CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

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

Palbociclib (Ibrance) with Fulvestrant for Metastatic Breast Cancer

May 3, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	IBRANCE in combination with fulvestrant for the treatment of women with HR +, HER2 – locally advanced or metastatic BC whose disease progressed after prior endocrine therapy
Eligible Stakeholder Role in Review:	Submitter and manufacturer
Organization Providing Feedback	Pfizer Canada

**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

Pfizer Canada (Pfizer) agrees with the pERC initial recommendation to reimburse palbociclib (PAL) in combination with fulvestrant (FUL) for the treatment of women with HR positive, HER2 negative locally advanced or metastatic breast cancer (mBC).

Overall, Pfizer believes that the Clinical Guidance Panel (CGP) represents a fair summary of the clinical evidence submitted to pCODR [1]. However, Pfizer respectfully disagrees with the Economic Guidance Panel (EGP)'s re-analyses of the economic evaluation, in particular with the EGP approach to address uncertainty for the comparison to everolimus (EVE) plus exemestane (EXE) [2].

In the absence of head-to-head clinical trial comparing PAL + FUL with therapies currently reimbursed by the public payers, Pfizer has submitted a network meta-analysis (NMA), that was considered as methodologically sound by the CGP. The hazard ratio (HR) estimates from the NMA were used to populate the cost-utility model.

The EGP concluded that "*the utilization of the HRs was a good approach for anastrozole, exemestane and letrozole on a basis that the HRs of progression-free survival (PFS) were statistically significant and HRs of overall survival (OS) showed a certain trend to significance. This was however not appropriate for everolimus + exemestane as both HRs for PFS and OS showed similar clinical benefits when compared to palbociclib + fulvestrant.*" The EGP established that in this case a HR equal to 1 should have been used in the economic model (EGP initial report, p5).[2]

While Pfizer does not dispute the uncertainty around the HR estimates obtained from the NMA, we believe however that the EGP modelling approach to set the HR equal to 1 is not methodologically sound and goes against general health economic evaluation principle [3] as well as the CADTH's guidelines for economic evaluation [4].

The premise of the EGP assumption to set the HR equal to 1 because the overlapping credible interval (CrI)s suggesting no statistically significant difference violates the fundamental principle of health technology assessment (HTA). Indeed, the landmark paper by Prof. Claxton states

that decisions should be made based only on the mean net benefit irrespective of whether differences are statistically significant [3]. This is also inconsistent with a previous CADTH decision, where the reviewers criticized that "*the investigators inappropriately concluded similar numerical efficacy between DPP-4 inhibitors as long as there was overlap in the 95% credible intervals of the effect estimates for each DPP-4 inhibitor versus the common comparator."* [5]

In addition, Pfizer notices that the EGP had only conducted deterministic analysis in their reanalysis that doesn't align with CADTH guideline for economic evaluation, section 13, where it is stipulated that parameter uncertainty should be addressed using a probabilistic analysis in order to provide decision-makers with unbiased estimates of the costs and outcomes of the technologies being evaluated [4]. In fact, deterministic analyses of parameter uncertainty are not recommended, especially when the parameters have associated uncertainty, e.g. 95% credible intervals [4].

For reasons mentioned above and in accordance with CADTH guidelines for the economic evaluation, Pfizer urges the EGP to reconsider their re-analysis by using a probabilistic approach. For instance, instead of setting the value of HR to 1, the value should be randomly drawn from a range of potential values, e.g. the 95% CrIs and by applying the utility values estimated by Lloyd formula, and a dose intensity of 100% for palbociclib, the results from the probabilistic analyses are shown in the table below.

	Δ C ($)	ΔE (QALY)	ICER ($/QALY)
Best estimate (mean)	**$ 23,400**	**0.091**	**$256,899/QALY**
Lower bound	$ 21,001	0.069	$213,236/QALY
Upper bound	$ 25,799	0.114	$300,561/QALY

The best estimate for ICER when compared to EVE + EXE as per the EGP's preferred assumption would be $256,899, with potential ICER ranges between $213,236/QALY and $300,561/QALY.

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

3.2 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, 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**
4	pERC recommendation	Par 4; lines 1-4	"*pERC further discussed the cost-effectiveness when compared with everolimus plus exemestane … based on this, pERC agreed with the EGP reanalysis setting the hazard ratio for PFS and OS to 1.*"
Pfizer acknowledges the uncertainty around the HR estimates from the NMA, but would like to reiterate that the EGP approach is methodologically incorrect as it does not align with both HTA convention and CADTH guidelines for economic evaluation. In line with CADTH guidelines, our pCODR submission addressed the uncertainty around the HR by adopting probabilistic techniques. It should be noted that we presented the probabilistic ICER=$157,051/QALY as the reference case when compared to EVE + EXE despite the fact that the deterministic ICER=$122,172/QALY was more favorable, precisely Pfizer recognized that the probabilistic analysis provides less biased estimates of costs and outcomes than a deterministic one. For this same reason, Pfizer believes it is inappropriate to use a deterministic analysis with the HR for PFS and OS set to 1. This will be equivalent to not giving due consideration to the uncertainties and variation around the HR and to determine with 100% certainty that the value of the HR for PFS and OS is equal to 1. Pfizer respectfully requests pERC to deliberate on the cost-effectiveness of PAL + FUL based on results of probabilistic analyses as shown in section 3.1			
6	Economic Guidance Report	Section 1.4 Last bullet point	"*The EGP conducted re-analyses investigating utility values… to reduce differences due to different methods of calculation.*"
Pfizer believes that the EGP may have misinterpreted how the utility values were implemented in our cost-utility model. In our primary analysis, PAL + FUL vs FUL alone, the utility values			

from the PALOMA 3 trial were used. In all other secondary analyses comparing PAL + FUL vs other treatment therapies, including EVE + EXE, we only used the Lloyd equation in the probabilistic analysis (it was programmed in the VBA) for both treatment therapies, we did not mix with PALOMA 3 utilities for PAL + FUL. Although it is possible to do so in the deterministic model, it was not done in our submitted analyses as it is stated in tables 5.8 and 5.9 of the pharmaco-economic report submitted to pCODR.			
5	Economic Guidance Report	Par 1 Lines 16-18	*"The EGP wanted to explore the impact of the parameters that have the most impact on the ICER in the context of the sequential analysis. Due to the way the submitted model was built this was not possible to assess."*
The submitted economic model allows such sensitivities analyses in the context of the sequential analysis. It is apparent from this comment and throughout the Economic Guidance Report that the EGP may not fully appreciate all the functionalities, especially with regards to the probabilistic analyses, that our economic model offers. We apologize that the companion user guide submitted along the economic model does not effectively present these features. Pfizer will welcome the opportunity to collaborate with EGP reviewers to show the full functionalities of the submitted model, in particular how to modify the parameters in the probabilistic analysis.			

REFERENCES

1. *pCODR initial Clinical Guidance Report - Palbociclib (Ibrance) + Fulvestrant (Faslodex) for Metastatic Breast Cancer, pERC Meeting February 21, 2019.*

2. *pCODR initial Economic Guidance Report - Palbociclib (Ibrance) + Fulvestrant (Faslodex) for Metastatic Breast Cancer, pERC Meeting February 21, 2019*

3. Claxton, K., *The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies.* Journal of Health Economics, 1999. **18**(3): p. 341-364.

4. *Guidelines for the economic evaluation of heath technologies: Canada. 4th 3d. Ottawa: CADTH; 2017 Mar.*

5. *CDR Clinical Review Report for Kazano.* *https://www.cadth.ca/sites/default/files/cdr/clinical/SR0367_Kazano_CL_Report.pdf*.

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.

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.