pan-Canadian Oncology Drug Review

Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

(Manufacturer)

Daratumumab (Darzalex) +VMP for Multiple Myeloma

August 29, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	DARZALEX® (daratumumab) in combo with bortezomib, melphalan and prednisone for multiple myeloma (newly diagnosed)
Eligible Stakeholder Role in Review (Submitter and/or Manufacturer, Patient Group, Clinical Organization Providing Feedback	Submitter and Manufacturer Janssen 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 the pCODR program.*

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

Please explain why the Stakeholder *agrees, agrees in part or disagrees with the Initial Recommendation. If the Stakeholder agrees in part or disagrees with the Initial Recommendation, please provide specific text from the recommendation and rational. Please also highlight the applicable pERC deliberative quadrants for each point of disagreement. The points are to be numbered in order of significance.*

- Janssen Inc. (Janssen) strongly agrees with the committee's decision that there is a significant net clinical benefit of DVMP, based on clinically meaningful improvements in progression-free survival, a trend to improved overall survival, and alignment with patient values of providing disease control, prolonged life, and no detriment to quality of life.

- With respect to the economic evaluation, Janssen agrees that uncertainty exists in the economic model due to the lack of median PFS and long-term OS data for DVMP at the interim analysis data cut-off, and emphasizes that this is a result of the superior efficacy outcomes observed with daratumumab-containing combination regimens.

- Janssen does not agree with the pCODR EGP's decision to shorten the time horizon of the submitted economic model to 10 years on the basis of "the uncertainty in survival estimates based on extrapolation of short-term trial data (27.8 months) and to reflect the clinical opinion of the CGP" (EGP Report p.7, section 1.4). A time horizon of 10 years for the economic model is inconsistent with the body of precedence set by at least eight previous pCODR assessments in multiple myeloma, and also poorly reflects the clinical course of disease in light of currently available treatments in both the first-line and relapsed/refractory settings. Notably, a time horizon of 20 years was recommended for daratumumab in the relapsed/refractory multiple myeloma setting for the daratumumab-bortezomib-dexamethasone and the daratumumab-lenalidomide-dexamethasone combination regimens, on the basis of clinical trials with follow-up periods of 13 and 17 months, respectively (pCODR Final Recommendation, Daratumumab (Darzalex), October 5, 2017). Furthermore, pCODR's previous recommendation for lenalidomide and dexamethasone in ASCT-ineligible first-line multiple myeloma, the same population for

which DVMP was reviewed, recommended up to a 20-year time horizon, at a time when effective second-line treatments such as daratumumab-based and carfilzomib-based combination regimens were not yet available to patients (pCODR Final Recommendation, Lenalidomide (Revlimid), December 3, 2015). Janssen therefore requests that the pCODR EGP revise the time horizon to a minimum of 20 years in the submitted model both in keeping with precedence and also as a fair reflection of the net clinical benefit that daratumumab offers as a first-line therapy for multiple myeloma patients.

- Janssen also does not agree with pCODR's assertion that "key limitations of the budget impact analysis model were the inability to evaluate the impact of the third-line therapies that were incorporated in the cost-effectiveness analysis model" and that "this parameter was not modifiable and therefore not explored by the EGP, but there may potentially be a large overall budget impact" (Initial Recommendation, p.12, section: Consideration for implementation and budget impact: Budget impact substantially underestimated). Janssen maintains that third-line therapies are outside the scope of the budget impact analysis for two primary reasons: 1) According to pCODR guidelines, the time horizon for the budget impact analysis model is for three years. Treatment times for therapies in both the reference and the new drug scenario are long enough such that patients will not progress to a third-line therapy within three years of starting their first-line therapy. This is distinct from the pharmaco-economic model, which has a much longer time horizon and for which the inclusion of third-line therapies is relevant since this would be reflected in clinical reality. In fact, the inclusion of third-line therapies in the model would result in a reduction in the incremental budget impact of DVMP, because a greater proportion of patients in the reference scenario would be eligible for daratumumab-based therapies in the third-line setting than in the DVMP listing scenario. As such, the inclusion of third-line therapies would increase the downstream cost of comparator regimens and decrease the overall incremental budget impact of funding daratumumab in the first-line setting.

b) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the provisional algorithm:

☐ agrees ☐ agrees in part ☐ disagree

Please explain why the Stakeholder *agrees, agrees in part or disagrees with the provisional algorithm. Please note that comments should relate* ***only to the proposed place in therapy of the drug under review*** *in the provisional algorithm. If feedback includes New Information or about other therapies that are included in the provisional algorithm, the information will not be considered and will be redacted from the posted feedback. Substantive comments on the provisional algorithm will preclude early conversion of the initial recommendation to a final recommendation.*

Not applicable to this feedback since no provisional algorithm was included as part of the initial recommendation.

c) 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 or provisional algorithm) 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, including the provisional algorithm, 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

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.