CADTH

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

Neratinib (Nerlynx) for Early Breast Cancer

Canadian Breast Cancer Network

December 5, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Neratinib/Nerlynx
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical Organization Providing Feedback	Patient Group Canadian Breast Cancer Network

**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

The Canadian Breast Cancer Network (CBCN) does not agree with the analysis put forth by the initial recommendation.

We raise concerns regarding the section which states *"pERC could not ignore the high level of uncertainty around the magnitude of the IDFS benefit given the treatment effect was estimated based on a subgroup analysis that was not pre-specified and exploratory in nature, as well as the limitations of the trial related to numerous protocol amendments, and the lack of OS data to confirm clinical benefit."* We would like to emphasize that this therapy is intended to treat a small population of patients at greater risk for recurrence and who have undergone treatment with numerous other agents including adjuvant treatment with trastuzumab. Due to these factors, it is understandable that adaptations may have been required to the clinical trial and that patient enrollment in the trials would have been limited.

Furthermore, we note that neratinib was approved by NICE in the UK with the same clinical trial data as an extended adjuvant therapy for patients upon completion of standard HER2 therapy. We believe that it is imperative that Canadian breast cancer patients are receiving treatment and care that is in alignment with our global counterparts.

Secondly, we are concerned about the section which states **"***pERC discussed the factors that could impact the feasibility of implementing a positive reimbursement recommendation for neratinib and noted that neratinib is expected to be an additional therapy in the adjuvant treatment of patients with HER2-positive, HR-positive early breast cancer."* CBCN disagrees with the assessment that neratinib would be an additional therapy in the adjuvant treatment of patients. Currently in Canada, there are no other therapeutic options approved and accessible to patients in this space following treatment with

trastuzumab. The primary goal of treatment for breast cancer patients and their physicians is to reduce the risk of recurrence and neratinib would provide patients and their physicians with an additional tool in their arsenal to address this unmet need for treatment options for patients with early breast cancer. It should also be noted that the patients most likely to benefit from treatment with neratinib would be those at greatest risk of recurrence and relapse and CBCN believes that clinicians should be given the option to assess which patients would be most likely to benefit from this therapy and to be able to treat them accordingly. As such in actual clinical practice the patient population that clinicians would be treating with neratinib would likely be much smaller than the perc recommendation predicts.

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

☐ agrees ☐ agrees in part ☐ disagree

unclear

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

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, 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.

CADTH

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

Neratinib (Nerlynx) for Early Breast Cancer

Canadian Organization for Rare Disorders

December 5, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Nerlynx for HER2+ Breast cancer_____
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical	Patient Group
Organization Providing Feedback	Canadian Organization for Rare Disorders

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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.*

"In reaching this conclusion pERC could not ignore the high level of uncertainty around the magnitude of the IDFS benefit given the treatment effect was estimated based on a subgroup analysis that was not pre-specified and exploratory in nature, as well as the limitations of the trial related to numerous protocol amendments, and the lack of OS data to confirm clinical benefit/"

b) Based on feedback from the patients represented in our submission, the Canadian Organization for Rare Disorders offers the highest condemnation of this recommendation as fundamentally counter to the best interests and the wishes of the patients. We put forward three key objections.

c) First, it is not clear what is meant by a "high level of uncertainty"; is pCODR able to quantify this and to comment on what is considered to be "high" enough to warrant rejection? Or is this a subjective judgment without an objective basis? We acknowledge that a neoadjuvant therapy that is intended to prevent tumour recurrence and to extend life is inherently challenging to assess. It cannot be expected that the clinical trials and indeed data based on real-world use would yield clear short-term outcomes based on objective performance measures. Moreover, given the fact that the therapy is intended for a small subset of patients who are at

the highest risk for recurrence and indeed have experienced almost every other form of treatment, including trastuzumab adjuvant therapy, it is not surprising that the number of patients in the clinical trials would be small and indeed the inclusion/exclusion criteria, trial design and protocol may have required adaptation as new information emerged.

d) Second, we do not accept pERC's rejection of the outcomes as not clinically meaningful and based on post hoc analysis. We do not agree that the results (difference in IDFS) are insignificant in magnitude nor biased because the analysis were based on post hoc subgroups. While we do not have access to the final NOC from Health Canada, we understand that Health Canada recognized the differences in IDFS as significant and they offered no concerns with regard to the trial design and subgroup analysis.

e) Consistent with our view, we note that NICE in the UK accepted the same clinical trial data without reservation, stating that neratinib reduced risk of cancer recurrence after trastuzumab, and was approved as extended adjuvant treatment in people who completed a standard course of HER2 standard adjuvant therapy. We do not see the pERC justification (citing of evidence) that warrant this interpretation and subsequent recommendation.

f) Rejection based on other neoadjuvant therapies

Third, patients and clinicians agreed that having access to another adjuvant therapy was an important option. In Canada, there are no other options, with pertuzumab not available and future therapies also not available at this time. For breast cancer patients, the primary goal is to reduce the risk of recurrence and to that end willingly endure many types of therapies with tremendous challenges and many adverse effects. Almost all HER2 positive patients will undertake an additional year of adjuvant therapy (trastuzumab) in the hopes of reducing risk of recurrence. While not all patients would choose to have an additional therapy, it should be available as an option to those who do want that additional protection, despite the side effects. Neratinib is demonstrated to reduce the risk of recurrence and to deny those who have endured all other treatments one additional form of protection is cruel and unconscionable

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

☐ agrees ☐ agrees in part ☐ disagree

Please explain why the Stakeholder *agrees, agrees in part or disagrees with the provisional algorithm. Please note that comments should relate* ***only to the proposed place in therapy of the drug under review*** *in the provisional algorithm. If feedback includes New Information or about other therapies that are included in the provisional algorithm, the information will not be considered and will be redacted from the posted feedback. Substantive comments on the provisional algorithm will preclude early conversion of the initial recommendation to a final recommendation.*

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