PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

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

Carfilzomib (Kyprolis) for Multiple Myeloma

June 21, 2016

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Carfilzomib in combination with lenalidomide and dexamethasone (Len-Dex) for patients with multiple myeloma following failure of one prior treatment.
Role in Review (Submitter and/or Manufacturer):	Submitter and Manufacturer
Organization Providing Feedback	Amgen Canada 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.*

1) Agree with the recommendation to fund carfilzomib in combination with Len-Dex for patients with multiple myeloma following failure of one prior treatment.
2) Agree with pCODR on the unmet need in this patient population and recognizing that carfilzomib with Len-Dex demonstrated a net clinical benefit when compared with Len-Dex alone, based on a statistically significant and clinically meaningful improvement in progression-free survival, a trend toward an improvement in overall survival, a management toxicity profile, and at least maintenance in patient's quality of life.
3) Disagree with pERC that the true ICER is likely at the higher end of the EGP's re-analysis range as the two factors that contribute to the upper bound of the range included wastage and the assumption of no benefit beyond 42 months. Wastage will be negligible with the introduction of 10mg vial and assuming no treatment benefit from 42 months and beyond is too abrupt a change as opposed to a form of linear decline in benefit. Amgen further argues that the ICER is in fact less than the lower bound of $270K as PERC did not use covariate adjustment for meaningfully different and statistically significant prognostic factors between arms that could not be used as stratification factors.

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.

__X__ 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.

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
p.4	Summary of pERC deliberations	Paragraph 2; line 9: "pERC agreed that the true ICER is likely at the higher end of the range"	The economic re-analysis by pCODR placed the ICER in the range of ~ $270K to $350K with the comment that the true ICER was expected to be at the higher end of the range. Two factors that contribute to the $350K figure include wastage and the assumption of no benefit beyond 42 months. Wastage will be negligible with the introduction of 10mg vial. And a decline in treatment benefit with an HR=1 at 42 months is too abrupt a change as opposed to some form of linear decline. Removing this pair of constraints alone would support an ICER at the lower range.
p.4	Summary of pERC deliberations	Paragraph 3; lines 2-3: "pERC agreed that the true ICER is likely at the higher end of the range"	As per the inclusion criteria of the ASPIRE trial, please reword to: "… patients who had progression on lenalidomide **+ dexamethasone** or within 60 days of treatment with lenalidomide **+ dexamethasone** if it was the last treatment received…**"**
p.5	Evidence in Brief	Paragraph 5; lines 1-4: "pERC discussed the eligibility criteria for the trial and noted… to bortezomib or lenalidomide."	As per the inclusion criteria of the ASPIRE trial, please reword to: "… noted patients were not allowed into the trial if they had disease progression on bortezomib or within 60 days of treatment with bortezomib, progression on lenalidomide **+ dexamethasone** or within 60 days of treatment with lenalidomide **+ dexamethasone** if it was the last treatment received…**"**
p.8	Economic Evaluation	Paragraph 4; lines 3-5: "Given that the inputs for PFS and OS were based on post-hoc … PERC agreed with the EGP's use of the intent-to-treat analysis for PFS and OS inputs"	Given that the EGP re-analysis produced a bounded ICER, Amgen believes that unadjusted and adjusted analyses should be used to inform a plausible point estimate for the ICER. Additionally adjusted analyses are not a violation of the ITT principle and the submitted adjusted analysis was run on the ITT population as defined in the statistical analysis plan. Arguments and context for adjustment are captured in Statistical Principles for Clinical Trials (ICH-E9, http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideli

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
			ne.pdf) The argument for using both adjusted and unadjusted analyses for interpretation is addressed on page 36, Section G of the E9 guideline *"When the potential value of adjustment is in doubt it is often advisable to nominate the unadjusted analysis as the one for primary attention, the adjusted analysis being supportive"* Furthermore, the EMA takes a similar view to post-hoc analysis "Guideline on adjustment for baseline covariates in clinical trials" (section 5.4, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/03/WC500184923.pdf) *"In case the baseline imbalance is for a prognostic factor, sensitivity analyses including the baseline measure as a covariate should be performed in order to assess the robustness of the primary analysis"* Amgen provided a detailed justification on methodology, statistical rationale and plausibility argument for prognostic importance of additional covariates included in the analysis.The intent of the adjustment is to determine the cost-effectiveness for the "average" patient. As the covariate adjustment has the largest influence on the change in the ICER, Amgen believes that the true ICER is significantly below the lower bound of ~ $270K/QALY.
p.8	Economic Evaluation	Paragraph 4, line 11: "pERC agreed that the true ICER is likely at the higher end of the range"	The economic re-analysis by pCODR placed the ICER in the range of ~ $270K to $350K with the comment that the true ICER was expected to be at the higher end of the range. Two factors that contribute to the $350K figure include wastage and the assumption of no benefit beyond 42 months. Wastage will be negligible with the introduction of 10mg vial. In terms of benefit extrapolation, Jackson et al[1] note NICE's recommendation for three scenario: pessimistic, optimistic and compromise. Assuming an HR=1 at 42 months corresponds to the NICE pessimistic scenario. Amgen argues that without further knowledge of the true treatment effect, the compromise scenario should be adopted. Taking this position on wastage and extrapolation of benefit would support an ICER substantially less than the $270K/QALY (refer to preceding comment).

1. Jackson et al (2016) Extrapolating survival data from Randomized trials using External Data: A Review of Methods. http://mdm.sagepub.com/content/early/2016/03/21/0272989X16639900.full

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.