CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Trastuzumab Emtansine (Kadcyla) for Early Breast Cancer

January 22, 2019

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

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.

Reports generated by pCODR are 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 report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

TABLE OF CONTENTS

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Hoffmann-La Roche Limited compared trastuzumab emtansine (T-DM1) to trastuzumab as adjuvant treatment for patients with HER2-positive early breast cancer who have residual disease, after pre-operative systemic treatment.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	Modelled patients with HER2-positive early breast cancer who have residual invasive disease, following neoadjuvant taxane and trastuzumab-based treatment. This is consistent with reimbursement request.
Type of Analysis	Cost Utility Analysis ($/QALY), Cost Effectiveness Analysis ($/LY)
Type of Model	Markov model with monthly cycles
Comparator	Trastuzumab ^
Year of costs	2019
Time Horizon	Lifetime (51-year time horizon to represent the lifetime of 100 years)
Perspective	Canadian public health care payer perspective
Cost of T-DM1 Source: Roche	T-DM1 is available in two vial sizes: • 100 mg vial: $2,128.93; $21.29/mg • 160 mg vial: $3,406.28; $21.29/mg At the recommended dose of 3.6 mg/kg intravenous every 21 days for 14 cycles or until disease progression or unacceptable toxicity, T-DM1 costs: • per day: $260.65 • per 21-day course: $5,473.73
Cost of trastuzumab (branded) Source: pCODR Submission of Pertuzumab-Trastuzumab Combo Pack	Trastuzumab is available as a 440 mg vial and costs $2,874.05 per vial or $6.53/mg. At the recommended dose of 6 mg/kg intravenous every 21 days, trastuzumab costs: • per day: $133.29 • per 21-day course: $2,799.06
Cost of trastuzumab (biosimilar)*	Trastuzumab biosimilar is available as a 440mg vial and costs $2155.54 per vial or $4.90/mg. At the recommended dose of 6 mg/kg intravenous every 21 days, trastuzumab (biosimilar) costs: • per day: $99.95 • per 21-day cycle: $2,099.00
Cost of trastuzumab (subcutaneous, SC)	Trastuzumab SC is available as a 600mg vial and costs $2625.00 per vial or $4.38/mg. At the recommended dose of 6 mg/kg intravenous every 21 days, trastuzumab (SC) costs: • per day: $125.00 • per 21-day course: $2,625.00
Discount Rate	1.5% annually for costs and effects
Model Structure	*Markov model was built on 6 health states:* • iDFS (invasive disease–free survival, with distinction for patients on/off adjuvant treatment) • Non-metastatic recurrence (includes locoregional recurrence and contralateral breast cancer) • Remission from a non-metastatic recurrence (no evidence of disease) • First-line metastatic breast cancer

	• Subsequent lines of treatment in metastatic breast cancer (including second-line of treatment and later lines) • Death
Key Data Sources (health states)	Movement out of the iDFS state was informed by background mortality data from Canadian life tables and the data from the KATHERINE[20] trial. iDFS extrapolations were guided by recurrence rates observed in the HERA[8] and BCIRG-006[21] trials. Transitions among the remaining health states were informed by published literature and the following trials: EMILIA[5], CLEOPATRA[19], and M77001[10].
Key Data Sources (quality of life, adverse events, costs)	Utilities (EQ-5D-3L) in the iDFS states were directly from the KATHERINE trial, and were also applied to the non-metastatic health states. Utilities in the metastatic health states were obtained from published literature. Rates of adverse events Grade ≥3 (>1% occurrence) were obtained from the KATHERINE trial. Costs for health-states, adverse events, and subsequent therapy were based on Ontario unit costs and local clinical opinion for resource utilization.

^ Trastuzumab was evaluated as a treatment mix (intravenous, subcutaneous, and biosimilar).
* An assumption of a 25% discount over the branded product was made by the sponsor (Roche).
model used body weight – 71.42 kg and BSA of 1.77 m^2

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. The CGP reported on the following issues:

Efficacy: The primary outcome iDFS, though an unvalidated endpoint, likely provides a more conservative estimate of treatment effect than the standard STEEP definition of DFS. The study met its primary endpoint of iDFS favoring T-DM1, while OS trended to favour T-DM1, but the results were not statistically significant. The overall conclusion of efficacy was limited by discrepancy in receipt of study drugs, unilaterally switching from T-DM1 to trastuzumab, dose reductions were not applied despite high toxicity in T-DM1 treatment, and discontinuation because of patient decisions. In addition, differences between Canadian practice patterns and the KATHERINE trial currently exist with neoadjuvant and subsequent treatments.

Safety: T-DM1 introduces more adverse events than trastuzumab, including serious side effects, which temporarily impacts quality of life during the treatment phase. However, no new safety signals were detected with T-DM1, and there was no difference in incidence of fatal AEs between the treatment groups.

Burden of illness and Need: One in four women who present with early stage HER2+ breast cancer and are treated with trastuzumab based treatments continue to have recurrence from their breast cancer within 10 years, suggesting a need for more effective therapies.

- EGP comment on CGP considerations: *The cost effectiveness was conducted based on transitions from iDFS health state and included quality of life. The main benefit of T-DM1 in the cost effectiveness model is the reduced probability of progressive disease, where progressive disease is expensive to treat, has lower quality of life, and reduced chance of survival.*

Generalizability of the trial evidence: The CGP agreed that the efficacy and safety outcomes from the KATHERINE trial can be generalized to male patients with breast cancer and patient who have had trastuzumab plus pertuzumab (or other HER2-targeted therapy) in the neoadjuvant setting. The CGP also

agreed that it is possible patients with ECOG PS >1 may be eligible for treatment (based on the discretion of the treating oncologist) although the preference would be to limit treatment to PS 0-1 (as in the KATHERINE trial).

- *EGP comment: The submitted economic model was based on the inclusion/exclusion criteria of the KATHERINE trial and provides no evidence for expanded eligibility. The budget impact analysis includes patients with residual disease who receive adjuvant therapy after surgery.*

Summary of patient input relevant to the economic analysis

Two patient advocacy groups provided input including 31 patients in the first group and 55 in the second. Most patients in the first group were non-Canadians. Only 6 patients in the first group and none in the second group had any experience with T-DM1, and some of these patients had metastatic breast cancer rather than early stage disease. Thus, it is unclear how representative these experiences by patients may be on the trade-offs of increased short-term toxicity and cure rate as measured by disease free survival in the adjuvant setting.

SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

Currently Funded Treatments. For the adjuvant treatment of patients with HER2-positive early breast cancer who have residual disease after pre-operative systemic treatment, PAG identified trastuzumab as the relevant comparator.

- EGP comment: *The cost-effectiveness analysis compared T-DM1 to trastuzumab, which is the relevant comparator.*

Eligible Patient Population. There is a potential for indication creep into the neoadjuvant setting (i.e., pre-operative), as well as a need to specify the inclusion and exclusion criteria.

- EGP comment: *The cost-effectiveness analysis was built on the inclusion/exclusion criteria and characteristics of the patient population in the KATHERINE trial, only in the adjuvant setting. The budget impact analysis investigates changes to currently available neoadjuvant treatments with the introduction of T-DM1 in the adjuvant setting, but not the use of T-DM1 in the neoadjuvant setting. The CGP have confirmed that there is no current evidence to support the use of T-DM1 as neoadjuvant treatment.*

Implementation Factors. T-DM1 is currently funded in the metastatic setting where patients receive intravenous administration, there is familiarity with the preparation, administration and monitoring of AE's.

- EGP comment: *The cost-effectiveness includes the increased health care resources for administration and monitoring, as well as including the impact of adverse events.*

Sequencing and Priority of Treatments. PAG seeks clarity on whether T-DM1 would be administered more than once (adjuvant, metastatic), where T-DM1 fits into treatment sequencing, and whether the 14 cycle T-DM1 treatment is time limited.

- EGP comment: *The CGP confirmed that in patients who progress on or after adjuvant T-DM1, the same agent would then not be used for treatment in the metastatic setting. The cost-effectiveness analysis was limited to T-DM1 as first-line therapy within the adjuvant setting, with drug administration time following the KATHERINE trial being at the discretion of the clinician. The budget impact model assumes that 14 cycles are completed within 1 year.*

Companion Diagnostic Testing. HER-2 testing is already available and used as inclusion criteria.

- EGP comment: *HER-2 testing was not included in the economic model, assuming that HER-2 status was established once with a biopsy of the initial tumour.*

SUMMARY OF REGISTERED CLINICIAN INPUT

Current Treatment(s) for the Indication Under Review: The current reimbursed treatment in the adjuvant setting is intravenous trastuzumab.

- *EGP comment: The cost-effectiveness includes possible changes with trastuzumab, with the comparator being a mix of trastuzumab applications (branded-intravenous, biosimilar, and subcutaneous), and scenario analysis compares T-DM1 to trastuzumab-intravenous only.*

Eligible Patient Population. The potential patient population would be beyond the inclusion criteria of the KATHERINE trial, because the demonstrated efficacy would provide potentially improved outcomes for patients who received trastuzumab plus another HER2 targeted therapy (such as pertuzumab) and for males.

- *EGP comment: The cost-effectiveness analysis was based on the inclusion criteria of the KATHERINE trial and provides no evidence for expanded eligibility. The budget impact analysis includes patients with residual disease who receive adjuvant therapy after surgery.*

Relevance to Clinical Practice. T-DM1 would satisfy an unmet need and the toxicity observed in the KATHERINE trial was expected. Thus, T-DM1 would be used for patients similar to the KATHERINE trial (with exclusion for cardiac dysfunction and inclusion of sufficient blood counts post-surgery). Further evidence would be helpful in establishing benefit for very small residual disease (i.e., ypT1a).

- EGP comment: *The cost-effectiveness analysis was based on the inclusion criteria of the KATHERINE trial and provides no evidence for expanded eligibility.*

Sequencing and Priority of Treatments. The use of T-DM1 in the adjuvant setting would not interfere with clinician's choice of other HER-2 therapies in the metastatic setting, excluding T-DM1 as first-line in the metastatic setting.

- EGP comment: *The cost-effectiveness analysis includes T-DM1 in the adjuvant setting for the T-DM1 treatment arm, and 56.25% of first-line therapies for early recurrence metastatic patients in the trastuzumab treatment arm. For late recurrence and subsequent lines, treatment mixes did not differ with T-DM1 being used for both treatment arms, with 3.75% in first-line late recurrences, and in subsequent lines including 50% T-DM1 for early recurrence, and 95% T-DM1 in late recurrence. The budget impact analysis includes adding T-DM1 to the adjuvant setting only, and sensitivity analysis investigates changes to the neoadjuvant setting.*

Companion Diagnostic Testing. HER-2 biomarker testing was completed at the surgery stage and no additional tested may occur, except for increased surveillance given the addition of a new therapy.

- EGP comment: *The cost of HER-2 biomarker testing occurred at the surgery stage and was not included in the economic model.*

Implementation Questions. T-DM1 drug administration should be limited to 14 cycles, including allowing temporary interruption only for mild toxicity.

- EGP comment: *The cost effectiveness analysis does not address interruptions to drug administration and assumes the drugs were administered uniformly.*

1.3 Submitted and EGP Reanalysis Estimates

The main cost drivers in the economic model were the cost of adjuvant therapy, and the cost of treatments in 1st line, and second and subsequent lines metastatic disease. The economic model assumes a favourable trade-off between the costs of adjuvant therapy versus later metastatic treatment costs. The key variable in the model that had the largest impact on the results was the choice of time horizon, decreasing the time horizon increases the ICER. All other variables did not affect the ICER in sensitivity analyses in the submission, and in the EGP's reanalysis.

Table 2. Submitted and EGP Estimates (probabilistic, 5,000 bootstrap simulations)

Estimates	Sponsor's Best Case	EGP Reanalysis			
Time Horizon	Lifetime	Lifetime	40 year	10 year	5 year
ΔE (LY)	2.59	2.59	2.42	0.47	0.12
In iDFS	3.45	3.44	3.28	1.00	0.40
In non-metastatic recurrence	-0.04	-0.04	-0.04	-0.04	-0.03
In remission	-0.38	-0.38	-0.38	-0.17	-0.04
In first-line metastatic	-0.20	-0.20	-0.20	-0.16	-0.12
In subsequent-line metastatic	-0.28	-0.28	-0.24	-0.17	-0.09
ΔE (QALY)	2.15	2.14	2.06	0.46	0.15
In iDFS	2.76	2.75	2.66	0.83	0.33
In non-metastatic recurrence	-0.04	-0.04	-0.04	-0.04	-0.03
In remission	-0.31	-0.31	-0.31	-0.14	-0.03
In first-line metastatic	-0.14	-0.14	-0.14	-0.11	-0.08
In subsequent-line metastatic	-0.12	-0.12	-0.12	-0.08	-0.05
ΔC ($)	-$8,910	-3,898	-$3,810	8,190	21,060
Total iDFS cost	$40,165	46,683	$46,569	45,013	44,601
Total non-metastatic recurrence cost	-$2,364	-2,459	-$2,457	-2,391	-1,727
Total remission cost	-$214	-603	-$599	-265	-56
Total first-line metastatic cost	-$21,583	-22,036	-$21,981	-16,855	-12,212
Total subsequent-line metastatic cost	-$21,375	-21,936	-$21,818	-14,618	-7,765
End-of-life cost	-$3,539	-3,547	-$3,524	-2,695	-1,781
ICER estimate ($/QALY)	T-DM1 dominates[&]	T-DM1 dominates[&]	T-DM1 dominates[&]	17,714/QALY	142,780/QALY

*EGP's estimates include all parameters modified as described below
[&] Less costly, more QALY's

Overall, the cost-effectiveness model captures the lifetime experience of the patient in terms of clinical outcomes, costs, and quality of life.

1. However, first long-term projection is problematic for 2 reasons:
   - There were low occurrence rates in 5-year KATHERINE trial where median or mean DFS and OS were not reached. iDFS was projected beyond 5-years based on literature values to estimate transitioning of patients to advanced health states, using conservative projected survival curves. OS was not projected from the clinical trial through parametric modelling, instead OS was

estimated as the summative probability of death from being in each health state (health states: iDFS, remission, 1st line, 2nd line) and probability of death in 1st line and 2nd line depended on treatment received. All probability of transitions (except from iDFS) and rates of death came from the literature, and there was a further adjustment based on life table background mortality. EGP tested the effect on the ICER of changing the constructed probability of deaths for each health state. A reduction of 50% of the probability of death in the health states (non-metastatic recurrence, remission, first-line and second-line metastatic breast cancer) produced minor changes in the ICER.

- Subsequent treatment after disease progression including risk of death were modelled on the best available data, however that data may be dated, and non-Canadian specific leading to uncertainty beyond the 5-year trial period. Based on CGP's opinion, significant improvements in cancer care have occurred in the last 5 years which may have impacted the results, such as improved survival in both treatment arms.

2. A second limitation is the unknown evolution of the comparator therapy. Specifically, it is unknown if, and at what time, trastuzumab will become available as a biosimilar and SC. In the submitters base case, the comparator is a mix of trastuzumab-branded, trastuzumab-biosimilar, and branded trastuzumab-SC. Given that having only IV trastuzumab available as therapy was explored in sensitivity analysis, and had a small impact on the ICER, the comparator-mix was accepted by the EGP. This results in a conservative ICER (overestimate of the ICER) where T-DM1 to being compared to a mix of cheaper treatments (the base case) as compared to a scenario where T-DM1 is compared to branded IV trastuzumab alone.

3. A third limitation is the effect of dosage and discontinuation. In the KATHERINE trial, there were differences between the treatment groups with regards to the percentage of patients who received the full 14 cycles dosing (difference=9.6%), and there were likely differences in benefit among the proportion of patients who received less than the full 14 cycles of dosing. For example, it is not clear if patients who received <4 cycles dosing would receive any benefit. The cost-effectiveness model assumes equal benefit for all patients, while a more sophisticated microsimulation model could have drawn from a distribution of dosing and benefits to account for differences between treatment in terms of dosing received and benefit received.

1.4 Detailed Highlights of the EGP Reanalysis

1. First, 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. CGP noted that iDFS was not the usual definition according to STEEP definition. In reanalysis, the time on treatment was set equal to the time until disease progression for each treatment.

2. Second, the unit costs for diagnostic costs included the typical physician billing fees. In reanalysis, the institutional costs for routine diagnostic tests (CT, ECG, mammography) were added to the unit costs. Institutional fees were obtained from the on-line OCCI calculator for 2017/2018 ambulatory care.

3. Third, concerning the time horizon, EGP presented ICER's with four alternate time horizons. These included a lifetime horizon of 51 years to demonstrate the ICER at the longest time horizon resulting in the lower bound of the ICER, time horizon of 10 years for which data is available within the literature, scenario using only the available evidence (5 years of trial data) to create the most conservative upper bound for the ICER and lastly the most clinically plausible scenario using a 40 year time horizon. The EGP presented these time horizons for the following reasons:

    - The time horizon of 51 years follows all patients until death. For an average age cohort of 49, this implies that no one will live beyond age 100. On average, the life expectancy with T-DM1 is

to the age of 82.7 years (+33.7 non-discounted life years after age 49) and for trastuzumab to the age 77.9 years (+28.9 non-discounted life years after age 49).

- The EGP had concerns that this lifetime horizon is optimistic as it implies both cohorts are able to live to the average life expectancy in Canada (about age 80).
- Thus, the EGP presented a range of time horizons, with an optimistic lifetime horizon, and a very conservative estimate with a short time horizon capturing only the KATHERINE trial data.
- Based on previous CADTH reviews of agents in the adjuvant setting for early breast cancer, the EGP noted that a 40-year time horizon is considered to be most clinically relevant for this population.

To add to this discussion,

- The ICER is dominant for any time horizon beyond 15 years in the submitter's reference case.
- After 17 years, all deaths are caused by background mortality.
- After 10 years, deaths that occurred in the model are based on predicted deaths coming from projections beyond the time period of external long-term data (literature). In reality, there is no data beyond 10-11 years follow-up period in this setting. The 10-year data suggest some OS benefit beyond the 5-year trial period.
- Thus, a lifetime time horizon (51 years) is likely optimistic, 5 years is conservative but based on trial data from KATHERINE, while 10 years is based on longer term data from the literature. In addition, the risk of death between 5 and 10 years, driven by external data, may be old and no longer represents current treatment practice.
- Although it would have been reasonable to model long term OS using the KATHERINE trial OS projections, it was acknowledged by the sponsor that these projections would be too optimistic.
- Different survival distributions of iDFS were statistically tested by submitter, and EGP tested the impact of the ICER for different survival distributions. Overall, the model chosen by the submitters was among the most conservative models.
- The data to transition between advanced health states (example, 1st line metastatic to 2nd line metastatic) may be outdated (i.e., lower possible probability of transition), and most of the transitions occurred early in the model. In the cost effectiveness model, at 1.4 years the different between treatments for transition to 1st line mBC (early recurrence) peaked, at 2.2 years the transition to 2nd line (+) metastatic breast cancer (early recurrence) peaked, at 3.4 years the transition to 1st line metastatic breast cancer peaked, and at 5.9 years the transition to 2nd line (+) metastatic breast cancer peaked. Thus, a five-year model captures the majority of transitions up to 1st line metastatic. A 10-year model captures a majority of the differences in transition to 2nd line (+) metastatic.

Table 3: Detailed Description of EGP Reanalysis

EGP's Reanalysis for the Best Case Estimate					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR ($/QALY)	Δ from baseline submitted ICER
Submitter's Base Case	-$8,910	2.15	2.58	(-$4,136/QALY) dominant	--
First. Time on treatment	-4,513	2.14	2.58	(-$2,107/QALY) dominant	+$2,029
Second. Unit costs	-8,318	2.15	2.58	(-$3,865/QALY) dominant	+$271
Best case estimates of above two parameters + alternate time horizon					
Lower bound-lifetime horizon (51 years)	-3,898	2.14	2.57	(-$1,822/QALY) Dominant	+$2,314
40 year horizon	-$3,810	2.42	2.05	(-$1,574/QALY) Dominant	+2,561
10 year horizon	8,190	0.46	0.47	$17,714/QALY	+$21,850
Upper bound - 5 year horizon	21,060	0.15	0.12	$142,780/QALY	+146,916

1.5 Evaluation of Submitted Budget Impact Analysis

The budget impact analysis was most sensitive to the following factors which decreased the budget impact: removing the assumption of increased rate of neoadjuvant prescription beyond current levels once T-DM1 is reimbursed (not all patients are currently prescribed neoadjuvant therapy), consideration of only adjuvant costs, administering fewer cycles of T-DM1, and the exclusion of a trastuzumab biosimilar. Overall, most sensitivity analyses resulted in moderate differences compared to the base case analysis.

Key limitations of the BIA model include: 1) unknown extent of use in the future of different administrations of trastuzumab (IV, SC, or biosimilar), 2) unknown market share of T-DM1, and 3) uncertain size of patient population which would be eligible for reimbursement (e.g., eligibility criteria with respect to adjuvant treatment, with surgery, and estimates for rates of HER-2+ rate of testing and status, pCR- residual disease).

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for T-DM1 when compared to trastuzumab is:

- Between best-case scenario dominance at lifetime horizon (T-DM1 less costly, improved QALYs) and worst-case scenario (5-year time horizon) $142,780/QALY.
- This range is based on choice of time horizon, with dominance occurring at a lifetime horizon, and $142,780/QALY occurring with a 5-year time horizon.
- Based on the most clinically plausible time horizon of 40 years, the EGP agrees that the true ICER is likely a dominant scenario.
- The extra cost of T-DM1 is between a cost savings of $3,898 (lifetime) to a positive incremental cost of $21,060 (5-years). At the 40-year time horizon the extra cost of T-DM1 is a cost saving of $3,810.
- The extra clinical effect of T-DM1 is between 2.14 QALYs (lifetime) and 0.15 QALYs (5-years). At the 40-year time horizon, the extra clinical effect of T-DM1 is 2.42 QALYs.

Overall conclusions of the submitted model:

- Overall, the cost-effectiveness model captures the lifetime experience of the patient in terms of clinical outcomes, costs, and quality of life.
- Long term projection is problematic for 2 reasons: First, there were low occurrence rates in 5-year KATHERINE trial where median or mean DFS and OS were not reached. Second, subsequent treatment after disease progression including risk of death were modelled on the best available data, however that data may be dated, and non-Canadian-specific leading to uncertainty beyond the 5-year trial period.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

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

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

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

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

REFERENCES

1. Byfield SD, Buck PO, Blauer-Peterson C, Poston SA. ReCAP: Treatment Patterns and Cost of Care Associated With Initial Therapy Among Patients Diagnosed With Operable Early-Stage Human Epidermal Growth Factor Receptor 2-Overexpressed Breast Cancer in the United States: A Real-World Retrospective Study. Journal of Oncology Practice. 2015;12(2):159-60.
2. CADTH. pan-Canadian Oncology Drug Review final economic guidance report. 1987 Pembrolizumab (Keytruda) for metastatic urothelial carcinoma. 15 February 2018. Available at: 1988 https://www.cadth.ca/sites/default/files/pcodr/pcodr_pembrolizumab_keytruda_muc_fn_egr.p1989 df. 1990
3. Canadian Cancer Registry Database at Statistics Canada. Number, percent distribution and age-standardized incidence rates (per 100,000) of female breast cancers for each stage, by geographic region and age group, Canada, 2011–2015
4. Canadian Partnership Against Cancer. Distribution of cases by stage at diagnosis for breast cancer (women only) – 2013 diagnosis year. 2013
5. Dieras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(6):732-742.
6. Guertin JR, Feeny D, Tarride JE. Age- and sex-specific Canadian utility norms, based on the 2013-2014 Canadian Community Health Survey. CMAJ. 2018;190(6):E155-E161.
7. IQVIA. Delta PA. Ontario wholesale list pricing. March 2019.
8. Jackisch C, Piccart M, Gelber RD, et al. HERA Trial: 10-Year Follow-up of Trastuzumab after Adjuvant Chemotherapy in HER2 Positive Early Breast Cancer - Final Analysis. Paper presented at: SABCS2015; San Antonio.
9. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. *Br J Cancer*. 2006;95(6):683-690.
10. Marty M, Cognetti F, Maraninchi D, et al. Randomized Phase II Trial of Efficacy and Safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol*. 2005;23(19):4265-4274
11. Murthy RK, Raghavendra AS, Hess KR, Fujii T, Lim B, Barcenas C, et al. Neoadjuvant Pertuzumab-containing Regimens Improve Pathologic Complete Response Rates in Stage II to III HER-2/neu-positive Breast Cancer: A Retrospective, Single Institution Experience. *Clinical Breast Cancer*. 2018;18(6):1283-8.
12. ODB. Ontario Ministry of Health and Long Term Care. Ontario Drug Benefit Formulary / Comparative Drug Index. Edition 43. Effective 31 May 2019. Available at: http://www.health.gov.on.ca/en/pro/programs/drugs/edition_43.aspx.
13. Ontario Case Costing (Web Page) Costing Analysis Tool. Updated 2017. Available online at: https://hsimi.ca/occp/occpreports/. Accessed: October 2019.
14. Ontario Health Insurance Plan (MOHLTC-SOB 2019). Ministry of Health and Long Term Care. Schedule of benefits. Physician services under the health insurance act. Effective 15 November 2018. Available at: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/.
15. Ontario Health Insurance Plan. Ministry of Health and Long Term Care. Schedule of benefits for laboratory services (MOHLTC-SOB-LabS 2019). 07 November 2017. Available at: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/lab/lab_mn2018.pdf.

Receptor 2-Positive Metastatic Breast Cancer Administered as First Line Treatment: The M77001 Study Group. *Journal of Clinical Oncology*. 2005;23(19):4265-4274.
16. Slamon D, Eiermann W, Robert N, al. et al.. Ten year follow-up of BCIRG-006 comparing doxorubicin plus cyclophosphamide followed by docetaxel (AC-T) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC-TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2+ early breast cancer. Paper presented at: The 38th Annual CTRC–AACR Breast Cancer Symposium 2015; San Antonio.
17. Spring L, Niemierko A, Haddad S, Yuen M, et al. Effectiveness and tolerability of neoadjuvant pertuzumab-containing regimens for HER2-positive localized breast cancer. *Breast Cancer Res Treat*. 2018;172(3):733 - 40.
18. Statistics Canada. Table 17-10-0057-01 Projected population, by projection scenario, age and sex, as of July 1 (x 1,000) - using the M1 medium growth scenario.
19. Swain S, Baselga J, Kim S, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372(8):724-734. (CLEOPATRA).
20. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. *N Engl J Med*. 2019;380(7):617-628.
21. J Slamon WE, NJ Robert, J Giermek, M Martin, M Jasiowka, JR Mackey, A Chan, M-C Liu, T Pinter, V Valero, C Falkson, T Fornander, TA Shiftan, S Bensfia, S Hitier, N Xu, V Bée-Munteanu, P Drevot, MF Press, J Crown, and On Behalf of the BCIRG-006 Investigators Slamon D. Ten year follow-up of the BCIRG-006 trial comparing ACT with ACTH with TCH in HER2+ early breast cancer patients. Paper presented at: San Antonio Breast Cancer Symposium2015; San Antonio.