CADTH

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

Avelumab (Bavencio) for Urothelial Carcinoma

March 23, 2021

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Avelumab (Bavencio®) for the first-line maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) whose disease has not progressed with first-line platinum-based induction chemotherapy
Eligible Stakeholder Role	Submitter and Manufacturer
Organization Providing Feedback	EMD Serono – Pfizer Alliance

3.1 Comments on the Initial Recommendation

a) Please indicate if the stakeholder agrees, agrees in part, or disagrees with the initial recommendation:

☒ Agrees ☐ Agrees in part ☐ Disagrees

- The EMD Serono – Pfizer Alliance agrees with the pERC's initial recommendation to fund avelumab in first-line maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) whose disease has not progressed with first-line platinum-based induction chemotherapy. We acknowledge and agree with pERC's recognition on the net clinical benefit of avelumab "(…) based on statistically significant and clinically meaningful improvements in overall survival, progression-free survival, a manageable toxicity profile, and no apparent detriment in quality of life. pERC agreed that avelumab aligns with the following patient values: preventing recurrence, controlling disease and maintaining quality of life".
- The EMD Serono – Pfizer Alliance supports an early conversion of the initial recommendation with the interest to advance patient access to avelumab for the indicated population in Canada.
- Although the EMD Serono – Pfizer Alliance understands the conditions behind the positive recommendation, we respectfully believe that some of the stated limitations of the economic evaluation are not justified by sufficient evidence and are not consistent with approaches that were taken in the assessment of similar treatments. As such, we provide the feedback below.

Economic evaluation

- The EMD Serono – Pfizer Alliance acknowledges that there is a balance between internal validation, based on statistical criteria, and external validation, based on real-world evidence or expert opinion. The decision to select the Exponential distribution for the extrapolation of avelumab + best supportive care (BSC) and BSC overall survival is not robust based on statistical evidence provided in our submitted model. Indeed, the Exponential distribution ranked 6th and 7th for the best distributions in the overall survival extrapolations of avelumab+BSC and BSC, respectively. In the submitted dossier, the long-term projections of BSC overall survival were externally validated based on multiple cohort studies of patients treated with cisplatin or carboplatin-based regimen in locally advanced or metastatic UC.
- CADTH's reanalysis increased the percentage of patients who received pembrolizumab as subsequent therapy after avelumab+BSC, from 0% in the submitted model to 14.86%. However, we are not able to identify the 14.86% in clinical trial data from the JAVELIN 100 trial: in Table 11 of the clinical study report (CSR), only 6.3% of patients received a PD1 or PD-L1 inhibitor after avelumab+BSC. First, the inclusion of subsequent pembrolizumab after maintenance treatment with avelumab+BSC is not consistent with Canadian clinical practice, as validated by input from Canadian medical oncologists. Furthermore, page 14 of the initial pERC recommendation states: "pERC agreed with the CGP that patients who progressed on avelumab maintenance treatment should not be treated with subsequent anti-PD1 therapy." The inclusion of subsequent pembrolizumab is therefore inconsistent with the conclusion given by the CGP (page 10), and agreed to by pERC, that patients who progressed on avelumab maintenance treatment should not be treated with subsequent anti-PD1 therapy. Given the

current costs associated with the PD-L1 therapies, the arbitrary inclusion by CADTH will result in increased total costs associated with avelumab+BSC. Therefore, the approach from CADTH affects the validity of the cost-effectiveness analysis and limits the interpretation of its results.

- The EMD Serono – Pfizer Alliance agrees with the update of the percentage of patients eligible for public coverage of avelumab. However, we are surprised with the decision to exclude second-line treatment costs. As with the drug program perspective only the drug costs are included, the exclusion of subsequent treatment costs leads to a total cost of $0 in the BSC arm in the current analysis. In the submitted analysis, the expected budget impact of introducing avelumab as a first-line maintenance therapy decreased by half due to the expected savings in second-line. Indeed, we estimated that the weighted subsequent monthly costs were $7,896 after BSC vs. $355 after avelumab+BSC. The EMD Serono – Pfizer Alliance would like to clarify that subsequent treatment costs in the budget impact analysis were calculated in the same manner as in the cost-effectiveness analysis, utilizing a weighted average by percentage of patients receiving subsequent therapies. We respectfully believe that since the inclusion of subsequent treatment costs was validated for the cost-effectiveness analysis, these costs should not be removed from the budget impact analysis. This decision results in a two-fold increase in the anticipated budget impact and is not representative of the expected expenses following introduction of avelumab to the market.
- The EMD Serono – Pfizer Alliance disagrees with the approach to assess a price reduction for avelumab to be cost-effective solely at a willingness-to-pay (WTP) threshold of $50,000 per QALY. We respectfully believe that a $50,000 threshold is challenging for oncology drugs. Furthermore, the approach to include a $50,000 per QALY WTP is not consistent with previous recommendations from pERC for UC treatments. As part of a retrospective analysis of pCODR recommendations from 2011 to 2017, Skedgel et al (2018) investigated whether there was “an implicit maximum WTP or cost-utility threshold in pCODR recommendations”.[1] This maximum threshold was approximately $140,000 per QALY, which is significantly higher than the threshold referenced by pERC.
- There is precedent from a recent pERC recommendation in Dec 2020 (pembrolizumab in HNSCC) that both $100,000/QALY and $50,000/QALY WTP thresholds are articulated. Providing a range of thresholds is more acceptable because it does not stipulate a single threshold as a final point estimate. Thus, pERC recommendations for treatments with similar mechanisms have not been consistent in setting these thresholds. Also, the $50,000/QALY threshold stated by pERC is not consistent with the WTP of $100,000/QALY stated in the funding recommendation for BAVENCIO® (avelumab) from the *Institut national d'excellence en santé et services sociaux*, published on March 3rd, 2021. In the absence of similar evaluations from pCODR in the first-line maintenance treatment of patients with advanced UC, we respectfully and firmly believe that other WTP thresholds, namely the $100,000/QALY should be included in the final pERC recommendation. This approach would represent a more comprehensive assessment of cost-effectiveness of avelumab.
- Notably, the list price of avelumab ($10,600 per 28 day cycle) is lower than other immuno-oncology drugs used as treatments for UC, such as pembrolizumab (i.e. $11,733 per 28-day cycle), as per their respective recommendations from pERC.
- Finally, the pERC noted that the ICER may overestimate the cost-effectiveness of avelumab given the non-incorporation of disutilities from adverse events. As part of the pCODR Checkpoint Meeting, we conducted a scenario analysis with the inclusion of adverse event disutilities for grade 3 or above. The deterministic ICER that was calculated with the addition of adverse event disutilities resulted in a 0.51% increase compared to the deterministic ICER in the reference case. Therefore, the inclusion of adverse event disutilities has little impact on the ICER.

References

[1] Skedgel, C., Wranik, D. & Hu, M. The Relative Importance of Clinical, Economic, Patient Values and Feasibility Criteria in Cancer Drug Reimbursement in Canada: A Revealed Preferences Analysis of Recommendations of the Pan-Canadian Oncology Drug Review 2011–2017. PharmacoEconomics 36, 467–475 (2018). https://doi.org/10.1007/s40273-018-0610-0

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
4	Summary of pERC deliberations	1, 5	Please replace “maitenance” to “maintenance”
4	Summary of pERC deliberations	7, 2	Please replace “eligibly” to “eligible”

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 recommendation (“early conversion”), which would occur two 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 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.

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
			No comment.

Template for Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

1 About Stakeholder Feedback

CADTH invites eligible stakeholders to provide feedback and comments on the pan-Canadian Oncology Drug Review Expert Review Committee (pERC) initial recommendation.

As part of the CADTH's pan-Canadian Oncology Drug Review (pCODR) process, pERC makes an initial recommendation based on its review of the clinical benefit, patient values, economic evaluation and adoption feasibility for a drug. The initial recommendation is then posted for feedback from eligible stakeholders. All eligible stakeholders have 10 business days within which to provide their feedback on the initial recommendation. It should be noted that the initial recommendation may or may not change following a review of the feedback from stakeholders.

CADTH 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 disagree with the initial recommendation, and to provide a rationale for their response. Please note that if a stakeholder agrees, agrees in part or disagrees with the initial recommendation, they 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 the key guiding principles for CADTH's pCODR process. 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 *Procedures for the CADTH Pan-Canadian Oncology Drug Review* are met, the final recommendation will be posted on the CADTH website two 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), 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. Please note that if any one of the eligible stakeholders does not support the initial recommendation proceeding to a final recommendation, pERC will review all feedback and comments received at a subsequent pERC meeting and reconsider the initial 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 pERC, and may not require reconsideration at a subsequent pERC meeting.

The final 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

- The following stakeholders are eligible to submit feedback on the initial recommendation:
    - The sponsor and/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
    - CADTH's Provincial Advisory Group (PAG)
- 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.
- The template for providing stakeholder is located in section 3 of this document.
- 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.
- Feedback on the initial recommendation should not exceed three 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.
- 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.
- References may be provided separately; however, these cannot be related to new evidence.
- 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 must be disclosable and will be posted on the CADTH website.
- The template must be filed with CADTH as a Microsoft Word document by the posted deadline.
- If you have any questions about the feedback process, please e-mail requests@cadth.ca