pan-Canadian Oncology Drug Review

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

Fulvestrant (Faslodex) for metastatic Breast Cancer

February 1, 2018

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Fulvestrant (Faslodex) for Breast Cancer
Role in Review (Submitter and/or Manufacturer):	Manufacturer
Organization Providing Feedback	AstraZeneca Canada

**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:

__x__ agrees ____ agrees in part ____ disagree

Please explain why the Submitter (or the Manufacturer of the drug under review, if not the Submitter) *agrees, agrees in part or disagrees with the initial recommendation.*

AstraZeneca Canada agrees with pERC's initial recommendation for fulvestrant for the hormonal treatment of non-visceral locally advanced or metastatic HER2- breast cancer in postmenopausal women, regardless of age, who, have not been previously treated with endocrine therapy and supports early conversion to a positive final recommendation.

There is an on-going need for individualized care in breast cancer. With the complex treatment pathway for patients with ABC and the introduction of costly combination therapies, it is imperative to identify the appropriate therapy for each patient.

In particular, there is a need for additional treatment in the first line setting with a unique mechanism of action that can degrade the ER and prevent estrogen-independent ER signalling as well as the estrogen-dependent signalling inhibited by AIs, thereby delaying disease progression for longer, whilst maintaining HR-QoL and prolonging survival.

Fulvestrant, a selective ER degrader (SERD), is the only endocrine therapy that targets, binds to, blocks and degrades the ER, potentially making it a more potent inhibitor of the ER pathway than AIs and tamoxifen.

As noted by the CGP, the prolonged expected survival of ER+/HER2- disease has resulted in the use of progression-free survival (PFS) as a clinically meaningful endpoint when considering the first line setting. The CGP also indicated that PFS may be especially meaningful when considering hormonal therapy, given its relative lack of toxicity, ease of administration, and limited requirements for monitoring.

The positive results from the pivotal Phase III FALCON study demonstrated that fulvestrant was more effective than anastrozole in the 1st line treatment of ER+

advanced breast cancer in women who were endocrine therapy-naïve.

After consultation with multiple stakeholders, the decision by AstraZeneca was to proceed to pCODR with the pre-specified patient population that benefited the most and aligned to guidance of submitting for the most cost-effective patient population.

The non—visceral subgroup from the FALCON study was prespecified. For FALCON the visceral group was specified after the finalization of the protocol, and included in the Statistical Analysis Plan (SAP) which was finalized prior to database lock and unblinding. A global interaction test was conducted and suggested there was no statistically significant effect modifiers of fulvestrant identified, specifically, treatment effects on progression-free survival were largely consistent across the prespecified patient subgroups (p=0.1061), with certain exceptions including patients with visceral disease (Robertson et al., 2016)

FALCON has provided the evidence required to demonstrate that fulvestrant provides a substantial and clinically meaningful 8.5 month increase in median PFS versus anastrozole, in the prespecified subgroup of patients who have non-visceral endocrine therapy-naïve ER+ HER2- ABC.

Fulvestrant has a well characterized safety profile, and is associated with a low rate of treatment-related severe AEs and discontinuations. The CGP highlighted that although new therapies have been developed and approved for use in metastatic ER+/HER2- ABC, specifically CDK4/6 inhibitors, these treatments create a level of complexity and increased toxicity compared with AI therapy not seen with fulvestrant.

Fulvestrant has a low cost of $1,165.79 per 28-day course of therapy relative to the higher cost CDK4/6 inhibitors like palbociclib + letrozole which cost $6,288.58 over the same 28-day course of therapy.

pERC discussed that the results of the indirect comparison of fulvestrant to palbociclib + letrozole were not conclusive, as a number of limitations were identified in the analysis. As per the CGR, AstraZeneca had raised to pCODR during the Checkpoint Meeting that the indirect comparison was not appropriate based on limitations in the publically available data, clinical practice and perspective and the lack of public funding for palbociclib + letrozole.

With the complex treatment pathway for patients with ABC, AstraZeneca strongly believes fulvestrant is cost-effective. All EGP reanalyses with the exception of the upper estimate were consistent with one another, had minimal impact on the ICER, and were aligned to the base case ICER submitted by AstraZeneca ($32,361/QALY). On the basis of the submitted model, cost-effectiveness acceptability curves were produced for fulvestrant and >80% of iterations were below a willingness-to-pay threshold of $100,000

AstraZeneca does support the lower bound estimate provided by the EGP's reanalysis and believes it is the most robust and appropriate. AstraZeneca does not agree with the $185,631/QALY upper bound estimate produced by the EGP. As seen with many oncology treatments, at the time of pCODR submission the survival data is not mature, therefore, parametric models are used to extrapolate the observed trends. It is not accurate to set the survival benefit to be equal beyond three years for the fulvestrant and anstrazole treatment groups. As noted by pERC this sudden change in the relative OS is not a clinically plausible scenario.

The median overall survival is not yet reached in the FALCON study. Importantly, the available evidence from FALCON does however, demonstrate a numerical advantage for

fulvestrant versus anastrozole, with greater separation in the OS curves for the non-visceral subgroup.

The FALCON trial was designed, based on positive results from the Phase II FIRST trial, which has 7 years of survival data. The FIRST study demonstrated a statistically significant and durable increase in median overall survival (nearly six months) with fulvestrant, when compared to anastrozole (54.1 months vs. 48.4 months, 5-year survival: 47.4% vs. 37.6%; 7-year survival: 30.1% vs. 18.1%, HR=0.7). It is important to note that the FIRST study demonstrated that fulvestrant had a greater numerical overall survival advantage than anastrozole in patients with non-visceral disease. The CONFIRM study provides further supporting evidence of a sustained OS benefit associated with fulvestrant. Overall, the robust survival data for fulvestrant reinforces why the ICER estimate is closer to the EGP lower bound estimate.

Fulvestrant would have a minimal budget impact. As noted by pERC, only a small number of patients would qualify for treatment with fulvestrant, as majority of patients in the clinical setting would have received adjuvant hormonal therapy.

pERC recognized fulvestrant aligns with patient values. Rethink and CBCN indicated that the many effects of metastatic breast cancer represent a significant and debilitating impact (both physical and social) on patients' and caregivers' quality of life. Patients value the benefits they receive with fulvestrant as highlighted by patient quotes in the CGR such as:

"I had my last scan in April and the fulvestrant still seems to be working for me. My oncologist is impressed because this is the first time, with all of the treatments that I have been on, that my tumors have actually begun to shrink"

"It's been amazing with my quality of life. I was at a bad point when I started it, and it really saved my life by allowing me to live my life"

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 two (2) Business Days after the end of the feedback deadline date.

__x__	Support conversion to final recommendation.	____	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	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity

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

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.