



pan-Canadian Oncology Drug Review

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

Bevacizumab (Avastin) Platinum Resistant Ovarian Cancer

May 5, 2016

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):

Avastin (bevacizumab) - In combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan, for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Role in Review (Submitter and/or Manufacturer):

Submitter_____

Organization Providing Feedback

Hoffmann-La Roche Limited_____

**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:

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.

Hoffmann-La Roche fully supports the clinical criteria supporting the use of Avastin (bevacizumab) as outlined by the pERC.

Hoffmann-La Roche looks forward to working with provinces to make Avastin available for Canadian patient with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

- 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 within 2(two) business days of the end of the consultation period.

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
Page 3	Economic Evaluation. Section 1.3 Submitted and EGP reanalyses estimates.	Last paragraph	<p>We believe that the ICER range provided by the EGP does not truly reflect the plausible ICER range for the following reasons:</p> <ol style="list-style-type: none"> <li data-bbox="851 538 1455 792">1. The range of the ICERs re-analyzed by the EGP is estimated to be between \$289,467/QALY and \$425,651/QALY. Both “best case estimates” by the EGP were the results of testing the cumulative effect of combining several conservative scenarios in the model at the same. As such, it could not properly reflect the true <i>range</i> the ICER. <li data-bbox="851 834 1455 1277">2. When the “best estimate” of the upper bound is re-analysed by the EGP in the model, the LYGs (.140 or 1.68 months) are considerably lower than the efficacy shown in the trial (3.3 months) and the CGP’s own estimate of 3.3 months (16.6 months vs. 13.3 months; pg41 of initial CGR). The fact that the EGP’s model is inconsistent with observed evidence is a testament to its poor fit. Therefore, the most conservative ICER overestimates the most likely mean ICER of bevacizumab in the treatment of recurrent platinum resistant ovarian cancer based on the AURELIA trial. <li data-bbox="851 1320 1455 1848">3. EGP recognizes the value in using KM data as it is real, observed data: “...using the KM data ensures that the overall survival accrued in the model is equivalent to that accrued during the clinical trial” (P3). However, this is inconsistent with selecting a model - in this case, the KM lower 95%CI with its gamma tail - that does not at all represent observed trial data. This lends poor face validity. The lower 95% confidence interval is a poor choice to represent the most likely, or average, survival and it is this average - or most likely - scenario that is important to the decision problem. Does the EGP have clinical reasoning to reject observed survival in favour of one that resembles the lower 95%CI?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
			<p>In the range provided by EGP, they arbitrarily use the lower 95% confidence interval to estimate OS due to uncertainty. If a true range was to be provided, the EGP should be using the lower <i>and</i> upper boundaries. The EGP should note that one is as probable as the other and both have low probabilities in general. This is even more relevant as approximately 40% of patients crossed over from the placebo arm to receive Avastin, which could bias the OS in favour of the placebo arm. By using the lower 95% confidence interval, the EGP is actually amplifying the effect of a known confounder instead of removing its effect.</p> <p>5. Modelling is used to provide the best estimate relevant to the decision problem. If there is a non-zero probability of survival beyond 4 years, the appropriate time horizon is beyond 4 years. Truncation of a time horizon biases results against the future for the present. Discounting and the EGP's re-analyses of cessation of any further treatment benefit beyond post-progression account for its concerns regarding differences in long-term survival curves.</p> <p>As such, we believe the true range for the ICER is between \$240,100 - \$300,296.</p>

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.