pan-Canadian Oncology Drug Review

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

Pertuzumab (Perjeta) Neoadjuvant Breast Cancer

July 16, 2015

INQUIRIES

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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 ____ agrees in part X disagree

Hoffmann-La Roche is disappointed with the initial recommendation from pERC as we believe pERC did not look at the totality of evidence to support the use of pertuzumab in the neo-adjuvant setting. As such, we ask that pERC reconsider their initial recommendation based on the following points and allow patients access in this area of high unmet need.

pCR as a valid endpoint

pCR Issue #1- Trial Level Correlation

pERC Statement: *"pERC acknowledged that at an individual level, patients with breast cancer who receive neoadjuvant treatment and who obtain a pCR have longer event-free survival and overall survival than patients who do not obtain a pCR. However, the committee noted that the meta-analysis indicated that differences in the frequency of pCR were not associated with improvements in event-free survival or overall survival at the trial level. That is, pCR cannot be reliably used in a trial to detect improvements in event-free survival or overall survival when comparing different treatments."*

Although, the meta-analysis was only able to find a patient-level correlation, the authors propose four potential explanations for the findings and then conclude the following based on their analysis;

- *"In view of the substantial improvements in survival for individual patients who attain pathological complete response, we believe that if a novel agent produces a marked absolute increase in frequency of pathological complete response compared with standard therapy alone in the intention-to-treat population, that agent* ***could also be reasonably likely to result in long-term improvements in EFS or OS.****"*

While there is no conclusive evidence of a link between pCR and long-term outcomes at a trial level, the meta-analysis author's conclusions state that it could be reasonably likely if there is a marked absolute increase in frequency of pathological complete response. Given that there is a significant unmet need for patients with high risk HER2+ locally advanced, inflammatory, or early stage breast cancer (>2 cm in diameter or node positive) and it is reasonably likely that it will significantly improve patient's survival (with an acceptable safety profile), the addition of pertuzumab is a valuable option for patients.

pCR Issue #2 – Patient Level Correlation

The meta-analysis states: *"The difference between patient-level analyses and trial-level analyses is a common source of confusion. Patient-level analyses, sometimes referred to as responder analyses, compare the clinical outcome of patients with and without pathological complete response, irrespective of the treatment group. These analyses are meaningful as* ***they predict improved survival for patients who attain pathological complete response****. Because these responder analyses are independent of the treatment group, they are not useful for comparisons of treatments at a trial level."*

The meta-analysis found a patient-level correlation which can "*predict improved survival for patients who attain pathological complete response.*" As such, it would be reasonable to assume that by increasing an individual patient's chance to achieve pCR through the use of pertuzumab, it will, in effect, increases that patient's individual chances of improved survival.

pCR issue #3- Use of other trials as evidence

pERC Statement: *"pERC noted that the NeoALTTO study demonstrated that patients with a pCR had longer overall survival and event-free survival compared with patients without a pCR similar to the Cortazar meta-analysis; however, the trial did not provide evidence that an improvement in the frequency of pCR is associated with an improvement in event-free survival or overall survival."*

The manufacturer does not think the NeoALTTO study is appropriate to evaluate the link between pCR and long-term outcomes. The study was not powered to detect differences in EFS and OS, and therefore, is not designed to show *"evidence that an improvement in the frequency of pCR is associated with an improvement in event-free survival or overall survival."* Furthermore, lapatinib added to trastuzumab (unlike pertuzumab added to trastuzumab), did not demonstrate an overall survival benefit in the metastatic setting. In addition, the ALTTO trial had notable trial design issues that may have resulted in the lack of long-term benefit that was previously suggested by NeoALTTO, such as under powering and increased toxicity which led to "*a significant percentage of patients who did not complete their assigned duration of adjuvant lapatanib*" (Sledge G., The Cancer Letter. 2014; Vol. 40 No.28). Lastly, a recent commentary with regards to NeoALLTO/ALLTO states that "these observations support the relationship between pCR and EFS in the FDA's meta-analyisis. The pCR and EFS results in in NEoALLTO and ALLTO certainly provide no evidence to challenge that relationship." (Berry D., The Cancer Letter. 2014; Vol. 40 No.28).

For comparison, it would be more prudent to use a neo-adjuvant trial that was powered to show a benefit in pCR and EFS and use a drug with a proven overall survival benefit in the metastatic and adjuvant setting. Therefore, a more appropriate comparison would have been trastuzumab which has demonstrated a comparable long-term clinical benefit in both the metastatic and neo-adjuvant (NOAH Trial) settings as seen in the following chart:

mBC Clinical Benefit	Neo-adjuvant Clinical Benefit
Trastuzumab	
OS HR 0.80 (p=0.046) TTP HR 0.51 (p<0.001)	Δ17.6% bpCR, Δ19.3% tpCR EFS HR 0.64 (95% CI, 0.44-0.93 p=0.016)
Pertuzumab	
OS HR 0.68 (p<0.001) PFS HR 0.62 (p<0.001)	Δ16.8% bpCR, Δ17.8% tpCR DFS HR 0.60 (95% CI, 0.28-1.27)

The NOAH trial provides further evidence on the relationship between pCR and long-term outcomes. As well, the similarities in data between trastuzumab and pertuzumab in the metastatic and neo-adjuvant settings provide additional evidence that pertuzumab is a valuable option for patients.

Disease-Free Survival and Progression-Free Survival Data

Roche provided updated disease-free survival and progression-free survival data to pCODR during the review. However, these data were not mentioned in the initial recommendation and the recommendation mentioned a "lack of survival data", so it is unclear if pERC discussed these data. The presentation at ASCO 2015 concludes that "Longer-term outcomes as defined by three-year survival rates, are in-line with the results of the primary endpoint (bpCR), **suggesting a benefit of P added to T+D that persists over time despite use of identical adjuvant therapy in the P+T+D and T+D arms**. **These results also support the association between pCR and improvements in long-term outcomes."** (Gianni L. et al., Five-year analysis of the phase II NeoSphere trial evaluating four cycles of neoadjuvant docetaxel (D) and/or trastuzumab (T) and/or pertuzumab (P), J Clin Oncol 33:5s, 2015 (suppl; abstr 505))

The long term disease-free and progression-free survival data suggest a benefit of adding pertuzumab in the neo-adjuvant setting.

Guidance on pCR and pertuzumab in the neo-adjuvant setting

Current Guidance on the use of pCR for regulatory approval

The FDA guidance states, "Since the release of the draft version of this guidance in May 2012, the FDA has participated in public discussions regarding this pathway for drug development. In March 2013, the FDA and the American Society of Clinical Oncology co-sponsored a public neoadjuvant breast cancer workshop with an international panel of breast cancer experts seeking to discuss the use of pCR to support accelerated approval. The panel **concluded that a large improvement in pCR rate based upon analysis of a full intent-to-treat population was reasonably likely to predict clinical benefit, and that the potential advantages of granting accelerated approval based upon pCR from a neoadjuvant randomized controlled trial generally outweighed concerns.** The panel emphasized that such trials should be limited to high-risk patients, and that a confirmatory trial should be ongoing at the time of accelerated approval."

Additionally, this notion of high-risk patients (those with aggressive tumour subtypes) showing the strongest association between pCR and EFS is also endorsed by the European Medicines Agency (EMA). EMA's guidelines, published in March 2014 and titled "The role of the pathological Complete Response as an endpoint in neoadjuvant breast cancer studies," stipulate that: "… approval based on pCR may be acceptable for patients with aggressive (high-risk) early stage breast cancer as add-on to an established (neo) adjuvant regimen, if there is a well characterised mechanism of action and provided the results show major increase in pCR with only minor changes in toxicity. Such results may lead to an approval with agreed conditions for confirmatory study data in terms of DFS/OS."

Regulatory agencies have concluded that a large improvement in pCR was reasonably likely to predict clinical benefit and the potential benefits generally outweigh the risk. This is especially true for drugs with a well characterized mode of action and minor changes in toxicity and for patients with aggressive early stage breast cancer.

Current Guidance on the use of pertuzumab in the neo-adjuvant setting

With regards to pertuzumab in this setting, the FDA guidance states, "The first supplemental biologics license application for a neoadjuvant breast cancer indication has also been submitted. This application was discussed at the September 5, 2013, meeting of the Oncologic Drugs Advisory Committee (ODAC), **whose members ultimately voted**

unanimously, with one abstention, in favor of approval. The application was recently granted accelerated approval. The favorable review of the application, both by ODAC and the FDA, **was based upon the robustness of the development program and the totality of the evidence. This included not only the absolute improvement in pCR rate in the intent-to-treat population, but importantly a statistically and clinically significant effect on OS in the metastatic setting, an extensive body of safety data from treatment of several thousand breast cancer patients, and a fully accrued adjuvant confirmatory trial.**"

Additionally, while there are currently no updated Canadian guidelines for the optimal use of neo-adjuvant therapies for HER2+ early stage breast cancer, there is one review article of pertuzumab by Canadian clinicians which concludes for neo-adjuvant use "**Until further data are available, pertuzumab use as a component of neoadjuvant treatment has received temporary approval in some jurisdictions, and its use appears reasonable.**" (Lamond NW, Younis T. Pertuzumab in human epidermal growth-factor receptor 2-positive breast cancer: clinical and economic considerations. Int J Womens Health. 31 2014; 6:509-21) As well, based on available evidence, the National Comprehensive Cancer Network (NCCN) guidelines **include the use of pertuzumab in combination with trastuzumab and chemotherapy, for pre-operative (neoadjuvant) treatment of HER2-positive breast cancer patients."** (NCCN clinical practice guidelines in oncology: Breast cancer. V3. 2014.)

Current guidance from the Oncologic Drugs Advisory Committee and the National Comprehensive Cancer Network (NCCN) guidelines are in favour of the use of pertuzumab in the neo-adjuvant setting while a Canadian review article concludes that its use appears reasonable based on available data.

Conclusion

We ask that pERC re-assess pertuzumab in the neo-adjuvant setting through a broader lens than just *"pCR has not validated as a surrogate outcome for either event-free survival or overall survival"* and provide a recommendation based on the totality of evidence about pCR and pertuzumab.

The totality of evidence includes an unprecedented benefit in the metastatic setting, similar toxicity profile with or without pertuzumab, a substantial increase in pCR and a strong trend in long term outcomes. These demonstrate that pertuzumab provides a net overall benefit to patients with high risk HER2+ locally advanced, inflammatory, or early stage breast cancer (>2 cm in diameter or node positive). This is supported by the statements noted above from the clinical trial investigators, Cortazar et al. meta-analysis, FDA/EMEA guidelines, ODAC committee, NCCN guidelines and a Canadian review paper.

If pERC provides a positive recommendation and allows patients access to pertuzumab in the neo-adjuvant setting, Roche would be willing to reduce the uncertainty by supporting provincial evidence building programs to collect longer term data and/or conditional funding until APHINITY (which is fully accrued) reports.

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.	X	Do not support conversion to final recommendation.
	Recommendation does not require reconsideration by pERC.		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	Comments and Suggested Changes to Improve Clarity
8	Cost-effectiveness estimates: pERC unable to determine the incremental cost-effectiveness ratio	The model was based on the EFS and OS data partitioned for patients achieving or not achieving pCR in the population of interest from both Cortazar et al. and Kim et al. These publications found a clear link between pCR and long term outcomes at an individual level. Therefore, the major underlying assumption of the model is that a patient who achieves a pCR will have better long term outcomes. In addition, as noted above, the meta-analysis states "*we believe that if a novel agent produces a marked absolute increase in frequency of pathological complete response compared with standard therapy alone in the intention-to-treat population, that agent could also be reasonably likely to result in long-term improvements in EFS or OS."* Therefore, it could be reasonably likely to associate the improvement in pCR with long term outcomes. As well, the EGP stated that "*unpublished data provided by the submitter demonstrated that the favourable effect of pertuzumab trastuzumab and docetaxel versus trastuzumab and docetaxel only, on pCR can also be observed on 3-year progression free survival (90% vs. 86% HR:0.69 CI 0.34-1.40), although not statistically significant. The 3 year progression free survival estimates from the partition survival model for both treatment options were 87% and 84% (HR:0.84) indicating that the observed treatment effects on progression free survival might be greater than the one observed through the submitted model.*" This data has now been presented at ASCO and concluded "*Longer-term outcomes as defined by three-year survival rates, are in-line with the results of the primary endpoint (bpCR), suggesting a benefit of P added to T+D that persists over time despite use of identical adjuvant therapy in the P+T+D and T+D arms. These results also support the association between pCR and improvements in long-term outcomes."* Lastly, the cost-effectiveness model has been published in a peer-reviewed journal demonstrating results similar to those found by the EGP. (Attard C.L. et al., Cost-effectiveness analysis of neoadjuvant pertuzumab and trastuzumab therapy for locally advanced, inflammatory, or early HER2-positive breast cancer in Canada. Journal of Medical Economics, 2015 Mar;18(3):173-88) Given all this evidence, we believe that pertuzumab in combination with trastuzumab and chemotherapy is a cost-effective regimen in the neo-adjuvant setting.
Page 9	Considerations for implementation and budget impact	The pERC states *"The submitted BIA had several limitations including the lack of province-specific epidemiological inputs."* Although not required by pCODR, Roche did provide province-specific epidemiological inputs. Please see tabs labelled "incidence data" and "BC stages" for these data.
		The pERC states *"The submitted BIA had several limitations including….the absence of an assumption on future generic substitution."* Roche does not understand what assumption pERC was referring to as there will never be a "generic pertuzumab." If

Page Number	Section Title	Comments and Suggested Changes to Improve Clarity
		pERC was referring to subsequent entry biologics, there is not expected to be a subsequent entry biologic of pertuzumab in the three years included in the budget impact model. As well, Health Canada has indicated that the authorization of a subsequent entry biologic is not a declaration of pharmaceutical or therapeutic equivalence to the reference biologic drug and does not support automatic substitution of an SEB for its reference biologic drug.

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

1 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.cadth.ca/pcodr 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.cadth.ca/pcodr 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.

2 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.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 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.