PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

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

Daratumumab (Darzalex) for Multiple Myeloma

October 5, 2017

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	DARZALEX® (daratumumab) for multiple myeloma (second-line or beyond)
Role in Review (Submitter and/or Manufacturer):	Submitter and Manufacturer
Organization Providing Feedback	Janssen Inc.

**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 _X_ 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.*

Janssen Inc. (Janssen) strongly agrees with the committee's decision that there is a significant net clinical benefit of daratumumab, based on clinically meaningful improvements in progression-free survival, unprecedented depth of remission rates, and alignment with patient values of having access to effective treatment options that provide disease control and prolong life. Janssen acknowledges that while appropriate caution must be used in drawing conclusions from network meta-analyses, Janssen agrees with the CGP's opinion highlighted by pERC that, based on registered clinician input, daratumumab-containing triplet regimens should be the more favored choice in second-line treatment compared to other triplet therapies for this patient population.

Janssen agrees that median treatment durations used in the economic model were estimates since long-term OS data were not yet available at the interim analysis and emphasizes that this is due to the superior efficacy outcomes observed with daratumumab-containing triplet regimens. However, Janssen does not agree with pERC's assertion that the true ICER is most likely at the higher end of the EGP's range of ICER estimates for both triplet regimens, (implying no treatment benefit after the end of the trial follow-up period) and notes that the EGP specifically does not express an opinion on when the treatment effect would cease. As part of the checkpoint meeting, Janssen provided references showing that an increase of 2.5 months in OS is expected for each additional month spent in PFS, based on analyses of different multiple myeloma trials (Felix et al. BMC Cancer 2013, 13:122). Notably, these data were validated in a report by the Institute for Clinical and Economic Review on treatment options in multiple myeloma and their associated cost-effectiveness (Ollendorf et al. ICER Report 9 June 2015). Consequently, Janssen maintains that truncating the treatment benefit at the end of the trial follow-up period is not reflective of clinical reality and that there is no evidence suggesting that the true ICER is near the higher end of the EGP's range of ICER estimates.

Janssen also does not agree with pERC's assertion that the drug administration costs were grossly underestimated in the submitted economic model, since pERC cites the EGP report to support this claim whereas administration costs were not specifically discussed in the EGP Report and also not included as a relevant factor in EGP reanalysis estimates. The drug administration costs used in the economic model were based on published literature, and Janssen has confirmed that the impact on ICERs would be minimal even if the drug administration costs were significantly increased.
Furthermore, Janssen maintains that the impact of additional administration, infrastructure, medical resources, and nursing and pharmacist costs due to the potential need to divide daratumumab infusions over 2 days is modest on the cost-effectiveness of the product. Janssen notes that dividing infusions over 2 days is not in accordance with the product monograph, and even if carried out this would be applicable to the first infusion only since all subsequent infusions have significantly decreased infusion times. Janssen emphasizes that the claim of increased resource utilization due to more frequent clinic visits is unsubstantiated given that, in the maintenance phase, daratumumab is infused once every 4 weeks for 3 hours, which represents fewer clinic visits than other novel IV-administered triplet regimens for patients with multiple myeloma.

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
5	Summary of pERC deliberations	Paragraph 2. Lines 19-21	Given the evidence outlined above demonstrating a treatment benefit after the end of the trial follow-up period, and in the absence of evidence indicating that the true ICER is most likely at the higher end of the EGP's range of ICER estimates for the DRd and DVd regimens, Janssen requests that the statement be reworded to align with the EGP Report: "The best estimate depends on the duration of the treatment effect. In the absence of data, the EGP is unable to confirm when the duration of treatment effect would cease."

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
			No comments

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments
Janssen requests that the following factual errors or inconsistencies please be corrected.			
1	Daratumumab-bortezomib-dexamethasone regimen cost	Line 3: cycles thereafter: $11,432.82 per 28-day course	This cost is incorrectly stated as it implies that bortezomib and dexamethasone are given in "cycles thereafter". Per the product monograph and the EGP Report p. 2, bortezomib and dexamethasone are only administered in cycles 1-8. Therefore, the treatment cost for "cycles thereafter" should be $6,697.82.
11	Cost-effectiveness estimates: Not cost-effective by EGP's estimates	Paragraph 8, Line 6	The EGP Report (p.6 and p.7) states that the treatment effects were truncated to four years (not two years) for both the DRd and the DVd regimen. This corresponds to the upper bounds of ICER estimates of $594,144 and $195,399 shown on p. 11 of the pERC recommendation.
12	Cost-effectiveness estimates: Not cost-effective by EGP's estimates	Paragraph 1, line 3.	Same as previous comment. The EGP Report (p.6 and p.7) states that the treatment effects were truncated to four years (not two years) for both the DRd and the DVd regimen. This corresponds to the upper bounds of ICER estimates of $594,144 and $195,399 shown on p. 11 of the pERC recommendation.

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.