CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

(Manufacturer)

Pertuzumab and Trastuzumab for Early Breast Cancer

November 29, 2018

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Perjeta-Herceptin (pertuzumab-trastuzumab) Indication: for the adjuvant treatment of HER2-positive early breast cancer patients at high risk of recurrence
Eligible Stakeholder Role in Review (Submitter and/or Manufacturer, Patient Group, Clinical Organization Providing Feedback	Manufacturer 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 pCODR.*

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

	Please explain why the Stakeholder *agrees, agrees in part or disagrees with the Initial Recommendation. If the Stakeholder agrees in part or disagrees with the Initial Recommendation, please provide specific text from the recommendation and rational. Please also highlight the applicable pERC deliberative quadrants for each point of disagreement. The points are to be numbered in order of significance.* Hoffmann-La Roche (Roche) disagrees with the pERC initial recommendation concerning pertuzumab in combination with trastuzumab and chemotherapy for the treatment of HER2-positive early breast cancer (eBC) patients at high risk of recurrence as it is not in the best interest of patients, or the healthcare professionals who treat and manage these patients. Despite adjuvant treatment with trastuzumab plus standard chemotherapy, up to 1 in 4 HER2-positive eBC patients experience recurrence or death within 10-11 years of diagnosis.(1-3) Roche requests that the pERC reconsider its initial assessment of the value of pertuzumab in HER2-positive eBC patients who continue to have unmet need despite an excellent standard of care (SOC) based on the following: 1. There is a clinically meaningful net clinical benefit of pertuzumab in combination with trastuzumab and chemotherapy in patients with HER2-positive eBC at high risk of recurrence. APHINITY was the largest international, multi-centre, phase III double-blind, placebo-controlled randomised study conducted of pertuzumab+trastuzumab+chemotherapy as adjuvant treatment in almost 5,000 HER2-positive eBC patients.(4,5) This study's primary analysis was the first to improve upon the high bar set by the current SOC in this curative setting and to demonstrate statistically significant superiority over placebo+trastuzumab+chemotherapy in the intention-to-treat population (ITT).

	APHINITY was a positive trial as it met its primary outcome in the ITT population with a statistically significant invasive disease-free survival (IDFS) hazard ratio estimate demonstrating a 19% reduction in the risk of recurrence or death (primary analysis) (IDFS HR = 0.813; 95% CI, 0.664 to 0.995; P = 0.0446; two-sided alpha = 5%). In a situation where the ITT analysis is positive, it is appropriate to investigate the consistency of the primary analysis results across pre-specified subgroups. There is strong clinical and biological rationale to selectively request funding for HER2-positive eBC patients with lymph node positive disease. In eBC, including HER2-positive breast cancer, lymph node involvement is associated with poor prognosis.(2,6,7) Patients in this pre-defined subgroup derived even greater benefit from the addition of pertuzumab with an IDFS hazard ratio estimate that was lower than in the overall ITT population. On average, patients in this large lymph node positive subgroup (N=3,005) derived a 23% reduction in the risk of recurrence or death (IDFS HR = 0.768; 95% CI, 0.616 to 0.958). The pERC's assessment of clinical benefit is incongruent with the opinions of treating physicians and the CGP, which stated there is likely a clinically meaningful net overall clinical benefit among lymph node positive HER2-positive eBC patients based on pre-specified subgroup analyses. This position is further supported by recommendations in established clinical guidelines.(8,9,10) The pERC's assessment of clinical benefit is also incongruent with regulators, including FDA, EMA and Health Canada, which have thoroughly reviewed the evidence and provided full approvals in HER2-positive eBC patient subgroups at high risk of recurrence.(11,12,13) The lymph node positive and hormone receptor negative patient subgroups are included in the definition of high-risk patients in section 5.1 of the SmPC and form the basis of the Health Canada-approved indication.(11) The addition of pertuzumab to the SOC in this curative setting, before patients recur (i.e. become metastatic and palliative), is aligned with patient values as it provides an additional almost 25% reduction in the risk of recurrence or death, has a tolerable safety profile and is not associated with a significant detriment to QoL, as acknowledged by the pERC. 2. A proven difference in overall survival at the time of primary IDFS analysis is an unreasonable expectation. The significant gains achieved with the current SOC mean that HER2-positive eBC patients may relapse after many years and thus it takes longer to observe a large magnitude of IDFS or OS benefit with the addition of pertuzumab. As shown in the Table below, at the time of the primary analysis, the adjusted two-sided alpha level for the first OS interim analysis was <0.00001, with cumulative power of 0%. The next interim OS data analysis is planned for 2.5 years after the final IDFS analysis (2019). These interim OS data are also expected to be immature as the analysis will only have 17.4% power to detect a statistically significant difference between treatment arms (two-sided alpha level of 0.0027). Only the final OS analysis will have cumulative power of 80% (two-sided alpha level of 0.0453) to detect a OR hazard ratio of 0.8. This final OS analysis is event-driven once 640 study deaths have occurred, estimated to be 9-10 years after last patient randomized (i.e. 2023). Even with sufficient follow-up, the OS results may be confounded by post-trial therapies. Furthermore, pre-specified subgroup analyses will again be descriptive. Given that Canada is falling behind the international standard of care by not providing access to pertuzumab for HER2-positive eBC patients in the curative setting, Roche requests that the pERC consider time-limited reimbursement to allow access until more mature data are available. Table: Planned OS Analysis Timings

Analysis	Percent Information	Adjusted two-sided alpha level	Cumulative Power
1st - at IDFS final	26%	<0.00001	0%
2nd	49%	0.0027	17.4%
3rd	70%	0.0139	47.9%
4th	100%	0.0453	80%

3. Incremental cost-effectiveness ratios (ICERs) can be estimated

The pERC was unsure of the clinically meaningful net clinical benefit, concluded that ICERs could not be determined, and that it was not possible to draw a conclusion on cost-effectiveness. We disagree with the conclusion that there is no clinically meaningful net clinical benefit. This is not aligned with the results of APHINITY nor the conclusions of the CGP (see aforementioned response #1).

We also disagree with the pERC's conclusion that ICERs cannot be determined. In the context of cost-effectiveness, the EGP began their analysis with clinical considerations. They note, according to the CGP, that there is a likely small yet clinically meaningful net benefit in the lymph node positive population. The EGP did not conclude that ICERs could not be determined. The EGP did note five relevant issues and, after making adjustments, proceeded to estimate two ICERs. In this EGR, the EGP never made a conclusion that ICERs were not estimable. The EGP determined two ICERs: $75,904/QALY for lymph node positive and $112,487/QALY for hormone receptor negative patients, respectively. Thus, in the context of cost-effectiveness, Roche requests the pERC reconsider its conclusion that there is no clinically meaningful benefit and that ICERs cannot be determined.

References

1. Slamon D, Eiermann W, Robert N, al. e. 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.
2. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017;389(10075):1195–1205.
3. Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. J Clin Oncol. 2014;32(33):3744–3752.
4. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med. 2017;377(2):122–131.
5. von Minckwitz G, Procter M, de Azambuja E, et al. Supplement to: Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. 2017. http://www.nejm.org/doi/full/10.1056/NEJMoa1703643.
6. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011;365(14):1273–1283.

7. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. 2005;353(16):1659-1672.
8. Denduluri N, Chavez-MacGregor M, Telli ML, et al. Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Clinical Practice Guideline Focused Update. J Clin Oncol. 2018;36(23):2433-2443.
9. NCCN. Clinical Practice Guidelines in Oncology – Breast Cancer v.2.2018 – October 5, 2018. 2018.
10. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v8-30.
11. https://www.ema.europa.eu/medicines/human/EPAR/perjeta#overview-section. Accessed on October 16, 2018.
12. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125409s113s118lbl.pdf Accessed on October 16, 2018.
13. https://pdf.hres.ca/dpd_pm/00047103.PDF Accessed on October 16, 2018.

b) 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) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
Initial Rec P3	Summary of pERC Deliberations	Para 2, Line 7	"pERC noted that the pre-specified subgroup analyses for the primary outcome, IDFS, demonstrated a **marginally** statistically significant improvement in favour of pertuzumab and trastuzumab in the node-positive subgroup, but not in the hormone receptor-negative subgroup." Roche suggests correcting by removing the word "marginally" because an effect estimate is either statistically significant or it is not. A large magnitude of benefit was observed in patients who had node-positive disease (IDFS HR = 0.768; 95% CI, 0.616 to 0.958).
Initial Rec P6; CGP P4 & P19	Overall Clinical Benefit; Key Efficacy Results	Para 2, Line 1	"The trial met its primary outcome and **marginally** crossed the pre-specified statistical boundary for superiority (upper confidence limit is the null value of 1.00), demonstrating a statistically significant improvement in IDFS in the pertuzumab treatment group (hazard ratio [HR] 0.81; 95% confidence interval [CI], 0.66 to 1.00; P=0.045)."

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
			It is not possible to marginally cross a statistical boundary and the upper limit of the confidence interval (not rounded) was 0.995. Roche suggests correcting to "The trial met its primary outcome demonstrating a statistically significant improvement in IDFS in the pertuzumab treatment group (hazard ratio [HR] 0.81; 95% confidence interval [CI], 0.66 to 1.00; P=0.045)."
Initial Rec P5 and P6	Overall Clinical Benefit; Patient Populations	Title and Para 1, Line 4	Title - "...majority of patients with **HER2**-positive (64%) and node-positive (63%)" Para1 - "The majority of patients had **HER2**-positive (64%) and node-positive disease (63%)." All patients in the trial were HER2-positive. Roche suggests correcting both to "majority of patients with **HR**-positive (64%) ...".
Initial Rec P7	Overall Clinical Benefit; Patient-reported Outcomes	Para 1, Line 3	"Mean global health scores were -11.2 (95% CI, -12.2 to -10.2) and -10.2 (95% CI, -11.1 to -9.2) in the pertuzumab and placebo groups, respectively; no clinically significant difference in mean scores was observed between the groups." Roche suggests correcting to "Mean **change from baseline to the end of taxane treatment in** global health scores were …"
Initial Rec P10	Economic Evaluation; Cost-effectiveness estimates	Para 1	"The submitter's base case incremental cost-effectiveness ratios (ICERs) for the node-positive and hormone receptor-negative subgroups were lower than the EGP's reanalyzed ICERs. This was primarily due to the following factors:" Roche suggests correcting to: "The EGP's reanalyzed incremental cost-effectiveness ratios (ICERs) were higher than the submitter's base case ICERs for the node-positive and hormone receptor-negative subgroups. This was primarily due to the following factors:"
Initial Rec P10; EGR P10	Economic Evaluation; Cost-effectiveness estimates	Para 3, Line 4	"... and (2) the duration of treatment effect and not adjusting the utilities for age for the hormone receptor-negative subgroup." Roche suggests correcting to: "... and (2) the duration of treatment effect and treatment

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
			mix for the hormone receptor-negative subgroup." Utilities were age-adjusted.
Initial Rec P10; EGR P7, P8	Economic evaluation; Detailed highlights of EGP reanalysis		The CGP and the EGP decided that "all early recurrences within 18 months of initiating adjuvant therapy are metastatic" (Initial Rec P10); or "the submitter made the assumption that all early recurrences within 12 months of initiating adjuvant therapy would be metastatic. The CGP felt that this assumption was unreasonable and stated that an assumption of 18 months was more realistic" (EGR P7, P8). The correct interpretation is that a distinction is made in the model between non-metastatic and metastatic recurrences; and between early metastatic and other metastatic recurrences. The pERC, the CGP and the EGP assumed that early [metastatic] recurrences, which have poorer prognosis and thus are modelled differently, should be defined as all metastatic recurrences within 18 months of initiating adjuvant therapy, instead of the 12-month timeframe used in the base case.
Initial Rec P4 & P11	Adoption Feasibility	Para 1, Line 1	"The Committee agreed with the pCODR Provincial Advisory Group that the fact that pertuzumab is only available in a package that includes both pertuzumab and trastuzumab (Perjeta-Herceptin Combo Pack) is a barrier to implementation." Pertuzumab is available as DINs 02405016 and 02405024.

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. Recommendation does not require reconsideration by pERC.	☒	Do not support conversion to Final Recommendation. 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, 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). (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 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), 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. 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.

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 pCODR staff, in consultation with the pERC chair and pERC members, and may not require reconsideration at a subsequent pERC meeting.

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 Submitter 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) 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.

c) 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.)

d) 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.

e) 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.

f) 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.

g) 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.

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

i) 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.