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

March 30, 2017

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Carfilzomib in combination with dexamethasone alone in the treatment of patients with relapsed multiple myeloma who have received 1 to 3 prior lines of therapy.
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 + dexamethasone (Kd) in the treatment of patients with RMM who have received 1 to 3 prior lines of therapy.
2) Agree with pCODR on the unmet need in this patient population and recognizing that Kd demonstrated a net clinical benefit when compared with bortezomib (bort) + dex (Vd), based on a statistically significant and clinically meaningful improvement in progression-free survival, a trend toward an improvement in overall survival, a manageable toxicity profile, and at least maintenance in patient's quality of life (QOL).
3) Disagree with pCODR on using 10-year time horizon in the HE model. Various data sources providing long-term survival estimates of R/RMM patients demonstrate a substantial proportion of these patients are still alive at 10 years, therefore, excluding the costs and outcomes of the patients alive thereafter is considered overly conservative.
4) Disagree with pCODR on modeling bort once weekly in the HE model without adjusting the efficacy outcomes in ENDEAVOR. There is no RCT that explored twice-weekly vs. once-weekly bort in the population of interest, and as a consequence there is no appropriate approach to conducting a reliable adjustment of efficacy outcomes in ENDEAVOR.

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.	____ 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 No.	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
p. 9	Registered Clinician Input	Paragraph 2; line 10: "pERC acknowledged input from... bort plus dex would be …"	"pERC acknowledged input from registered clinicians and concluded that Kd would be a reasonable treatment option for patients ineligible for the triplet therapy with KRd."
p.11	Adoption Feasibility	Paragraph 1, line 3: "Based on clinical opinion… who are not eligible for triplet…"	"Based on clinical opinion, it is anticipated that the doublet therapy with Kd will be the preferred treatment option in patients who are not eligible for triplet therapy"
p.11	Cost-effectiveness estimate: Time Horizon	Paragraph 1; line 14: "In addition, the CGP confirmed that bort is dosed once per week in clinical practice compared with twice – weekly dosing. pERC considered the clinical rationale for both of these inputs and accepted the changes made by the EGP."	The cost-effectiveness model submitted to pCODR includes efficacy inputs derived from the ENDEAVOR trial, which are unquestionably associated with the specific Kd and Vd doses and dosing schedules in the trial. Therefore, changing the dose or schedule would require an adjustment of the outcomes observed in the trial according to the updated dose or dosing schedule. There is no RCT trial that explored twice-weekly vs. once-weekly bort in the population of interest, and as a consequence there is no appropriate approach to conducting a reliable adjustment of efficacy outcomes in ENDEAVOR. It is very likely that, by reducing the dose or dosing schedule of bortezomib, the model results would increase the actual ICER of Kd in that setting.
p. 11	Cost-effectiveness estimate: time horizon	Paragraph 1;line 9: "pERC therefore accepted the EGP's use of a 10-year time horizon."	A 20-year time horizon is considered to be the most appropriate time period capturing all the important differences in costs and outcomes between Kd and Vd. Various data sources providing long-term survival estimates of R/RMM patients demonstrate that a substantial proportion of these patients are still alive at 10 years: 1) Data from the SEER registry, matched to ENDEAVOR patient characteristics, show that 29.0% of patients are alive at 10 years. 2) Orlowski *et al.*[1] published long-term results from a study in R/RMM comparing bort monotherapy with bort in combination with pegylated liposomal doxorubicin and dexamethasone. The analyses reveal that 13.2% of patients receiving bort monotherapy were alive at 9.2 years. Orlowski *et al*. enrolled patients diagnosed with MM in the early 2000s, and the standard of care has improved since. Significant improvement in OS has been reported by Kumar *et al*.[2] in patients diagnosed in 2006-2010 compared with 2001-2005 due to the introduction of novel agents: 10-15% higher OS at 5 years for the overall

			MM population and 25% higher OS at 6 years in patients aged 65 years or more. Moreover, improved outcomes are expected for Vd compared to bort alone.[3] Consequently, the proportion of patients receiving Vd in ENDEAVOR that would be alive at 9.2 years is expected to be significantly higher than that of Orlowski *et al*, justifying a time horizon longer than 10 years. 3) Despite the median age is between 65 and 70, R/RMM patients remain a heterogeneous population in terms of age, and incidence in younger patients cannot be neglected. For example, ENDEAVOR and ASPIRE trials enrolled R/RMM patients that were as young as 30 and 31 years old, respectively. In summary, the 10-year time horizon is considered not appropriate, as it neglects the costs and outcomes of the patients still alive after 10 years, consequently significantly overestimating the ICER of Kd vs. Vd.
p.7	Patient reported outcomes: Maintenance of quality of life	Paragraph 1; lines 6: "however, the minimal important difference (MID, 5 points) was not met. Similar treatment differences were observed on the QLQ-C30… the MIDs were not reached."	The observed between-group difference in QLQ-C30 Global Health Status (GHS)/QOL (point estimate of 3.51) was statistically significant (2-sided p-value<0.0001), demonstrates an improvement in QOL for Kd compared with Vd. Statistically significant differences between the treatment arms in ENDEAVOR were consistently observed for the QLQ-C30 GHS at all time points when Day 1 of the corresponding cycle overlapped (Weeks 12, 24, 36, 48, 60, and 72). Additionally, the between-group differences tended to slightly increase over time and exceeded the MID (5 points) at later visits (Week 60: 5.36 points; Week 72: 5.84 points), and approached the MID even at earlier visits (Week 36: 4.42 points; Week 48: 4.89 points). In conclusion, it is important to highlight that the observed differences in QOL were statistically significant favouring Kd over Vd, as well as clarifying that the between-group difference reached the MID at later visits and was close to the MID at earlier visits.
p.10	Economic Evaluation	Paragraph 6; line 2: "When combined with bort …, dex costs:"	"When combined with bort and at the recommended dose of 20 mg on days 1, 2, 4, 5, 8, 9, 11, 12 of a 21-day cycle, dexamethasone costs:"

1. Orlowski et al. J Clin Oncol. 2007 Sep 1;25(25):3892-901. Epub 2007 Aug 6.

2. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia*. 2013;28(5):1122-1128. doi:10.1038/leu.2013.313.

3. *European Public Assessment Report (EPAR). Velcade. 21 November 2013, EMA/CHMP/775037/2013. [Online]. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000539/WC500161881.pdf*.

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.