CADTH

pan-Canadian Oncology Drug Review Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation (Sponsor)

Trastuzumab Emtansine (Kadcyla) for Early Breast Cancer

January 22, 2020

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	trastuzumab emtansine (T-DM1) (Kadcyla) for the adjuvant treatment of HER2-positive early breast cancer patients who have residual invasive disease following neoadjuvant taxane and trastuzumab-based treatment
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical Group):	Manufacturer
Organization Providing Feedback	Hoffmann-La Roche Ltd

**The pCODR program may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by the pCODR program.*

3.1 Comments on the Initial Recommendation

a) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the Initial Recommendation:

agrees	agrees in part	disagree

Hoffmann-La Roche Ltd. agrees with the initial recommendation of trastuzumab emtansine (T-DM1) (Kadcyla®) for the adjuvant treatment of HER2-positive early breast cancer patients who have residual invasive disease following preoperative systemic treatment, specifically neoadjuvant taxane and trastuzumab-based treatment as per the approved indication. Roche agrees that the KATHERINE trial demonstrated meaningful improvement in invasive disease-free survival (primary endpoint) and distant recurrence-free survival and that overall survival data is not yet mature. Roche agrees with pERC's support of 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. Roche also agrees with the pERC that the results from the KATHERINE trial are generalizable to male patients with breast cancer.

Roche suggests that iDFS has been validated in the literature, based on the March 2019 Lancet Oncology publication by Saad et al., provided in the submission, in which they state their analysis demonstrating surrogacy of DFS with OS includes a broad definition of DFS (including DFS and iDFS). This data in combination with the CGP's assertion that iDFS offers a more conservative definition (Hudis et al, 2007) supports the validation of this endpoint.

Roche agrees that T-DM1 has a manageable toxicity profile.

Roche agrees that T-DM1 aligns with patients values in that it reduces the risk of recurrence and that it is cost-effective based on ours and the EGP's reassessed estimate of the ICER.

Roche suggests that for those patients who would have otherwise been eligible for T-DM1 as per the KATHERINE trial but missed the opportunity, the decision to switch to T-DM1 for the remainder of their full course of adjuvant HER2-directed systemic therapy should be a decision made between the patient and their treating clinician.

The requirement in the KATHERINE trial to initiate T-DM1 as adjuvant therapy within 12 weeks of surgery was to ensure a more homogenous patient population. However, in the real world setting, patients may not initiate their adjuvant therapy within 12 weeks of surgery for many reasons, some which may not be clinically related (e.g. health services related). Therefore Roche does not recommend setting this as a criterion for reimbursement.

In summary, Roche supports early conversion of this initial recommendation to a final recommendation to expedite public access for T-DM1.

b) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the provisional algorithm:

agrees | agrees in part | disagree

N/A

c) Please provide editorial feedback on the Initial Recommendation to aid in clarity. Is the Initial Recommendation or are the components of the recommendation (e.g., clinical and economic evidence or provisional algorithm) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
4	Summary of pERC deliberations	3	Suggest removing "pERC agreed that T-DM1 is not reimbursed in the first-line metastatic setting and would not be used in that setting" (For example, please see current CCO Regimen Monograph KADC (March 2018) "Treatment of patients with HER2 positive, unresectable locally advanced or metastatic breast cancer, who have ECOG status ≤ 1, LVEF ≥ 50% and who received prior treatment with trastuzumab plus chemotherapy for metastatic disease, **or developed disease**

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
			recurrence during or within 6 months of completing adjuvant treatment with trastuzumab plus chemotherapy."
11	Appendix 1	Table Row 3	Suggest removing "pERC agreed that T-DM1 is not reimbursed in the first-line metastatic setting and would not be used in that setting" (For example, please see current CCO Regimen Monograph KADC (March 2018) "Treatment of patients with HER2 positive, unresectable locally advanced or metastatic breast cancer, who have ECOG status ≤ 1, LVEF ≥ 50% and who received prior treatment with trastuzumab plus chemotherapy for metastatic disease, **or developed disease recurrence during or within 6 months of completing adjuvant treatment with trastuzumab plus chemotherapy."**

3.2 Comments Related to Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the Stakeholder would support this Initial Recommendation proceeding to Final pERC Recommendation ("early conversion"), which would occur two (2) Business Days after the end of the feedback deadline date.

Support conversion to Final Recommendation.	Do not support conversion to Final Recommendation.
Recommendation does not require reconsideration by pERC.	Recommendation should be reconsidered by pERC.

If the eligible stakeholder does not support conversion to a Final Recommendation, please provide feedback on any issues not adequately addressed in the Initial Recommendation based on any information provided by the Stakeholder in the submission or as additional information during the review.

Please note that new evidence will be not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are providing is eligible for a Resubmission, please contact the pCODR program.

Additionally, if the eligible stakeholder supports early conversion to a Final Recommendation; however, the stakeholder has included substantive comments that requires further interpretation of the evidence, including the provisional algorithm, the criteria for early conversion will be deemed to have not been met and the Initial Recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information

1 About Stakeholder Feedback

pCODR invites eligible stakeholders to provide feedback and comments on the Initial Recommendation made by the pCODR Expert Review Committee (pERC), including the provisional algorithm. (See www.cadth.ca/pcodr for information regarding review status and feedback deadlines.)

As part of the pCODR review process, pERC makes an Initial Recommendation based on its review of the clinical benefit, patient values, economic evaluation and adoption feasibility for a drug. (See www.cadth.ca/pcodr for a description of the pCODR process.) The Initial Recommendation is then posted for feedback from eligible stakeholders. All eligible stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation. It should be noted that the Initial Recommendation, including the provisional algorithm may or may not change following a review of the feedback from stakeholders.

pERC welcomes comments and feedback from all eligible stakeholders with the expectation that even the most critical feedback be delivered respectfully and with civility.

A. Application of Early Conversion

The Stakeholder Feedback document poses two key questions:

1. **Does the stakeholder agree, agree in part, or disagree with the Initial Recommendation?**

   All eligible stakeholders are requested to indicate whether they agree, agree in part or disagrees with the Initial Recommendation, and to provide a rational for their response.

   Please note that if a stakeholder agrees, agrees in part or disagrees with the Initial Recommendation, the stakeholder can still support the recommendation proceeding to a Final Recommendation (i.e. early conversion).

2. **Does the stakeholder support the recommendation proceeding to a Final Recommendation ("early conversion")?**

   An efficient review process is one of pCODR's key guiding principles. If all eligible stakeholders support the Initial Recommendation proceeding to a Final Recommendation and that the criteria for early conversion as set out in the *pCODR Procedures* are met, the Final Recommendation will be posted on the CADTH website two (2) Business Days after the end of the feedback deadline date. This is called an "early conversion" of an Initial Recommendation to a Final Recommendation.

   For stakeholders who support early conversion, please note that if there are substantive comments on any of the key quadrants of the deliberative framework (e.g., differences in the interpretation of the evidence), including the provisional algorithm as part of the feasibility of adoption into the health system, the criteria for early conversion will be deemed to have **not** been met and the Initial Recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting. If the substantive comments relate specifically to the provisional algorithm, it will be shared with PAG for a reconsideration. Please note that if any one of the eligible stakeholders does not support the Initial Recommendation proceeding to a Final pERC Recommendation, pERC will review all feedback and comments received at a subsequent pERC meeting and reconsider the Initial Recommendation. Please also note that substantive comments on the provisional algorithm will preclude early conversion of the initial recommendation to a final recommendation.

B. Guidance on Scope of Feedback for Early Conversion

Information that is within scope of feedback for early conversion includes the identification of errors in the reporting or a lack of clarity in the information provided in the review documents. Based on the feedback received, pERC will consider revising the recommendation document, as appropriate and to provide clarity.

If a lack of clarity is noted, please provide suggestions to improve the clarity of the information in the Initial Recommendation. If the feedback can be addressed editorially this will done by the CADTH staff, in consultation with the pERC chair and pERC members, and may not require reconsideration at a subsequent pERC meeting. Similarly if the feedback relates specifically to the provisional algorithm and can be addressed editorially, CADTH staff will consult with the PAG chair and PAG members.

The Final pERC Recommendation will be made available to the participating federal, provincial and territorial ministries of health and provincial cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

2 Instructions for Providing Feedback

a) The following stakeholders are eligible to submit Feedback on the Initial Recommendation:
   - The Sponsor making the pCODR Submission, or the Manufacturer of the drug under review;
   - Patient groups who have provided input on the drug submission;
   - Registered clinician(s) who have provided input on the drug submission; and
   - The Provincial Advisory Group (PAG)

b) The following stakeholders are eligible to submit Feedback on the provisional algorithm:
   - The Sponsor making the pCODR Submission, or the Manufacturer of the drug under review;
   - Patient groups who have provided input on the drug submission;
   - Registered clinician(s) who have provided input on the drug submission; and
   - The Board of Directors of the Canadian Provincial Cancer Agencies

c) Feedback or comments must be based on the evidence that was considered by pERC in making the Initial Recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

d) The template for providing *Stakeholder Feedback on pERC Initial Recommendation* can be downloaded from the pCODR section of the CADTH website. (See www.cadth.ca/pcodr for a description of the pCODR process and supporting materials and templates.)

e) At this time, the template must be completed in English. The Stakeholder should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply.

f) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½" by 11" paper. If comments submitted exceed three pages, only the first three pages of feedback will be provided to the pERC for their consideration.

g) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the

recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the Initial Recommendation, and should not contain any language that could be considered disrespectful, inflammatory or could be found to violate applicable defamation law.

h) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR program.

i) The comments must be submitted via a Microsoft Word (not PDF) document to pCODR by the posted deadline date.

j) If you have any questions about the feedback process, please e-mail pcodrsubmissions@cadth.ca

Note: CADTH is committed to providing an open and transparent cancer drug review process and to the need to be accountable for its recommendations to patients and the public. Submitted feedback will be posted on the CADTH website (www.cadth.ca/pcodr). The submitted information in the feedback template will be made fully disclosable.