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PAN-CANADIAN  
ONCOLOGY DRUG REVIEW

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

## **Abemaciclib (Verzenio) for Metastatic Breast Cancer**

July 5, 2019

## Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s): VERZENIO™ (abemaciclib) for advanced or metastatic breast cancer

Eligible Stakeholder Role in Review Manufacturer

Organization Providing Feedback Eli Lilly Canada 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 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

Lilly Canada (Lilly) appreciates the opportunity to provide feedback to pCODR on pERC's initial recommendation for VERZENIO™ (abemaciclib).

We agree with pERC's initial recommendation for abemaciclib in the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with fulvestrant in women with disease progression following endocrine therapy and respectfully request that such initial recommendation be maintained in pERC's final recommendation.

However, we **disagree** with the initial recommendation that abemaciclib, in combination with a non-steroidal aromatase inhibitor (NSAI), be restricted to use in those patients who are unable to tolerate or have a contraindication to other available CDK 4/6 inhibitors. Using pERC's deliberative framework - in particular, overall clinical benefit and patient-based values - Lilly respectfully requests a revised recommendation that grants abemaciclib parity criteria consistent with the other available CDK 4/6 inhibitors, based on the following:

1. As concluded by the Clinical Guidance Panel (CGP), "there is a net overall clinical benefit to the addition of abemaciclib...as *initial therapy* [emphasis added] with a non-steroidal AI"<sup>1</sup>. In assigning a restricted use for abemaciclib, the initial recommendation has placed undue emphasis on diarrhea, an unpleasant, though largely manageable side effect. In doing so, it has created an inaccurate impression that abemaciclib has a worse safety profile than ribociclib and palbociclib, when evidence supports otherwise. In essence, abemaciclib has been held to a higher standard than the other two therapies in the CDK 4/6 class. A fairer conclusion would be that adverse event profiles differ across the class; all require careful clinical management of toxicities by the treating oncologist.
2. Similarly, abemaciclib was held to a higher standard with respect to the conclusions drawn about overall survival (OS) data. The initial recommendation states that it has tempered its assessment of net clinical benefit for abemaciclib with a NSAI because of the absence of mature OS data. Yet, ribociclib received an unrestricted recommendation in the same population, despite similar concerns of the absence of mature OS data at the time of review (and which is still lacking). A higher standard

for abemaciclib was also applied to the assessment of the network meta-analysis (NMA). This introduces an inconsistency in the assessment of abemaciclib compared to other CDK 4/6 therapies.

3. Metastatic breast cancer is a heterogeneous disease that is often catastrophic for the patient and each patient is unique in terms of the clinical and personal experience of the disease. Patients require an expert clinician to lend tailored clinical judgement to their treatment *and the patient's preferences*. A core patient value is additional choice. In the case of CDK 4/6 inhibitors, with only three therapeutic options, that neither physician nor patient is well served by a restriction on one of the therapies that is not firmly grounded in evidence. The restricted recommendation for abemaciclib is inconsistent with the decisions made by other major health technology assessment (HTA) bodies globally, including NICE<sup>2</sup>, SMC<sup>3</sup> and PBAC<sup>4</sup>, which have recommended all three agents at parity.

**The initial recommendation for abemaciclib rests on an evidentiary assessment that is inconsistent when compared to the recommendations of other CDK 4/6 inhibitors (ribociclib & palbociclib).**

- *Diarrhea is manageable and does not require substantial monitoring. Other CDK 4/6 inhibitors also have toxicities (e.g. neutropenia, QTc prolongation) that may be life threatening and require substantial resources.*

Importantly, in its overall assessment of clinical benefit, the CGP noted “no major concerns regarding the effectiveness and toxicity of abemaciclib”<sup>1</sup>. Diarrhea is a manageable adverse event (AE) for which physicians have extensive experience. Diarrhea is known to be associated with other therapies (e.g. everolimus, lapatinib, ribociclib); 35% of patients on ribociclib had any-grade diarrhea.<sup>5</sup> As a result, many centres are equipped with programs aimed to help both patients and physicians with diarrhea education and management. Diarrhea related to abemaciclib is also predictable - the median time to onset was 8 days after starting therapy - and it resolves quickly if managed with loperamide or dose reduction. Of note, discontinuations associated with diarrhea while on abemaciclib was low [1.8%].

Other CDK 4/6 inhibitors have notable grade 3 and 4 treatment-related AEs - ribociclib [83%], and palbociclib [75%] - compared to abemaciclib [55%]<sup>6</sup>. Dose reductions due to AEs occurred in approximately 40% to 50%<sup>5,7</sup> of patients on palbociclib or ribociclib, congruent with abemaciclib [46.5%]. While neutropenia, commonly associated with other CDK4/6 inhibitors (palbociclib [55%], ribociclib [59%])<sup>5,7</sup>, has a limited impact on quality-of-life, it can have potentially serious consequences for patients and place a burden on the healthcare system (e.g. cost of monitoring and bloodwork). Similarly, QTc prolongation is a toxicity where pERC has noted “significant concerns about the capacity and resources required”<sup>5</sup> in some jurisdictions to monitor and manage for ribociclib (e.g. frequent clinic visits, electrocardiograms (ECG)).

Importantly, there is no substantive evidence to recommend different reimbursement criteria for abemaciclib compared to other CDK 4/6 inhibitors as they all have different adverse event profiles that require monitoring and management.

- *The respective CGP had similar concerns regarding the NMAs across reviews for other CDK 4/6 inhibitors and abemaciclib - there is significant uncertainty due to heterogeneity across trials, limited data for some variables and notably, the lack of mature OS data for the CDK 4/6 class.*

The initial recommendation for abemaciclib was held to a higher evidentiary standard than other CDK 4/6 inhibitors based on the assessment of the NMA. With the submitted NMA for other CDK 4/6 inhibitors, the respective CGP expressed concern of uncertainty because of considerable heterogeneity and lack of mature OS data. In fact, the credibility and validity of these NMA were questioned and it was concluded that results should be interpreted with caution. Despite this uncertainty in comparative evidence, pERC noted that, “the choice between palbociclib and ribociclib would be dependent on relative overall cost, treatment availability, patient values and preferences and clinical factors such as tolerability to adverse events”.<sup>5</sup> Neither recommendation was restricted as a result. This is in contrast to the NMA for abemaciclib which was characterized by similar limitations and for which a restricted recommendation has been proposed.

Abemaciclib with a NSAI achieved a clinically significant increase in PFS of 13.42 months compared to placebo with a NSAI (28.18 months versus 14.76 months), reducing the risk of disease progression or death by 46%. Peer-reviewed meta-analyses (which were included in the abemaciclib submission) have concluded comparative efficacy and safety across CDK 4/6 inhibitors: “The addition of CDK 4/6 inhibitors to an AI significantly improved PFS, ORR and CBR when compared with an AI used alone, with acceptable safety profile, similarly in three randomized phase III trials”.<sup>8</sup> There was no statistically significant difference noted in the overall rates of grade 3 or 4 AEs for abemaciclib compared to the other CDK 4/6 inhibitors.<sup>6,8</sup>

- *Overall quality-of-life (QOL) for abemaciclib + NSAI was maintained compared to NSAI alone, and was not fully accounted for pERC.*

The CGP for abemaciclib “assumed that there was no detriment in QOL in patients treated in the combination treatment group compared to placebo arms”.<sup>1</sup> The standard approach for assessing overall QOL is global health status (as measured by the European Organization for Research and Treatment (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30)). For abemaciclib with a NSAI, there was no clinically meaningful difference in overall global health status. While there was a clinically meaningful difference in the diarrhea symptom score favoring NSAI alone, it did not negatively impact overall quality-of-life. This is further supported by the results of the EORTC-QLQ-Breast 23 (BR-23) where no clinically meaningful differences were observed in the functional and symptom scales. Similar results were observed with other CDK 4/6 inhibitors, where no clinically meaningful difference was observed in overall quality-of-life.

- *The evidence for abemaciclib was evaluated in a manner inconsistent with the evaluation of other drugs in the same therapeutic area where no comparative evidence exists*

Previous recommendations have been consistent in not commenting on the place in therapy of the new agent in relation to other approved agent(s) in the absence of evidence of superior efficacy. Examples include choice of therapy for EGFR-positive non-small cell lung and cancer (NSCLC), ALK-positive NSCLC, BRAF mutated metastatic melanoma and metastatic castration-resistant prostate cancer. In these situations, the choice of drug was left to the treating physician based on the patient’s clinical circumstances. It is concerning that the initial recommendation for abemaciclib has deviated from this past practice given similar efficacy and cost across the CDK 4/6 class.

**The initial recommendation for abemaciclib inappropriately limits the exercise of clinical judgement in the treatment of a heterogeneous end-stage cancer.**

Given that metastatic breast cancer is a heterogeneous disease affecting unique individual patients, physicians should have discretion to exercise their clinical judgment in selecting the optimal therapy for their patients based on their co-morbidities and the side effect profile of the CDK 4/6 inhibitor. The CGP noted that, “when patients were asked what level of side effects and how much impact on one’s quality of life would be worth extending progression-free disease by 6 months, the message sent by patients was this assessment can only be determined by an individual patient, in this circumstance”.<sup>1</sup> pERC noted in a previous CDK 4/6 recommendation that, “the ability of patients to tolerate treatment should be left up to the treating oncologist”.<sup>9</sup>

Lilly has evaluated the efficacy of abemaciclib with a NSAI using post-hoc subgroup analysis based on different prognostic factors (e.g. liver metastases, tumor grade).<sup>10</sup> While all subgroups benefited from the addition of abemaciclib to NSAI, patients with poor prognostic factors received significant clinical benefit from the combination therapy. It is important to note that other CDK 4/6 inhibitors have not published full data on patients with poor prognostic factors. These published data may have clinical relevance for both patients and physicians in deciding when best to use which CDK 4/6 inhibitor.

As noted, metastatic breast cancer is a heterogeneous disease and each patient should have the opportunity to have an expert clinician tailor their treatment to their needs and preferences. A core patient value is access to additional treatment choice - neither physician nor patient benefits from a restriction on one of the therapies that is not firmly grounded in evidence, particularly so given similar efficacy and cost across the CDK 4/6 class. As such, we respectfully request a reconsideration of the initial recommendation.

**References**

1. Abemaciclib for advanced or metastatic Breast Cancer - Initial Clinical Guidance Report. 2019 May 3.
2. NICE technology appraisal guidance [TA563] - Final appraisal document. 2019 Jan 17.
3. SMC detailed advice [SMC2135]. 2019 May 13.
4. PBAC March 2019 meeting.
5. Ribociclib (Kisqali) Metastatic Breast Cancer - pERC Final Recommendation. 2018 Apr 18.
6. Messina C., et al. CDK4/6 inhibitors in advanced hormone receptor-positive/HER2-negative breast cancer: a systematic review and meta-analysis of randomized trials. Breast Cancer Res Treat. 2018 Nov;172(1):9-21.
7. Palbociclib (Ibrance) Resubmission ABC - pERC Final Recommendation. 2016 Nov 21.
8. Ramos-Esquivel A., et al. Cyclin-dependent kinase 4/6 inhibitors as first-line treatment for post-menopausal metastatic hormone receptor-positive breast cancer patients: a systematic review and meta-analysis of phase III randomized clinical trials. Breast Cancer. 2018 Jul;25(4):479-488.
9. Palbociclib (Ibrance) Fulvestrant MBC - pERC Final Recommendation. 2019 May 03.
10. Di Leo A., et al. Prognostic characteristics in hormone receptor-positive advanced breast cancer and characterization of abemaciclib efficacy. NPJ Breast Cancer. 2018 Dec 18;4:41.

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
3	Endocrine Naive/Sensitive	3	Global health status should be noted as a outcome of interest.

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
			It should be noted that the lack of a clinically meaningful difference in overall quality-of-life (i.e. global health status) suggests that abemaciclib + NSAI maintained comparable overall quality-of-life as placebo + NSAI.
1-2	<u>Endocrine Naive/Sensitive</u>	Bottom half of page 1, top half of page 2	Upon initial review of the recommendation, the rationale for the decision was not clear. The recommendation was confusing given there was separate wording for the conditional recommendation and eligible patients. This has potentially limited the opportunity to provide appropriate feedback on the recommendation.

### 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.

- |                          |   |                                     |  |
|--------------------------|---|-------------------------------------|--|
| <input type="checkbox"/> | Support conversion to Final Recommendation.<br>Recommendation does not require reconsideration by pERC. | <input checked="" type="checkbox"/> | Do not support conversion to Final Recommendation.<br>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.

## 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](http://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](http://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.

## 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](http://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](mailto:submissions@pcodr.ca).

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