pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The CADTH 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 reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug: Trastuzumab Emtansine (Kadcyla)

Submitted Funding Request:
For the adjuvant treatment of patients with HER2-positive early breast cancer, who have residual disease, after pre-operative systemic treatment. Kadcyla should be continued for 14 cycles or until disease progression or unacceptable toxicity. If Kadcyla is discontinued in the event of toxicity, treatment with trastuzumab may be continued to complete one year of HER2-directed therapy.

Submitted by:
Hoffmann-La Roche Limited

Manufactured by:
Hoffmann-La Roche Limited

NOC Date:
November 25, 2019

Submission Date:
July 2, 2019

Initial Recommendation Issued:
January 3, 2020

Approximate per Patient Drug Costs, per Month (28 Days)	Trastuzumab emtansine costs $2,128.93 per 100 mg vial and $3,406.28 per 160 mg vial. At the recommended dose of 3.6 mg/kg intravenously every 21 days for 14 cycles, trastuzumab emtansine costs $260.65 per day and $5,473.73 per 21-day cycle.

pERC RECOMMENDATION

☒ **Reimburse**
☐ **Reimburse with clinical criteria and/or conditions***
☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC recommends the reimbursement of trastuzumab emtansine (T-DM1) (Kadcyla) for the adjuvant treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer, who have residual disease, after preoperative systemic treatment.

Treatment should be continued for 14 cycles or until disease progression or unacceptable toxicity. pERC made this recommendation because it was satisfied that there may be a net clinical benefit of adjuvant treatment with trastuzumab emtansine compared with trastuzumab, based on the clinically meaningful improvement in invasive disease-free survival (iDFS) and distant recurrence-free survival. However, pERC was uncertain as to how trastuzumab emtansine compares with trastuzumab with regards to outcomes important to decision-making, such as overall survival (OS) due to a lack of mature data. pERC also acknowledged that trastuzumab emtansine has a manageable but not insignificant toxicity profile with some detriment in quality of life (QoL).

pERC agreed that trastuzumab emtansine aligned with patients' values of having an alternative treatment option that reduces the risk of recurrence. The Committee was not satisfied that the addition of trastuzumab emtansine aligned with patients' values of maintenance of QoL, minimal side effects, and reduced burden of cost.

pERC concluded that based on the submitted and pCODR Economic Guidance Panel (EGP)'s estimate of the incremental cost-utility ratio, trastuzumab emtansine is cost-effective.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS	No next steps were identified. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

Approximately 27, 200 new cases of breast cancer will be diagnosed in 2019 in Canada, with about one in eight women being diagnosed in their lifetime. Of these breast cancers, 15% to 30% overexpress HER2, which has historically been associated with a more aggressive disease course and earlier metastatic potential, particularly to the central nervous system. Patients with HER2-positive disease who achieve pathologic complete response (pCR) after neoadjuvant treatment have a better OS compared with those who do not achieve such response. However, a significant proportion of women with HER2-positive breast cancer do not achieve pCR and are at a relatively high risk of recurrence and death. The current standard of care for HER2-positive early breast cancer is 12 months of adjuvant trastuzumab in combination with anthracycline and/or taxane-based chemotherapy. While trastuzumab is generally well tolerated, it is associated with cardiac toxicity, such as cardiomyopathy; decreased ejection fraction; and in severe cases, symptoms of congestive heart failure. In addition, there is a need for treatments with greater efficacy for patients with HER2-positive early breast cancer. pERC therefore agreed that more effective and tolerable therapies leading to a decrease in cancer recurrence and improvement in cure are needed in this patient population.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberated on the results of one open-label, randomized, phase III trial (KATHERINE), which assessed the efficacy and safety of T-DM1 (Kadcyla). The trial compared T-DM1 with trastuzumab for the adjuvant treatment of patients with HER2-positive early breast cancer who had residual disease after preoperative systemic treatment. After a median follow-up of forty-one months, TDM-1 compared with trastuzumab demonstrated a statistically significant improvement in the primary end point of iDFS. Key secondary end points of Standardized Definitions for Efficacy End Points (STEEP)-defined iDFS and distant recurrence-free survival were also significant. pERC agreed that these improvements were clinically meaningful but noted that OS is the most clinically meaningful end point in this setting. Although OS was a secondary end point, there was no significant difference in the five-year survival rates between treatment groups with median OS not reached in either group. pERC agreed that it would be important to determine the impact of T-DM1 on patients' long-term survival once mature OS results are available. pERC also deliberated on the safety profile of T-DM1 and acknowledged that, overall, patients treated with T-DM1 experienced greater toxicity compared with patients treated with trastuzumab. pERC acknowledged that the addition of emtansine to trastuzumab would be expected to increase toxicities. Of note, pERC highlighted the occurrence of peripheral sensory neuropathy only in patients treated with T-DM1 but acknowledged that peripheral sensory neuropathy was mostly reversible. pERC also noted a protocol deviation in the KATHERINE trial in which investigators did not withhold or reduce the dose of T-DM1 for toxicity as pre-specified in the study protocol. Despite this, patients in the T-DM1 treatment group still had higher rates of dose reduction, interruption, and discontinuation due to adverse events (AE) compared with trastuzumab. pERC therefore agreed that this protocol deviation may have led to an underestimation of the toxicity impact of T-DM1, given there will likely be greater discontinuation with T-DM1 in clinical practice. However, pERC acknowledged there is a potential for some overestimation of the toxicity with T-DM1 given dose reductions/interruptions were not followed per protocol. Overall, with respect to toxicity, pERC concluded that although the toxicity of T-DM1 was not insignificant, clinicians would be familiar with managing these toxicities in the metastatic breast cancer setting. pERC further deliberated on QoL outcomes and noted that a higher proportion of patients on T-DM1 experienced a meaningful deterioration of QoL compared with trastuzumab. pERC also considered the generalizability of the KATHERINE trial results and agreed that male patients with breast cancer were included in the trial; therefore, the overall trial results would be generalizable to this population of patients. pERC, however, did not support the generalizability of the trial evidence to patients with node-negative breast cancers less than 1 cm (T1a/bN0) tumours as further evidence would be required to determine efficacy in this population. Overall, pERC concluded that there may be a net clinical benefit with T-DM1 compared with trastuzumab, based on the clinically meaningful improvement in iDFS and distant recurrence-free survival. However, pERC was uncertain as to how T-DM1 compares with trastuzumab with regards to OS due to a lack of mature OS data. pERC also acknowledged that T-DM1 has a manageable but not insignificant toxicity profile and there was some detriment in QoL.

During deliberations, pERC considered patient group input that indicated patients with breast cancer value having access to effective treatment options that control the disease, reduce the risk of recurrence, have tolerable side effects, and reduce the financial burden to patients. Based on the improvement in iDFS and distant recurrence-free survival, pERC agreed that T-DM1 aligned with patient values of achieving disease control and reducing the risk of recurrence. However, the Committee was not satisfied that the addition of T-DM1 aligned with patients' values of maintaining QoL and offering minimal side effects.

pERC deliberated on the cost-effectiveness of T-DM1 compared with trastuzumab and concluded that based on the submitted economic model, T-DM1 is cost-effective or dominant. pERC noted that both the submitted and EGP best estimate of the incremental cost-effectiveness ratio (ICER) were scenarios where T-DM1 is more effective and less costly than trastuzumab which represent a dominant scenario. pERC discussed that the EGP explored the impact of a number of scenarios on cost-effectiveness estimates and noted that the ICER was robust, and remained dominant, to most changes, including changes that drastically reduced the long-term projections for OS. Based on discussions with the Clinical Guidance Panel (CGP), the EGP's best estimate included changes to the duration of treatment; institutional costs for diagnostic testing, which were not included in the submitted base case; and exploration of a number of different time horizons. Almost all these changes resulted in dominant scenarios with T-DM1, except for scenarios using a five- and 10-year time horizon. pERC agreed with the EGP that the 40-year time horizon is appropriate for this patient population. Overall, pERC agreed that based on the submitted and EGP's ICER estimates, T-DM1 is cost-effective or dominates trastuzumab.

pERC discussed the factors that could impact the feasibility of implementing a positive reimbursement recommendation for T-DM1 and noted that the eligibility for treatment with T-DM1 should align with the KATHERINE trial criteria. pERC noted that there is a lack of clarity as to whether or not patients currently on trastuzumab should be switched to T-DM1 in this setting. pERC noted that collaboration among provinces would be of value to develop a common approach to the appropriate time frame for switching and for the appropriate number of treatment cycles for patients who may switch from trastuzumab to T-DM1. pERC agreed with the registered clinician input that if a patient who received T-DM1 and had a recurrence during treatment or shortly thereafter (within six months), it would not be beneficial to re-treat these patients with T-DM1. Furthermore, T-DM1 could be used in the metastatic setting after patients have received standard first-line metastatic treatment with a HER2-directed therapy (e.g., trastuzumab and pertuzumab). pERC also noted the CGP's agreement that re-treatment may be beneficial in patients with a longer time to recurrence after adjuvant T-DM1 therapy. pERC agreed that T-DM1 is not reimbursed in the first-line metastatic setting and would not be used in that setting. pERC noted that the budget impact of T-DM1 was low, based on both the submitted and EGP's reanalysis. pERC agreed that it is likely that the budget impact of T-DM1 is offset by long-term cost savings among patients who do not experience relapse and therefore, do not require further treatments in the metastatic setting. pERC further noted that a number of scenarios were explored by the EGP in the budget impact analysis (BIA), including greater market uptake, inclusion of wastage, exclusion of trastuzumab biosimilar, and exclusion of the prevalent population. None of these scenarios had a big impact on the BIA. Lastly, pERC acknowledged that there would be additional costs to monitoring patients with the added toxicity of T-DM1.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and BIA
- guidance from the pCODR clinical and economic review panels
- input from two patient advocacy group(s): Rethink Breast Cancer and the Canadian Breast Cancer Network
- input from registered clinicians
- input from PAG.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the safety and efficacy of T-DM1 (Kadcyla) for the treatment of patients with HER2-positive early breast cancer who have residual invasive disease following neoadjuvant taxane and trastuzumab-based treatment.

Studies included: One phase III, international, multi-centre, open-label, randomized controlled trial

The pCODR systematic review included one international, multi-centre, open-label, phase III randomized control trial (KATHERINE), which compared T-DM1 with trastuzumab for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual disease after preoperative systematic treatment. Eligible patients were randomized in a 1:1 ratio receiving either T-DM1 at a dose of 3.6 mg/kg of body weight or trastuzumab at a dose of 6 mg/kg intravenously every three weeks for 14 cycles. Patients received a loading dose of 8 mg of trastuzumab if more than six weeks had elapsed since the preceding dose of trastuzumab. Patients who discontinued T-DM1 early due to toxicity could complete the 14 cycles of trastuzumab at the discretion of the investigator.

Patient populations: Median age of 49 years, prior neoadjuvant HER2-directed therapy with trastuzumab and pertuzumab

The KATHERINE trial (n = 1,486) included patients with histologically confirmed HER2-positive, nonmetastatic, invasive primary breast cancer at presentation. Of the 743 patients randomized to each trial group, 740 patients received T-DM1 and 720 patients received trastuzumab. Almost all patients were female except for two male patients in the T-DM1 group and three male patients in the trastuzumab group. The median age in both treatment groups was 49 years. Most patients in both treatment groups had neoadjuvant HER2-directed therapy with trastuzumab alone (n = 1,196; 80.5%), and a similar proportion of patients in both groups had trastuzumab plus pertuzumab (overall, n = 272; 18.3%).

Key efficacy results: Clinically meaningful improvement in iDFS

The key efficacy outcome deliberated on by pERC included iDFS, which was the primary end point, STEEP definition of iDFS, disease-free survival, OS, distant recurrence-free survival, QoL, and safety. Results were based on an interim analysis of the KATHERINE trial.

The primary end point of the study was met at the pre-specified interim analysis for iDFS. The three-year event-free rate for iDFS was 88.3% in the T-DM1 group compared with 77.0% in the trastuzumab group. There was a 50% reduction in the risk of an iDFS event with the T-DM1 treatment group compared with the trastuzumab group (unstratified hazard ratio [HR]: 0.50; 95% confidence interval [CI], 0.39 to 0.64; $P < 0.001$). The KATHERINE trial also assessed iDFS according to STEEP criteria, which included patients with second primary non-breast cancer as an invasive-disease event; there was a 49% reduction (unstratified HR: 0.51; 95% CI, 0.40 to 0.66) in the risk of iDFS events with the STEEP definition in the T-DM1 group compared with trastuzumab group.

The estimated three-year event rate for DFS was 87.4% in the T-DM1 group and 76.9% in the trastuzumab group, with a 47% reduction in the risk of a DFS event in the T-DM1 group compared with the trastuzumab group (HR: 0.53; 95% CI, 0.41 to 0.68). A total of 42 (5.7%) deaths occurred in the T-DM1 treatment group

compared with 56 (7.5%) deaths in the trastuzumab group. There was no statistically significant difference in OS between treatment arms. However, data are immature at the interim analysis for OS.

Distant recurrence events occurred in 78 (10.5%) patients in the T-DM1 treatment group compared with 121 (16.3%) patients in the trastuzumab group, with a three-year event rate estimated at 89.7% and 83.0% in the T-DM1 and trastuzumab groups, respectively. There was a 40% reduction in distant recurrence events with T-DM1 compared with trastuzumab (HR: 0.60; 95% CI, 0.45 to 0.79).

Patient-reported outcomes: Slight detriment to QoL with T-DM1

QoL data were collected in the KATHERINE trial using the European Organisation for Research and Treatment of Cancer Quality of life Questionnaire Core 30 (EORTC QLQ-C30) and Quality of Life Breast Cancer-Specific (QLQ-BR23) questionnaires. Mean changes from baseline were similar for global health status for both treatment groups. A higher proportion of patients in the T-DM1 treatment group compared with the trastuzumab group reported a clinically meaningful deterioration in role function, appetite loss, constipation, fatigue, nausea/vomiting, and systemic therapy side effects.

Limitations: Non-validated outcome of iDFS, protocol deviations, subsequent therapies not reflective of clinical practice

iDFS, the primary outcome of the KATHERINE trial, is not validated in the literature, making the strength of association between iDFS and OS unknown. The pCODR methods team noted that due to the varying definitions of iDFS and DFS in the literature, cross-trial comparisons are challenging and provide challenges for analysis and interpretation. The KATHERINE trial was also open label, introducing reporting and performance bias among patients and investigators, as treatment assignments were not blinded.

There was a higher proportion of protocol deviations in the T-DM1 group related to dose alterations (not holding or reducing doses as per protocol) in the T-DM1 group by investigators; an analysis was conducted to assess for deviation bias, which excluded patients who did not prescribe to the per-protocol dose, which revealed a minimal impact of deviation bias on efficacy outcomes. Patients in the T-DM1 group had a higher proportion of dose reductions, interruptions, and discontinuations due to an AE, which may be indicative of greater toxicities in the T-DM1 group overall. The toxicity of T-DM1 may have been underestimated due to the greater number of protocol deviations related to not holding or reducing doses for toxicities that occurred in the T-DM1 group.

Double the number of patients in the trastuzumab group compared with the T-DM1 group received follow-up anticancer therapies. Discussions with the CGP revealed that subsequent therapies in the trastuzumab group were not reflective of clinical practice; for example, there was limited use of T-DM1, which is an established subsequent therapy following trastuzumab in the recurrent setting.

Safety: Greater overall AEs associated with T-DM1

Any-grade AEs occurred at greater frequency in the T-DM1 group compared with the trastuzumab group (98.5% versus 93.3%, respectively). Similarly, AEs ≥ grade 3, serious AEs, treatment-related AEs, and withdrawals due to an AE occurred at a greater frequency in the T-DM1 group than in the trastuzumab group. Peripheral sensory neuropathy ≥ grade 3 occurred in 1.4% (n = 10) of patients in the T-DM1 group and in no patients in the trastuzumab group. There was one patient death in the T-DM1 group due to an AE, with none occurring in the trastuzumab group.

Need and burden of illness: Unmet need for patients with high risk of recurrence

Breast cancer is the most common cancer diagnosed among Canadian women. The HER2 receptor is overexpressed in approximately 15% to 20% of breast cancers. HER2-positive breast cancers tend to present with aggressive tumours and poor prognoses. Patients who receive neoadjuvant treatment and who achieve pCR, especially those with a HER2-positive subtype, have better OS compared with patients who do not achieve such response. Approximately 30% to 40% of women who are treated with neoadjuvant systemic therapy with trastuzumab-containing regimens do not achieve pCR and are faced with poor outcomes and disease recurrence. More effective therapies leading to decreases in cancer recurrence and improvement in cure are needed.

Registered clinician input: Manageable toxicity, use of subsequent T-DM1

Input was received from seven oncologists and two pharmacists. Clinicians affirmed that T-DM1 has significant benefit over current standard treatment of trastuzumab monotherapy. The toxicity of T-DM1 was not considered to be excessive and clinicians stated that T-DM1 should be a prioritized treatment as it can prevent patients from relapsing. Contraindications of T-DM1 included concomitant contraindications to standard trastuzumab, such as cardiac dysfunction. The number of anti-HER2 therapies should be advised by clinical trial evidence and practice guidelines. Registered clinician input indicated that if a patient received T-DM1 and recurred during treatment or shortly thereafter (within six months), it would not be beneficial to re-treat these patients with T-DM1. There is also currently no evidence to suggest that T-DM1 would not be effective in the metastatic setting after standard first-line metastatic treatment with a HER2-directed therapy (e.g., trastuzumab and pertuzumab).

PATIENT-BASED VALUES

Values of patients with early breast cancer: Reduced risk of recurrence, treatment effectiveness, and improved QoL

Two patient groups provided input on T-DM1 for the treatment of HER2-positive early breast cancer. Reducing risk of recurrence and accessing effective treatments were reported to be the most important considerations for patients. Survey respondents valued having more effective treatment options for their disease earlier on and proper side effect management, which is critical to their QoL. The ability to work and engage in daily tasks as well as financial challenges associated with loss of income and drug and travel costs were highlighted as issues faced by patients with early breast cancer.

Patient values on treatment: Reduced disease recurrence and manageable side effects

Survey respondents with experience with T-DM1 (n = 6) reported significant improvement in their QoL with minimal and tolerable side effects. All six patients stated they would recommend T-DM1 to other patients with early breast cancer. Both patient groups concluded that the reduced risk of recurrence and the ability to manage side effects were key values to patients, and that T-DM1 aligns with these values.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analyses

The EGP assessed cost-effectiveness and cost-utility analyses of T-DM1 for patients with HER2-positive early breast cancer who have residual disease, following neoadjuvant taxane and trastuzumab-based treatment.

Basis of the economic model: KATHERINE trial data and long-term extrapolation of OS

Key cost inputs included drug costs, health states costs, drug wastage and vial sharing, subsequent therapies, and AEs. Key clinical effects considered in the analysis included iDFS, OS, and utilities that were obtained from the KATHERINE trial. Given that the OS data are not mature, the long-term clinical effect estimates with T-DM1 are uncertain.

Drug costs: Treatment costs for T-DM1 and trastuzumab

T-DM1 costs $2,128.93 per 100 mg vial and $3,406.28 per 160 mg vial. At the recommended dose of 3.6 mg/kg intravenously every 21 days for 14 cycles, T-DM1 costs $260.65 per day and $5,473.73 per 21-day course. Trastuzumab (branded) costs $2,874.05 per 440 mg vial. At the recommended dose of 6 mg/kg intravenously every 21 days, trastuzumab costs $133.29 per day and $2,799.06 per 21-day course.

Cost-effectiveness estimates: Dominant (less costly and more effective) ICERs for T-DM1 compared with trastuzumab

pERC deliberated the cost-effectiveness of T-DM1 compared with trastuzumab for patients with HER2-positive early breast cancer who have residual disease, following neoadjuvant taxane and trastuzumab-based treatment. The sponsor's best estimate of the ICER demonstrated that T-DM1 was dominant (less costly and more quality-adjusted life-years gained).

The main cost drivers were costs of adjuvant therapy and cost of treatments in the first-line, second-line, and subsequent lines of metastatic disease. Time horizon was the variable in the model that had the

largest impact on results, where a shorter time horizon resulted in lower ICERs. No other variables appeared to have a big impact on the ICER in sensitivity analyses by the sponsor or the EGP.

The EGP's reanalysis was based on the following:

- The base-case model assumed that the time on treatment was equal to the average number of cycles for all patients in each treatment until iDFS was reached. In reanalysis, the time on treatment was set equal to the time until disease progression for each treatment.
- Institutional costs for routine diagnostic tests (CT, ECG, mammography) were added to the unit costs, in addition to typical physician billing fees.
- Four alternate time horizons, including a lifetime horizon of 51 years, 10 years, 5 years, and 40 years. The time horizon of 40 years was considered the most clinically plausible scenario.

Based on previous CADTH reviews of drugs in the adjuvant setting for early breast cancer, a 40-year time horizon was considered by the EGP to be the most clinically relevant for this population. Based on the 40-year time horizon, the EGP's best estimate was that T-DM1 was dominant compared with trastuzumab. At the 40-year time horizon the extra cost of T-DM1 is a cost saving of $3,810 and the extra clinical effect of T-DM1 is 2.42 quality-adjusted life-years.

The EGP noted three limitations that could not be addressed in the EGP's reanalysis as there was no alternative evidence for sensitivity analyses. These included 1) uncertainty about the data used to estimate long-term DFS and OS as the trial follow-up period was short. Furthermore, there was uncertainty about the relevance of the literature used to determine long-term outcomes (transition probabilities) as the CGP noted that improvements in cancer care have been made with the introduction of better agents in last five years; 2) uncertainty as to when biosimilar and subcutaneous trastuzumab may be introduced; and 3) assumption of equal benefit of treatment regardless of a dose reduction or discontinuation of T-DM1. Although reliable values were not available, the EGP did conduct sensitivity analyses to explore the sensitivity of the model to these factors and noted that the use of a treatment mix yielded conservative estimates and drastically altering the constructed probability of deaths for each health state did not have a big impact on the ICER.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Eligibility for treatment to mostly follow KATHERINE trial criteria

pERC discussed the factors that could impact the feasibility of implementing a positive reimbursement recommendation for T-DM1 and noted that the eligibility for treatment with T-DM1 should align with the KATHERINE trial criteria. pERC noted that the budget impact of T-DM1 was low based on both the submitted and EGP's reanalysis. pERC agreed that it is likely that the budget impact of T-DM1 is offset by long-term cost savings among patients who do not experience relapse and therefore, do not require further treatments in the metastatic setting. pERC further noted that a number of scenarios were explored by the EGP in the BIA, including greater market uptake, inclusion of wastage, exclusion of trastuzumab biosimilar, and exclusion of the prevalent population. All of these scenarios did not have a big impact on the BIA. Lastly, pERC acknowledged that there would be additional costs to monitoring patients with the added toxicity of T-DM1.

pERC addressed a number of implementation questions from PAG (outlined in Appendix 1).

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Avram Denburg and Dr. Anil Joy, who were not present for the meeting
- Dr. Maureen Trudeau, who was excluded from chairing and voting due to a conflict of interest
- Daryl Bell, who did not vote due to his role as a patient member alternate.

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 early breast cancer, through their declarations, one member had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, one of these members was excluded from voting.

Information sources used

pERC 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 its 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*. Hoffmann-La Roche Limited, as the primary data owner, did not agree to the disclosure of clinical information, therefore, this information has been redacted in publicly available guidance reports.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers 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.

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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
PAG is seeking clarity on patients who would be eligible for treatment; and, if trastuzumab emtansine is recommended for reimbursement, whether the specific trial inclusion and exclusion criteria or the broader funding criteria would be applied. PAG identified that it would also be important to have clarity on patient eligibility in the following clinical settings: • Patients who had prior trastuzumab plus pertuzumab (or other HER2-targeted therapy) as this is not funded as neoadjuvant therapy in any jurisdiction • Patients with T1a/bN0 tumours • Male breast cancer	• pERC agreed that the eligibility of patients should be aligned to the KATHERINE trial criteria. • pERC supported the generalizability of the trial evidence to patients treated with trastuzumab and pertuzumab (or other HER2-targeted therapy) in the neoadjuvant setting as these patients were included in the KATHERINE trial. • pERC does not support the generalizability of the trial evidence to patients with T1a/bN0 tumours as further evidence would be required to determine efficacy in this population. • pERC noted that male patients with breast cancer were included in the trial; therefore, the overall trial results would be generalizable to this population of patients.
Time-Limited Basis • Patients currently receiving adjuvant trastuzumab. If it is appropriate to switch these patients, is there an appropriate time frame (i.e., patients < 6 months into adjuvant treatment versus between months 9 and 12)? • Whether it would be appropriate to switch patients from adjuvant trastuzumab to trastuzumab emtansine within the 12-week time frame as per the KATHERINE trial, and for time frames beyond 12 weeks, should these patients switch to trastuzumab emtansine or remain on trastuzumab? • Patients who recently completed their one year of adjuvant trastuzumab.	• pERC noted that there is a lack of clarity as to whether or not patients currently on trastuzumab should be switched to T-DM1. pERC noted that collaboration among provinces would be of value to develop a common approach to the appropriate time frame for switching and for the appropriate number of treatment cycles for patients who may switch from trastuzumab to T-DM1. • There is no direct clinical data to support the initiation of T-DM1 as adjuvant therapy if more than 12 weeks have passed since surgery. • As the KATHERINE trial did not investigate the use of T-DM1 in patients who have already completed adjuvant treatment with trastuzumab, there is no evidence to make an informed decision on T-DM1 use for this population.
Sequencing • Appropriate metastatic treatments for patients who progress during or shortly after completing (e.g., ≤ 6 months) trastuzumab emtansine (e.g., trastuzumab emtansine, pertuzumab plus trastuzumab) and sequencing of these treatment options? • Would it be reasonable to treat with trastuzumab emtansine in the metastatic setting after receiving adjuvant trastuzumab emtansine? What would be the appropriate time frame (i.e., between adjuvant treatment and development of metastatic disease) for re-treatment with trastuzumab emtansine subsequently? • Guidance on number of anti-HER2 therapies that should be available in the metastatic setting.	• pERC agreed with the registered clinician input that if a patient received T-DM1 and recurred during treatment or shortly thereafter (within 6 months), it would not be beneficial to re-treat these patients with T-DM1. • pERC also agreed with registered clinicians that T-DM1 would be used in the metastatic setting after standard first-line metastatic treatment with a HER2-directed therapy (e.g., trastuzumab/pertuzumab). pERC also noted the CGP's agreement that re-treatment may be beneficial in patients with a longer time to recurrence after adjuvant T-DM1 therapy. pERC agreed that T-DM1 is not reimbursed in the first-line metastatic setting and would not be used in that setting. • pERC agreed that there is no evidence to determine the optimal number of HER2 therapies patients should receive in the metastatic setting.
• PAG is seeking guidance on whether the cap of 14 total cycles should be considered if trastuzumab emtansine is recommended for	• pERC agreed with the CGP that patients should complete either 14 cycles of adjuvant treatment or a

reimbursement, and if 14 total cycles of anti-HER2 therapy should be completed within a specific time frame.	total of one year (18 cycles) of HER2-targeted therapy, whichever comes earlier.

CGP = Clinical Guidance Panel; HER2 = human epidermal growth factor receptor 2; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; T-DM1 = trastuzumab emtansine; T1a/bN0 = node-negative breast cancers less than 1 cm.