERC further noted that although it was reasonable to have conducted the indirect comparison with trastuzumab plus capecitabine a better comparison in the Canadian context would have been to trastuzumab plus vinorelbine or other chemotherapies. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the manufacturer regarding the evidence used in the indirect comparison between T-DM1 and trastuzumab plus capecitabine. pERC further reiterated that there are limitations associated with indirect and cross trial comparisons and agreed with the EGP that the confidence intervals were wide. Therefore, pERC reiterated that the presented evidence was insufficient to draw any conclusions on the comparative efficacy of T-DM1 versus trastuzumab plus capecitabine.

pERC discussed the feasibility of implementing a recommendation for T-DM1. pERC noted that T-DM1 is administered based on weight and the reconstituted drug is stable for only 24 hours. Therefore, in situations where excess T-DM1 cannot be used for other patients, wastage may have a significant budget impact. Input from pCODR's Provincial Advisory group indicated that HER2 testing is well established and widely available and so many patients will already have access to testing. In addition, pERC discussed that

the availability of T-DM1 in the second line treatment setting will likely lead to changes in the treatment algorithm for HER2-positive unresectable locally advanced or metastatic breast cancer. However, pERC noted that there is currently no evidence available to inform how the introduction of T-DM1 will impact practice patterns. More specifically, pERC noted that at this time there is no evidence to make an informed recommendation on the use of T-DM1 after patients progress on first-line pertuzumab. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the Provincial Advisory Group regarding guidance on the sequencing of treatments following failure with pertuzumab (Perjeta Herceptin Combo Pack) in the first line setting. pERC noted that treatments for metastatic breast cancer are evolving more quickly than studies can be done to inform the optimal sequencing of these therapies. In light of this, provinces may want to consider collecting data prospectively on patients who progress after receiving first line pertuzumab and subsequently receive T-DM1 in order to develop evidence on the efficacy of T-DM1 when used in this sequence.

Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the Provincial Advisory Group regarding safe drug administration practices for T-DM1. pERC agreed that due to the similarity in the names of the two different breast cancer drugs, trastuzumab and trastuzumab emtansine (T-DM1), further clarity is required. Jurisdictions may wish to consider labelling trastuzumab emtansine using Kadcyla, its brand name, or using T-DM1, which is its acronym for the chemical name that is typically used in clinical practice. pERC noted that this may help to avoid possible prescribing errors .

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from two patient advocacy groups (Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer (Rethink))
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- pCODR's Provincial Advisory Group.
- the Submitter (Hoffman-La Roche Ltd.)

The pERC Initial Recommendation was to recommend funding trastuzumab emtansine (T-DM1; Kadcyla) in the second-line setting for patients with HER2-positive, unresectable locally advanced or metastatic breast cancer conditional on its cost-effectiveness being improved to an acceptable level. Feedback on the pERC Initial Recommendation indicated that the manufacturer and pCODR's Provincial Advisory Group agreed in part with the initial recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the efficacy and safety of 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.

Studies included: one randomized controlled trial

The pCODR systematic review included open-label randomized controlled superiority trial, EMILIA (Verma 2012), which evaluated T-DM1 (n=495, 3.6 mg/kg i.v. every 21 days) compared to lapatinib (1250 mg daily, orally) plus capecitabine (n=496, 1000 mg/m^2 every 12 hours to a maximum daily dose of 2000 mg/^{2} on days 1-14, orally, every 21 days). The EMILIA study did not blind study participants, the treating

physicians, or investigators to the treatment assignment. Treatment was administered until disease progression or unmanageable toxicity.

The pCODR review also provided contextual information on an indirect comparison of T-DM1 with trastuzumab plus capecitabine and a summary of preliminary results from TH3RESA, a randomized controlled trial comparing T-DM1 to treatment by 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.

Patient populations: ECOG performance status 0 or 1

The majority of patients in the EMILIA study had an ECOG status of 0 or 1 (60% and 35% of patients, respectively). Patients had received prior trastuzumab in the metastatic or adjuvant setting.

Study entry was restricted to patients with a left ventricular ejection fraction (LVEF) of ≥ 50% and an ECOG performance status 0 or 1. pERC concluded that there was no evidence to support the use of T-DM1 in a broader patient population. Patients were also excluded from the EMILIA study if they had prior treatment with T-DM1, lapatinib, or capecitabine in the metastatic setting. Pre-specified sensitivity analyses were conducted in 16 subgroups including line of therapy. pERC felt that it would be reasonable to allow time-limited access to patients who have already received lapatinib or capecitabine in the metastatic setting. pERC noted that this time-limited access should be for patients who would otherwise meet the eligibility criteria of the EMILIA study.

Key efficacy results: statistically and clinically significant OS and PFS benefit

Key efficacy outcomes deliberated on by pERC included overall survival and an independent review committee assessment of progression-free survival, the co-primary outcomes of the EMILIA study, as well as objective response rates.

pERC noted that there were both statistically and clinically significant differences in overall survival (median 30.9 months vs. 25.1 months, HR=0.68, 95% CI 0.55 to 0.85) and in progression-free survival (median 9.6 months vs. 6.4 months, HR=0.65, 95% CI 0.55 to 0.77, p<0.001) in favour of the T-DM1 arm compared to the lapatinib-capecitabine arm. pERC considered the magnitude of the benefit to be very meaningful and also noted that an improvement in overall survival in previously treated metastatic patients is an unusual and important outcome. The objective response rate was also statistically significantly higher in the T-DM1 arm compared to the lapatinib-capecitabine arm (43.6% vs. 30.8%, p<0.001). Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the Provincial Advisory Group regarding the efficacy of T-DM1 in third line patients. pERC noted that the subgroup of patients receiving third line or later therapy in the EMILIA study (n=512) was larger than the subgroups receiving first- or second-line therapy. pERC also noted that in this subgroup of patients 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. pERC also discussed the preliminary results from the ongoing TH3RESA study. Although OS data are not yet mature, in this study median progression-free survival was significantly longer in the T-DM1 arm compared to the treatment of physician's choice arm (6.2 vs. 3.3 months, respectively), with a HR=0.528, 95% CI 0.422 to 0.661; p<0.0001) pERC therefore agreed that there is a clinical benefit of using T-DM1 in the 3rd line setting or beyond. However pERC noted that there is no evidence to support re-treatment with T-DM1 following progression in a previous line and noted that the subgroup of third line or beyond patients in EMILIA and TH3RESA had not received prior T-DM1.

Quality of life: longer time to deterioration of QoL

The time to deterioration of health related quality of life was evaluated in the EMILIA study using the Functional Assessment of Cancer Therapy – Breast Trial Outcome Index (FACT-B TOI) questionnaire. pERC noted that median time to a decline in quality of life score was longer in the T-DM1 group compared to the lapatinib plus capecitabine group (7.1 vs. 4.6; HR=0.80, 95% CI 0.67 to 0.95, p=0.012) indicating that T-DM1 increased the time to deterioration of quality of life.

Safety: acceptable toxicity profile

pERC reviewed the toxicity profile of T-DM1 based on the results of the EMILIA study and concluded that the overall tolerability of T-DM1 was acceptable relative to other cancer therapies. pERC noted that 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%, respectively). Of note, there were a higher proportion of patients with any grade of toxicity as well as grade 3 or above diarrhea and palmar-plantar erythrodyesthesia (hand-foot syndrome) on the lapatinib-capecitabine arm of the trial compared to the T-DM1 arm. Conversely, higher proportions of patients had any grade of elevation of alanine aminotransferase and any grade or grade 3 or above thrombocytopenia and elevated aspartate aminotransferase occurred in the T-DM1 arm compared to the lapatinib plus capecitabine arm.

Comparator information: uncertainty in indirect comparison with trastuzumab plus capecitabine

pERC noted that both pCODR's Provincial Advisory Group and the pCODR Clinical Guidance Panel considered trastuzumab + capecitabine to be a relevant treatment option in the second line setting for patients with HER2 positive breast cancer but felt a better comparison in the Canadian context would have been to trastuzumab plus vinorelbine. pERC considered the results of the indirect comparison of T-DM1 to trastuzumab plus capecitabine that was conducted by the manufacturer and felt that there was considerable uncertainty in the clinical estimates from the indirect comparison. It was also noted that the manufacturer did not provide sensitivity analyses around these estimates. In general, pERC noted that there are significant limitations with indirect and cross-trial comparisons and did not consider the analysis sufficient to draw any definitive conclusion on the comparative efficacy of T-DM1 to trastuzumab plus capecitabine.

Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the manufacturer regarding the evidence used in the indirect comparison between T-DM1 and trastuzumab plus capecitabine. pERC considered the manufacturer's question that pERC re-consider the appropriateness of the indirect comparison and the indirect cost-effectiveness analysis given that the best available evidence and methods were used. pERC acknowledged that while there are limitations in the availability of direct comparative evidence, pERC agreed with the EGP that there was still considerable uncertainty in the clinical estimates from the indirect comparison based on the wide confidence intervals observed. pERC further reiterated that independent of the validity of the methodology used by the manufacturer, there are limitations associated with indirect and cross trial comparisons. Therefore, pERC maintained that, overall, the presented evidence was insufficient to draw firm conclusions on the comparative efficacy of T-DM1 and trastuzumab plus capecitabine.

Need: more effective treatments that extend survival and have better tolerability

pERC noted that breast cancer deaths are the second most common cause of cancer mortality in Canadian women (5,100 deaths in 2012) and that approximately 15 to 20% of all breast cancers are HER2 positive. pERC also noted that HER2 positive breast cancer is considered more aggressive and may result in a poorer prognosis. In general, women with metastatic breast cancer (MBC) have a 5-year survival rate of approximately 15%. In women with HER2-positive MBC, the use of the anti-HER2 humanized monoclonal antibody trastuzumab, in addition to cytotoxic chemotherapy has been found to significantly improve progression-free survival and overall survival compared to cytotoxic chemotherapy alone. Thus anti-HER2 treatment is considered a standard first-line treatment approach for HER2-positive metastatic breast cancer. pERC noted that the majority of patients with MBC who initially respond to trastuzumab and chemotherapy will demonstrate disease progression within 1 year of treatment initiation. In these patients, second line treatment options include lapatinib plus capecitabine or trastuzumab plus chemotherapy. pERC noted that despite such therapies, there remains a need for new and improved targeted therapies both in terms of efficacy and tolerability.

PATIENT-BASED VALUES

Values of patients with HER2-positive MBC: prolonged survival and acceptable quality of life

Input from two patient advocacy groups indicated that patients with metastatic breast cancer value extended life expectancy while maintaining an acceptable quality of life. Therefore, pERC considered that the clinically and statistically significant improvements in OS and PFS and the prolonged time to deterioration of quality of life observed in the EMILIA study aligned with these important patient values.

Patient values on treatment: maintaining quality of life without side effects

Based on input provided by patient advocacy groups, pERC noted that many patients are willing to tolerate the potential adverse effects of a treatment if it was found to prolong their survival, even for a relatively short period of time. pERC discussed the results from the EMILIA study that showed a manageable adverse event profile and prolonged time to deterioration in quality of life. pERC also noted survey responses from two Canadian patients who had experience with T-DM1. Both reported that T-DM1 had a positive impact on their disease and quality of life. Therefore, pERC considered that T-DM1 aligned with patient values.

ECONOMIC EVALUATION

Economic model submitted: cost utility and cost-effectiveness

The pCODR Economic Guidance Panel assessed a cost-utility and cost-effectiveness analysis that compared trastuzumab emtansine (Kadcyla) to lapatinib plus capecitabine as a second-line treatment for patients with HER2-positive, unresectable locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane. This comparison was based on the results of the EMILIA study. The pCODR review also assessed an indirect comparison of T-DM1 to trastuzumab + capecitabine.

Basis of the economic model: clinical and economic inputs

Costs considered in the analysis included the cost of the planned dose of the drugs excluding wastage, the cost of adverse events, the cost of administering the drugs, and supportive care costs.

The clinical effect considered in the analysis was based on extrapolation of overall survival and progression-free survival from one phase-III clinical trial and utilities based on an algorithm that considered adverse events.

Drug costs: confidential price submitted

pERC noted that T-DM1 is available in two vial sizes of 100mg and 160mg and the drug dose is based on a patient's weight. pERC further noted that the drug is only stable for 24 hours following reconstitution. In the event that not all of the reconstituted drug is used for a patient and another patient is not available for treatment within 24 hours, drug wastage would occur.

At the list price, T-DM1 costs $2,508 per 100mg and $4,012.80 per 160mg vial. The manufacturer also submitted a confidential price of $[redacted] per 100mg vial and $[redacted] for 160mg/vial for T-DM1.

- At the list price and the recommended dose of 3.6 mg/kg, the average daily cost of T-DM1 is $300.96 and the average cost per 28-day course is $8,426.88. This cost does not take wastage of any excess T-DM1 into consideration. When wastage is taken into consideration, the average daily cost is $310.51 and the average cost per 28-day course is $8694.40.
- Based on the confidential price and the recommended dose of 3.6 mg/kg, the average daily cost of T-DM1 is $[redacted] and the average cost per 28-day course is $[redacted]. (The cost of trastuzumab emtansine is based on a confidential price submitted by the manufacturer and cannot be disclosed to the public according to the *pCODR Disclosure of Information* guidelines).

Lapatinib costs $23.50 per 250 mg tablet. Capecitabine costs $1.83 per 150 mg tablet or $6.10 per 500mg tablet.

- At the recommended dose of 1250mg lapatinib orally once daily and capecitabine 1000 mg/m^2 twice daily on days 1-14 every 21 days, lapatinib + capecitabine costs $145.15 per day and $4,064.29 per 28-day course.

Trastuzumab costs $2,697.90 per 440 mg vial. Capecitabine costs $1.83 per 150 mg tablet or $6.10 per 500mg tablet.

- At the recommended loading dose of trastuzumab of 8mg/kg loading dose and capecitabine 1000 mg/m^2 BID Days 1-14 every 21 days, trastuzumab + capecitabine costs $187.86 per day and $5,260.14 per 28-day course.
- At the recommended dose of trastuzumab of 6mg/kg every 3 weeks and capecitabine 1000 mg/m^2 BID Days 1-14 every 21 days, trastuzumab + capecitabine costs $157.19 per day and $4,401.69 per 28-day course.

Cost-effectiveness estimates: influenced by inadequate model structure and assumptions of post-progression survival and carryover benefit

pERC deliberated upon the cost-effectiveness of T-DM1 and discussed the pCODR Economic Guidance Panel's (EGP's) critique of the manufacturer's economic analysis. pERC noted that the estimates of incremental cost-effectiveness provided by the submitter were largely influenced by an inadequate model structure and assumptions made on post-progression survival and carry over benefit. pERC discussed that over half the clinical benefit included in the submitted model was due to an assumption of a post-progression survival benefit. pERC also noted that assumptions made regarding a carry-over benefit further impacted the submitted results. pERC noted that the submitted model had structural limitations that prevented the EGP from modifying these assumptions and as a result any reanalysis provided by the EGP is impacted by these inherent limitations in the model. Therefore, the EGP could not provide an upper limit to the cost-effectiveness estimates. pERC noted that as a result of these structural limitations in the submitted model, over half of the estimated clinical benefit came from the assumption made on post-progression survival. pERC also noted that the estimates of incremental cost-effectiveness were also impacted by how the progression-free survival and overall survival benefit were extrapolated beyond the trial period. It was noted that in the manufacturer's submitted model, the majority of the clinical benefit is a result of improved post-progression survival, which is not realistic from a clinical perspective.

Upon reconsideration of the pERC initial recommendation, pERC discussed feedback received from the manufacturer regarding the plausibility of post-progression benefit in patients following treatment with T-DM1 and considered the submitters question as to whether T-DM1 provided significant post-progression survival benefit. pERC acknowledged that the data provided in the manufacturer's feedback suggests similar hazard ratios for pre and post progression survival (HR=0.68 and HR=0.71, respectively) in patients that had received T-DM1. However, pERC considered that although there appears to be benefit in the post-progression state, pERC was not able to establish why this benefit occurred and nor could it determine the magnitude of this benefit that can be attributed to T-DM1. pERC further noted that limitations in the economic model prevented the Economic Guidance Panel (EGP) from varying either progression-free survival or overall survival within the model and the EGP could not assess post-progression survival independent of pre-progression survival. pERC acknowledged that, as a result, the EGP was unable to estimate the amount of benefit attributed to the post-progression state. In addition, pERC noted that the costs of post-progression treatments were not incorporated into the model, therefore, the potential impact on cost-effectiveness of all the costs and benefits in the post-progression state is not fully understood at this time. Lastly, pERC noted that the manufacturer had previously not made the hazard ratios for pre and post progression survival (HR=0.68 and HR=0.71, respectively) disclosable so this information was not provided to pERC. It was only after the Initial Economic Guidance Report was completed and the pERC Initial Recommendation was issued that the manufacturer made this information fully disclosable and the EGP and pERC were able to transparently use it to inform in a publicly available recommendation.

pERC noted that the estimates of incremental cost-effectiveness provided by the submitter were also impacted by the time horizon and assumptions related to drug wastage; however, the EGP was able to adjust for these factors in their reanalyses.

Upon reconsideration of the pERC initial recommendation, pERC discussed feedback received from the manufacturer regarding the plausibility of the manufacturer's 7 year time horizon as opposed to the EGP's shortened 5 year time horizon. pERC considered input from the pCODR Clinical Guidance Panel and acknowledged that a time horizon of 5-10 years is within a clinically plausible range for survival in this patient population with metastatic breast cancer and agreed with the EGP's re-adjusted estimates from a 5 year to a 7 year time horizon. Based on this adjustment of the time horizon, the EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) was revised to a lower estimate. Upon deliberation of

the EGP's reanalysis estimates pERC concludes that T-DM1 is still not cost effective at the submitted price and the EGP's reanalysis estimates.

pERC also discussed the cost-effectiveness of T-DM1 in comparison to trastuzumab plus capecitabine. pERC considered that, based on the indirect comparison there was insufficient evidence to draw definitive conclusions on the efficacy of T-DM1 compared to trastuzumab plus capecitabine. pERC further noted that although it was reasonable to have conducted the indirect comparison to trastuzumab plus capecitabine a better comparison in the Canadian context would have been to trastuzumab plus vinorelbine or trastuzumab with other chemotherapies. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the manufacturer regarding the evidence used to present an indirect comparison between T-DM1 and trastuzumab plus capecitabine. pERC further affirmed the limitations associated with indirect and cross trial comparisons and concluded that the presented evidence was not sufficient to draw firm conclusions on the comparative efficacy of T-DM1 versus trastuzumab plus capecitabine. Overall, pERC concluded that T-DM1 was not cost-effective at the submitted confidential price compared with lapatinib plus capecitabine or trastuzumab plus capecitabine.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: treatment algorithm sequencing

pERC noted that the following factors would be important to consider if a funding recommendation for T-DM1 was implemented. pERC noted that T-DM1 has a short stability period of 24 hours once reconstituted. pERC noted that since T-DM1 is administered based on the weight of the patient, in instances where vial sharing is not feasible, there is a likelihood of wastage of any excess T-DM1. pERC noted this may increase the budget impact for provinces but wastage was not addressed in the submitter's budget impact analysis.

pERC noted the Provincial Advisory Group's concern regarding the optimal sequencing of therapy in the second line setting. pERC acknowledged that there is currently no evidence available on the effectiveness of T-DM1 in those patients who progress after receiving pertuzumab in the first-line setting. pERC concluded that the optimal sequencing of T-DM1 and other treatments in this patient population is currently unknown and pERC was therefore unable to make an informed recommendation on the use of T-DM1 in patients progressing on first line pertuzumab. Upon reconsideration of the pERC initial recommendation, pERC discussed feedback received from the Provincial Advisory Group regarding guidance on sequencing of treatments following failure with pertuzumab in the first line setting. pERC noted that treatments for metastatic breast cancer are evolving more quickly than studies can be done to inform the optimal sequencing of these therapies. In light of this, provinces may want to consider collecting data prospectively on patients who progress after receiving first line pertuzumab and subsequently receive T-DM1 in order to develop evidence on the efficacy of T-DM1 when used in this sequence.

Upon reconsideration of the pERC initial recommendation, pERC discussed feedback received from the Provincial Advisory Group regarding safe drug administration practices for T-DM1. pERC agreed that due to the similarity in the names of the two different breast cancer drugs, trastuzumab and trastuzumab emtansine (T-DM1), further clarity is required. Jurisdictions may consider labelling trastuzumab emtansine using Kadcyla, its brand name, or using T-DM1, which is its acronym for the chemical name that is typically used in clinical practice. pERC noted that this may help to avoid possible prescribing errors.

DRUG AND CONDITION INFORMATION

Drug Information	• Anti-HER2 antibody, trastuzumab, conjugated to a microtubule-inhibitory agent, DM1 • Available as a 100 mg vial and 160 mg vial • Recommended dose of 3.6 mg/kg i.v. every 21 days until disease progression or unmanageable toxicity
Cancer Treated	• HER2-positive, unresectable locally advanced or metastatic breast cancer • Second-line treatment following trastuzumab plus taxane
Burden of Illness	• Breast cancer is the most common cancer in women and the 2nd most common cause of cancer mortality in Canadian women • Approximately 15-20% of all breast cancers are HER2-positive, resulting in a more aggressive clinical phenotype and a poorer prognosis
Current Standard Treatment	• Lapatinib plus capecitabine • Trastuzumab plus chemotherapy
Limitations of Current Therapy	• Need for treatment options that provide greater efficacy in terms of PFS and OS

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Chaim Bell, Economist
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Wasney, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Peter Venner, Oncologist
Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Dr. Bill Evans who was not present for the meeting
- Dr. Maureen Trudeau, Dr. Tallal Younis, Carole McMahon and Jo Nanson who were excluded from voting due to a conflict of interest

All members participated in deliberations and voting on the final recommendation except:

- Dr. Maureen Trudeau, Dr. Tallal Younis, Carole McMahon and Jo Nanson who were excluded from voting due to a conflict of interest

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of trastuzumab emtansine (Kadcyla) for metastatic breast cancer, through their declarations, nine members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, and four of these members were excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. Hoffman-La Roche Ltd., as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

Use of this recommendation

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

Disclaimer

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report. This document is composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR document).