PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Pertuzumab (Perjeta) for Metastatic Breast Cancer

August 1, 2013

INQUIRIES

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

pan-Canadian Oncology Drug Review
1 University Avenue, suite 300
Toronto, ON
M5J 2P1

Telephone: 416-673-8381
Fax: 416-915-9224
Email: info@pcodr.ca
Website: www.pcodr.ca

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Perjeta-Herceptin Combo Pack
Role in Review (Submitter and/or Manufacturer):	Submitter/Manufacturer
Organization Providing Feedback	Hoffmann-La Roche

**pCODR 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 Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ agrees X agrees in part ____ disagree

Hoffmann- La Roche fully supports the clinical criteria as outlined by the pERC. We would like to highlight the pERC statements that: "based on the results of the CLEOPATRA trial pERC considered that there was an overall net clinical benefit for pertuzumab". Additionally, "input from two patient advocacy groups indicated that patients with metastatic breast cancer valued treatments that extend overall survival and progression free survival in order to maintain the best possible quality of life. Therefore, pERC considered that the improvements in progression-free survival and overall survival demonstrated in the CLEOPATRA study align with patient values."

Roche considered supporting the conversion of the initial recommendation to a final recommendation in order to ensure that patients can get access to pertuzumab as quickly as possible. However, we are concerned with the lack of clinical rationale provided to support the economic modeling assumptions made by the EGP. In addition, we believe the methods and assumptions made by the EGP are flawed and as such, the value of pertuzumab is underestimated. We are concerned this will affect funding at the provincial level which could then delay patient access to pertuzumab. As such, we are asking for reconsideration based on economic (and subsequently clinical) terms. Additionally, we would like to correct and clarify the stability of trastuzumab and how it relates to wastage.

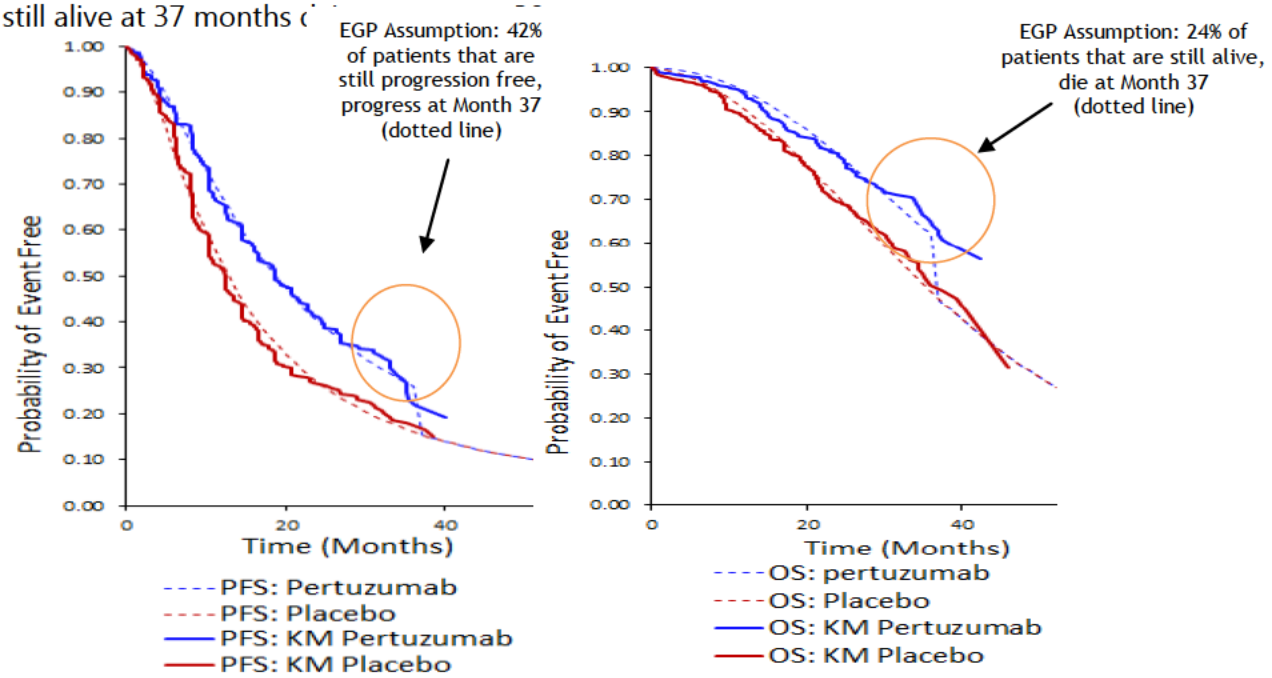
In order help facilitate our review of the recommendation, Roche requested that pCODR provide the specific EGP modifications to the Roche supplied pharmaco-economic model to better understand how the assumptions stated resulted in changes to the model. However, these were not provided by pCODR as it was considered "outside the scope of this feedback step, which is to focus on the pERC initial recommendation itself." Therefore, we attempted to reverse engineer the various outputs and analyses the EGP stated they conducted during their review of the economic evidence in order to identify how the model was adapted.

ICER Re-analysis #1

"As the clinical benefit may attenuate over time, particularly after discontinuation of treatment, this may be an optimistic assumption. The EGP removed the risk reduction from pertuzumab beyond the trial duration (37 months). In other words, after this time, patients in each group had equal risks of both progression and death."

Clinical Issues with Re-Analysis #1

The stated assumption was that patients in each group should have equal risks of both progression and death beyond the trial period. After multiple reverse engineering attempts, we believe that in order to make this assumption (and to achieve an ICER of $303K/QALY), the EGP assumed that the number of progression-free patients in the pertuzumab arm was immediately reduced to the same number of progression-free patients in the placebo arm. Similarly, we concluded that the EGP assumed that the number of patients still alive in the pertuzumab arm was immediately reduced to the number of patients still alive in the placebo arm. In other words, although the trial data showed that 26% of pertuzumab patients were still free of progression at the end of the trial period, the EGP assumption resulted in only 15% that were still progression free. Additionally, although 62% of patients were still alive beyond the trial period, the EGP assumption resulted in only 47% that were still alive (as seen in the figures below for PFS and OS). This is equivalent to 24% of patients who were still alive at 37 months c



The CADTH guidelines state that a possible modeling method is to create an "....immediate loss of treatment effect or survival curves converge after the end of the clinical study. This is *the most conservative option* of the three listed for an economic analysis. This option *may not be clinically relevant*, because the clinical effect of an outcome (final or surrogate) may not stop immediately after the end of a trial. If chosen as the base case, the clinical relevance must be justified." The EGP offered no clinical rationale for this assumption.

Should the EGP wish to demonstrate the cost-effectiveness of pertuzumab using the CADTH definition of *the most conservative option*, it would have been more appropriate to remove the

treatment effect immediately following the trial duration by giving both treatment arms the same transition probabilities of progression and death. Although this assumption *would still require adequate clinical rationale and is considered the most conservative approach*, it is deemed more appropriate than the EGP's assumption of a large group of patients immediately progressing and dying, following the trial duration. The transition probabilities for PFS and OS are very similar post trial period. As such, this resulted in an ICER of $245,253/QALY, which is very similar to our submitted base case of $238,014/QALY.

Questions for CGP and pERC consideration:

a) **Is it clinically reasonable to assume that 42% of patients that were still progression free will progress right at the end of the trial period?**

b) **Is it clinically reasonable to assume that 24% of patients who were still alive will die right at the end of the trial period?**

If these assumptions are not clinically plausible, the calculated ICER of $303K/QALY is not a realistic or plausible ICER and therefore should not be included in the recommendation.

ICER Re-analysis #2

"In the submitted model, it was assumed there was a carry-over benefit from pertuzumab in post-progression survival. However, there is no direct support for post-progression survival gain from pertuzumab in the clinical trial data…. Therefore the EGP considered it most appropriate to exclude any carry-over benefits in the model, and reanalyzed the model with equal risk of death from progressed disease in both treatment groups."

Clinical Issues with Re-Analysis #2

In the review, it was acknowledged that although there is a lack of evidence, the pERC "recognized that it may be clinically plausible for a carry-over benefit of pertuzumab once treatment is stopped". Additionally, the CGP "considered a carry-over effect possible from a clinical perspective." This suggests that a reasonable estimate of the ICERs includes a scenario where there is some carryover effect and it should therefore be considered part of the range of plausible values.

Question for pERC consideration:

Is a carry-over benefit considered a clinically plausible scenario?

If this is a clinically plausible scenario, then the manufacturer submitted ICER of $238, 014/ QALY should be included in the recommendation.

Economic Issues with Re-Analysis #2

We conclude that the EGP only included the placebo arm in re-calculating the benefit post progression. A more appropriate approach would be to include a pooled benefit of patients in both the placebo and pertuzumab arm. We believe this is more appropriate as the post progression data of pertuzumab patients was collected, and as such, should not be totally removed from the analysis.

By using the pooled data, we calculated an ICER of $254,027/QALY.

Question for pERC consideration:

Is it clinically reasonable to assume that the data collected post progression for pertuzumab patients is incorrect and should not be included in the analysis?

If this is not a reasonable assumption, please consider the pooled analysis of post progression survival ICER of $254,027/QALY (instead of $262,263/QALY).

In summary, we believe that the stated ICER of $303,726/QALY is based on unrealistic clinical assumptions and may have been calculated incorrectly. Although still considered a conservative approach, a more reasonable estimate, based on the assumption that the risks of progression and death are similar beyond the trial period, results in an ICER of $245,253/QALY. Additionally, as the CGP and pERC agree that there is a clinical possibility of post progression survival, the submitted ICER of $238,014/QALY should be included as a reasonable estimate of the cost-effectiveness of pertuzumab.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

____ Support conversion to final recommendation.
Recommendation does not require reconsideration by pERC.

X Do not support conversion to final recommendation.
Recommendation should be reconsidered by pERC.

c) Please provide feedback on the initial recommendation. 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
5	**Drug costs: potential for drug wastage due to packaging of pertuzumab with trastuzumab**		"The pack includes one 420 mg vial of pertuzumab and one 440 mg vial of trastuzumab, that once reconstituted is stable for approximately 24 hours." As per the Canadian product monograph, "a vial of trastuzumab reconstituted with BWFI, containing 1.1% benzyl alcohol, as supplied, is stable for 28 days after reconstitution when stored refrigerated at 2°C -8°C, and the solution is preserved for multiple use." As such, these vials can either be used for the same patient on

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
			their next visit or another patient (adjuvant or metastatic) within the 28 days, minimizing any wastage. In practice, it is common practice for hospitals to "vial share" Herceptin and have "Herceptin days" where all patients (adjuvant and metastatic) are treated at the same time to reduce any wastage. Also note that per the Canadian product monograph, trastuzumab diluted in infusion bags containing 0.9% Sodium Chloride Injection, has been shown to be stable for up to 24 hours at temperatures up to 30°C prior to use. In clinical practice, trastuzumab solution would be diluted into infusion bags just prior to use. Therefore, wastage at this point would be expected to be minimal. Additionally, in a study presented at CADTH 2012 (Bugden - CADTH 2012), wastage of chemotherapy drugs was assessed in Manitoba. It was found that trastuzumab had the lowest percentage wastage of any IV oncology drug at only 0.4%. This is expected to be the same with the introduction of the Perjeta™-Herceptin® Combo Pack. Therefore, please correct the stability information provided in the pERC recommendation document (page 5) and the associated implications as part of the statement in the recommendation (page 1).
5		Last Paragraph	"For the first 28-day course, which includes the recommended loading dose and assumes a patient weight of 70 kg, the average daily cost is $128 and the average cost per 28-day course is $3,597. For subsequent 28-day courses, the average daily cost is $225 and the average cost per 28-day course is $6,295. " Please note that the daily and 28-day course costs are reversed between the loading and maintenance doses.

3.2 Comments Related to Submitter or Manufacturer-Provided Information

Please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the Submitter (or the Manufacturer of the drug under review, if not the Submitter) 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 Secretariat.

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments

About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.pcodr.ca for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.pcodr.ca for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

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

1 Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

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 *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.pcodr.ca for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) 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. Similarly, the Submitter (or the Manufacturer of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

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 forwarded to the pERC.

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 Secretariat.

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

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.