pan-Canadian Oncology Drug Review Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Lenalidomide (Revlimid) for Multiple Myeloma

December 3, 2015

1 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	REVLIMID (lenalidomide), ndMM NTE
Role in Review (Submitter and/or Manufacturer):	Manufacturer
Organization Providing Feedback	Celgene 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) Celgene agrees and supports the recommendation for funding Revlimid for first-line treatment of patients with multiple myeloma who are not eligible for autologous stem cell transplantation.
2) Celgene agrees with pERC that based on the efficacy and safety of Ld, continuous treatment is now a real option and represents a paradigm shift in multiple myeloma treatment. Furthermore, the opportunity to combine con-Ld with other MM treatments, now and into the future, will further improve patient outcomes.
3) Celgene received feedback from our HCP expert advisors on the initial recommendation. Although there was general agreement and support for conversion to the final recommendation, an area of concern brought up by the advisors is related to the suggested criteria limitation to patients with ECOG status of ≤2. Although the FIRST trial was studied in higher performance status patients, experts feel that con-Ld would also be a valuable option for patients with ECOG > 2. They acknowledged that the criteria's inclusion of the ECOG status of ≤2 excludes a patient population in the real world that may also benefit from con-Ld. These patients may be frail, have a range of co-morbidities, and have mobility restrictions. Options such as MPB may not be feasible given the toxicity and requirement for travel. Other options such as MP or MPT, although oral, are clinically inferior to con-Ld. Con-Ld may provide these patients a highly tolerable,

effective and convenient treatment option.

4) Celgene disagrees that the duration of treatment is unknown. The Initial Clinical Guidance Report notes on page 35, that the median duration of treatment for con-Ld from the FIRST trial was 18.4 months.

5) Celgene agrees with pERC that despite the lack of a head-to-head RCT, the body of evidence suggests that the incremental benefit of con-Ld over MPB is unlikely to be zero. Moreover, Celgene disagrees with the Economic Guidance Panel (EGP) to using the assumption of equal efficacy between con-Ld and MPB. As noted by pERC, the body of evidence available suggests this is highly implausible.

   Kumar et al. (2010) showed in their indirect comparison for first-line therapy for patients with MM a statistically non-significant difference between MPB vs. MPT for the outcome of OS (HR 0.80, 95% CI 0.54-1.00). Furthermore, an NMA conducted by NICE (2011) in the same population of interest concluded that the OS benefit between MPB and MPT were "*virtually identical*". Consequently, if MPB and MPT are the same and it was demonstrated in the FIRST trial the superiority of con-Ld vs. MPT, it is highly likely for con-Ld to have better efficacy than MPB.

6) Celgene disagrees with the Clinical Guidance Panel's cited limitations of the submitted NMA. The NMA was conducted in accordance with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines, *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, PICOS-T (Patient, Interventions, Comparisons, Outcomes, Study Design, and Time period*) inclusion/exclusion criteria, and the *Cochrane Handbook for systematic reviews of interventions*. Moreover, the evidence included reflects the full body of evidence noted by pERC.

   MPT-T studies were excluded from the network because they would have increased heterogeneity and increased uncertainty in the results from the difference in use of MPT-T and the patient population. The FIRST study utilized fixed duration MPT whereas the MPT-T studies used continuous therapy. Moreover, a previously conducted NMA by the NICE ERG also excluded these studies in its assessment of MPT and MPB for the same reasons. Thus, the approach taken is consistent with other HTA assessments given the study question. The CGP does not provide any rationale how continuous dosing of thalidomide was relevant given MPT was utilized as a fixed duration treatment in FIRST.

   The CGP cited multiple linkages and few studies included in the network. The number of linkages required to establish a network is not a limitation as long as there is no major heterogeneity across studies. Note if MPT-T was added to the network, the issues of multiple linkages would pose a greater limitation. In absence of a head-to-head clinical trial, more studies is always preferable to less to establish a network. However, in this specific context, the number of trials included in the network represents the full body of appropriate evidence to characterize the relative efficacy between con-Ld and MPB.

   The CGP cited different doses of MPT used in the MPT regimen across studies. Despite that slight difference in the MPT doses exists, there is no heterogeneity in relative efficacy of MPT vs. MP in OS and PFS across all these studies (I^2 =0%). Thus, the relative effect of MPT (fixed duration) vs. MP should be considered very reliable/consistent.

The CGP cited differences in the follow-up duration between studies. Although the median follow-up time of the FIRST trial is not as long as that of the VISTA, the

relative treatment efficacy in OS and PFS of con-Ld vs. MPT was further improved based on the 2014 data cut (from the 2013 data cut). Thus, we can reasonably assume the relative efficacy of con-Ld vs. MPT in a further data cut would remain the same or even better.

The CGP cited there was no assessment of model fit (i.e. fixed vs. random effects). Given there is no heterogeneity across studies, use of results from the random effect model would further increase the uncertainty of the results as the results would be heavily driven by the prior assumption used in the analysis. We did assess the model fit between the fixed and random effect model using the "Deviance Information Criterion (DIC)" as suggested by the NICE DSU. A lower value of the DIC indicates a better model fit. The DIC for the fixed effect model is -3.755 and -3.086 for the random effect model, suggesting that the fixed effect model yields a better model fit.

Based on an assessment and utilization of all available evidence and the use of recommended evidence based methods endorsed by HTA agencies, the submitted NMA represents the best possible evidence to estimate the magnitude of clinical benefit. Moreover, based on the NMA con-Ld could be considered cost-effective, assuming a cost-effectiveness threshold of approximately $100,000/QALY.

7) Celgene disagrees with the EGP to shorten the time horizon of the cost-effectiveness model. There appears to be a continued misunderstanding between a modeling time horizon and average life expectancy. The modeling time horizon represents the length of time required within a model by a cohort of patients to all reach death. The economic model utilized data from the FIRST trial where the age of patients enrolled ranged from 40 to 92 years of age. The economic model simulates over the course of time the differential progression of these patients through their disease and eventually death. It is plausible that the course of disease of a 40 year old patient requires 38 years in order to progress to death. The modeling time horizon does not represent the expected average amount of additional time a patient will survive with treatment. The submitted economic model provided the estimated average time a patient would survive which is plausible.

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 Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
3	Summary of pERC Deliberations	Paragraph 3, line 1	The sentence indicates that lack of provincial funding for MPT is "due to restrictions on the distribution of thalidomide." This rationale is factually incorrect as the distribution and requirements for prescribing thalidomide are no different from lenalidomide. It should simply be noted that lack of accessibility is due to provinces choosing to not fund thalidomide.
1	pERC Recommendation	Paragraph 2, line 7-9	The recommendation notes that there is considerable uncertainty in the magnitude of benefit due to the lack of direct comparative evidence between MPT and MPB. It is unclear, at this point in the recommendation, why the lack of evidence between these two regimens is the reason for uncertainty. Should this be between con-Ld and MPB?

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
5	Key efficacy results	Paragraph 2	During the checkpoint meeting, Celgene provided recently updated and publicly available data on OS from the FIRST trial. It is unclear why this information was not included in the recommendation. The updated survival data based on a March 3, 2014 interim analysis showed median OS was 58.9 months for con-Ld and 48.5 months for MPT, respectively (HR 0.75; 95% CI 0.62, 0.90).

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.