CADTH

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

Neratinib (Nerlynx) for Early Breast Cancer

December 5, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Neratinib (Nerlynx) for Early Breast Cancer
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical	Sponsor
Organization Providing Feedback	Knight Therapeutics Inc.

**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 Sponsor is concerned that misinterpretation of evidence related to the reimbursement request and disregard for important points reported in the clinical guidance report may have led to an erroneous conclusion by pERC. Primary concerns in order of importance: statements regarding the establishment of the subgroup which comprises the indicated patient population; the presumptive suggestion that pertuzumab and T-DM1 in neoadjuvant and adjuvant treatment minimize neratinib's clinical value or affect its adoption feasibility; mischaracterization of protocol amendments; and the validity and importance of the pivotal trial's primary endpoint to inform pERC's decision-making and the generalizability of the trial's results.

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

☐ agrees ☐ agrees in part ☐ disagree

As the submission was made before the formal use of provisional algorithms in pCODR's process, this section is not applicable.

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
3 8	SUMMARY OF pERC DELIBERATIONS AND KEY EFFICACY RESULTS: MODEST DIFFERENCE IN IDFS IN FAVOUR OF NERATINIB; POST-HOC EXPLORATORY SUBGROUP ANALYSIS	Page 3, Para 2 Lines 10-12 **Comment:** "… pERC discussed that there was a very high-level of uncertainty around the magnitude of the IDFS benefit considering that the subgroup analysis was not pre-specified in the trial protocol and it was a post-hoc exploratory analysis of the ExteNET trial data." Page 8, Para 2 Lines 5-6	**Sponsor:** i) Neratinib demonstrated a clinically significant and statistically significant improvement in iDFS in the ITT population. Results were consistent at both 2 and 5-years. ii) HR status and time from completion of trastuzumab were in fact pre-specified analyses and subjects were stratified by HR status. The label population accounts for 47% of the ITT cohort. iii) In the pre-specified HR+ subgroup, the absolute treatment difference at 2- and 5-years was 4.1% and 4.4%, with hazard ratios of HR 0.49; 95% CI, 0.31-0.75) and 0.60 (95% CI: 0.43, 0.83) respectively. iv) The two-sided p-value for the interaction test for HR status in the primary analysis was 0.045, strongly suggesting that HR status is an effect modifier (CSR section 11.4.8.1). v) The subgroup data are further supported by biological rationale (i.e. hormone receptor cross-talk [1, 2]. Multiple clinical studies across a variety of HER2-targeted agents have demonstrated favourable outcomes in HR+ EBC patients [3, 4]. vi) Critically, the label population is consistent with the Health Canada indication and it would not have been possible to request a broader indication. The label population reflects how neratinib is likely to be used in practice.
3	SUMMARY OF pERC DELIBERATIONS	Para 2 Lines 19-21 **Comment:** "numerous protocol amendments that occurred … added to the	**Sponsor**: There were 3 major protocol amendments (Amendments 3, 9, and 13). All other changes were related to translations of documents. Despite the changes in study sponsorship and protocol amendments, the study is credible for the following reasons: **i)** A single CRO ran the study from beginning to end and all operational

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
		uncertainty in determining the magnitude of clinical benefit of neratinib"	aspects remained consistent throughout the study, which maintained the integrity of the study. ii) The protocol amendments were not made based on an early look at the data (the study was unblinded for the primary 2-year analysis in July 2014 but death events remained blinded). iii) Consistent with the other operational aspects of the trial, the IDMC and monitoring plan remained unchanged throughout. Lastly, the CGP report affirmed that "these changes were based on external information and therefore unlikely to have an impact on the control of type-I error rate" (sec 1.2.1 Systematic Review Evidence). To suggest the "numerous" protocol amendments would impact the magnitude of clinical benefit of neratinib or undermine its credibility is not supported.
9	OVERALL CLINICAL BENEFIT; Registered clinician input: Neratinib best offered to higher risk patients; benefits of trastuzumab emtansine more clinically meaningful in this setting with less toxicity	Para 1 Lines 12-15 **Comment:** "Clinicians also stated a preference for the use of trastuzumab emtansine following neoadjuvant treatment … of trastuzumab emtansine as more favourable."	**Sponsor:** Neoadjuvant treatment is still only offered to a minority of patients. It is therefore inaccurate to assume that T-DM1 will obviate the need for extended adjuvant therapy, given the fact that many patients are receiving trastuzumab-based adjuvant therapy. It would be inappropriate for patients who have been or are currently receiving trastuzumab-based adjuvant treatment to also receive T-DM1 adjuvant therapy. This better aligns with pERC's assertion on Pg. 4, Para 2; Line 3 "pERC acknowledges neratinib is the only treatment option available as extended adjuvant treatment."
4	SUMMARY OF pERC DELIBERATIONS	Para 2 Lines 5-7 **Comment:**	**Sponsor:** The reduced risk of disease recurrence in the label population has been accepted by regulators and HTA

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		"pERC was unsure whether neratinib adequately addresses the outcomes considered important to patients including reducing the risk of recurrence, maintenance of HRQoL, and minimal side effects."	agencies across the world, based on the information provided in response to the first point, regarding the validity of the label population. Quality of life for both treatment arms of ExteNET declined in the first month, but not by clinically meaningful levels, and both arms demonstrated similar QoL results for the remainder of the study. The CONTROL study demonstrates that with prophylaxis, the incidence, duration and total episodes of diarrhea can be reduced, and tolerability and treatment discontinuation improved. Diarrhea prophylaxis features in the product monograph (s3.1). In addition, neratinib is not associated with long-term or serious adverse events common to other HER2-targeted therapies, especially cardiac-related toxicities. In the same section, pERC acknowledges that "…patient input indicated patients value that neratinib is an oral treatment and are willing to accept the pill burden associated with neratinib treatment."
4	SUMMARY OF pERC DELIBERATIONS	Para 3 Lines 7-8 **Comment:** "the lack of OS data to confirm clinical benefit"	**Sponsor:** iDFS is a frequently-used and accepted endpoint in adjuvant early breast cancer because it is challenging to demonstrate OS benefit in this setting. The FDA has supported iDFS as an acceptable surrogate endpoint in the adjuvant setting.

References

1. Alameddine, R.S., et al., *Crosstalk between HER2 signaling and angiogenesis in breast cancer: molecular basis, clinical applications and challenges*. Curr Opin Oncol, 2013. **25**(3): p. 313-24.
2. Arpino, G., et al., *Crosstalk between the estrogen receptor and the HER tyrosine kinase receptor family: molecular mechanism and clinical implications for endocrine therapy resistance*. Endocr Rev, 2008. **29**(2): p. 217-33.
3. Cameron, D., 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): p. 1195-1205.
4. Perez, E.A., 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): p. 3744-52.

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.