pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: Lenalidomide (Revlimid)	
Submitted Reimbursement Request: The combination of lenalidomide, bortezomib, and low-dose dexamethasone, for the treatment of newly diagnosed multiple myeloma patients in whom stem cell transplantation is not intended	
Submitted By: Celgene Inc.	**Manufactured By:** Celgene Inc.
NOC Date: Not Available	**Submission Date:** December 21, 2018
Initial Recommendation: May 31, 2019	**Final Recommendation:** June 19, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	Lenalidomide costs $424.00 (25mg), $403.00 (20mg), $382.00 (15mg), $361.00 (10mg), $340.00 (5mg) per capsule. • For induction, lenalidomide costs $282.67 per day and $7,914.67 per 28 day cycle [25 mg orally once a day on days 1 to 14 during cycles of a 21-day cycle (8 cycles max)] • For maintenance (cycles 9 onwards), lenalidomide costs $424.00 per day and $11,872.00 per 28 day cycle [25 mg orally once a day on days 1 to 21 for a 28 day cycle (until progression)]

pERC RECOMMENDATION

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions***

☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends to reimburse lenalidomide (Revlimid) in combination with bortezomib and low-dose dexamethasone in patients with newly diagnosed multiple myeloma in whom stem cell transplantation is not intended if the following condition is met.

- Feasibility of adoption is addressed (budget impact).

Reimbursement should be in patients with a good performance status and treatment (with lenalidomide plus low-dose dexamethasone for the maintenance phase) should continue until unacceptable toxicity or disease progression. pERC made this recommendation because it was satisfied that there is a net clinical benefit of lenalidomide plus bortezomib and low-dose dexamethasone (VLd) compared with lenalidomide plus dexamethasone (Ld) in this setting based on a statistically significant and clinically meaningful improvement in progression-free survival and overall survival and a manageable toxicity profile. pERC was also satisfied that VLd aligns with patient values of having a treatment that controls the disease and disease related symptoms and has a manageable toxicity profile.

pERC concluded that VLd may be cost-effective, at the list price, compared with Ld. pERC was unable to make an informed recommendation on the comparison of VLd to CyBorD. Although pERC acknowledged that there is likely a net clinical benefit of VLd compared with CyBorD, in the absence of reliable cost-effectiveness estimates comparing VLd with CyBorD, the cost-effectiveness remains unknown. Depending on where the market share for

	VLd is taken from (Ld or CyBorD), pERC agreed that the budget impact analysis (BIA) could be substantial as CyBorD is a significantly less costly therapy than VLd. pERC therefore had concerns that the budget impact may be underestimated.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Optimal Sequencing of Available Therapies After Progression on Lenalidomide plus Bortezomib and Dexamethasone** pERC concluded that the optimal sequencing of therapies for patients with newly diagnosed multiple myeloma in whom stem cell transplantation is not intended is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments. pERC recognizes that provinces will need to address this issue upon implementation of a reimbursement recommendation for VLd, and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value. **Budget Impact and Adoption Feasibility** pERC noted that in the submitter's analysis, the market share for VLd in a scenario where VLd is reimbursed is taken from melphalan plus prednisone plus bortezomib (VMP), a combination agent which is not widely used in the Canadian setting. pERC agreed that VLd will likely instead replace Ld or CyBorD (pending the provision of an analysis to determine the cost-effectiveness of CyBorD compared to VLd). Depending on where the market share for VLd is taken from (Ld or CyBorD), pERC agreed that the budget impact analysis (BIA) could be substantial as CyBorD is a significantly less costly therapy than VLd. **Time Limited Need for Patients who have recently Started Treatment with Ld** At the time of implementing a reimbursement recommendation for VLd, jurisdictions may consider addressing the time-limited need of adding bortezomib (V) to the treatment regimen for patients who recently initiated treatment with Ld. However, pERC noted that this may not apply to patients who have been on Ld for a prolonged period of time and are responding well. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

Multiple myeloma is an incurable plasma cell neoplasm that represents 1.3% to 1.5% of all new cancers in Canada with an estimated 2,900 new cases annually with 1,450 patients dying from myeloma. The median age at diagnosis is 69 years with a five-year overall survival estimated at 48.5%. Without effective therapy, multiple myeloma results in a significant decrease in quality of life and is universally fatal. Approximately half of patients newly diagnosed will not be eligible for stem cell transplant due to advanced age, comorbidities and/or impaired functional status. Choosing the appropriate patients for autologous stem cell transplant (ASCT) is at the discretion of the treating physician. Current standard frontline systemic therapy regimens in Canada for patients who are transplant-ineligible include combinations of bortezomib with an alkylating agent (melphalan or cyclophosphamide) and a corticosteroid; or lenalidomide and dexamethasone. Regardless of the choice and duration of initial therapy, myeloma will eventually relapse in the vast majority and further therapy will be required, therefore pERC noted that there is a need for more effective therapies in this setting.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

The pCODR systematic review included one open label, randomized, phase III randomized, trial, SWOG-S0777, which compared the efficacy and safety of lenalidomide (Revlimid) in combination with bortezomib (Velcade) and low-dose dexamethasone (VLd) to lenalidomide plus low-dose dexamethasone (Ld) as a first-line treatment in patients with newly diagnosed multiple myeloma in whom stem cell transplantation is not intended. pERC noted that the SWOG-S0777 trial demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) and overall survival (OS) for VLd compared with Ld. pERC noted that OS is an end point that is not often achieved in myeloma studies and acknowledged the clinical significance of improvements in OS. pERC noted that quality of life was not measured in the SWOG-S0777 trial. pERC also discussed the toxicity profile of VLd and agreed with the pCODR Clinical Guidance Panel (CGP) that toxicities were manageable. pERC further noted that the alternative dosing schedule of bortezomib that is used in Canada (subcutaneous dose given once weekly) compared with the twice weekly intravenous dosing of bortezomib in the SWOG-S0777 trial will substantially reduce toxicities associated with treatment, particularly neuropathy. pERC therefore agreed toxicities on the trial may have been overestimated. Overall, pERC agreed that there is a net clinical benefit of VLd treatment compared with Ld in the treatment of patients with newly diagnosed multiple myeloma in whom stem cell transplantation is not intended.

pERC discussed the generalizability of the SWOG-S0777 trial results. In the absence of direct evidence comparing VLd to CyBorD, real-world evidence was available comparing the efficacy of Ld with CyBorD. The conclusions of this comparison noted that Ld and CyBorD have similar efficacy. This was also supported by the CGP and input from registered clinicians. Based on this, pERC agreed that the evidence from the SWOG-S0777 trial can be generalized into the population of patients who may be treated with CyBorD. Given that VLd demonstrated a statistically significant and clinically meaningful improvement in PFS and OS when compared with Ld, pERC concluded that VLd is also likely more effective than CyBorD. pERC also discussed whether or not the definition of transplant ineligibility used in the SWOG-S077 trial is generalizable to the Canadian population. pERC noted that in Canada, a majority of patients who are 70 and younger with fewer comorbidities would be considered for frontline high-dose therapy and stem cell transplant. Thus, the definition of transplant-ineligible in Canada is different compared to the definition used in the SWOG trial. This difference was likely due to variations in practice, in particular in the US at the time of the study, in which patients who eligible for frontline novel therapy (bortezomib-based or lenalidomide-based) were not necessarily considered for immediate stem cell transplantation. Despite these differences in the definition of transplant ineligibility, pERC felt that the results of the trial demonstrating superiority of VLD over LD could still be generalizable to the Canadian context. pERC further agreed that the SWOG-S0777 trial results can be generalized in patients with myeloma and complications of amyloidosis as a consequence of the disease but not in patients with primary amyloidosis. Lastly, pERC agreed that there is insufficient evidence to support or refute the use of VLd as an induction regimen prior to transplant or as treatment in other settings other than first-line treatment in patients in whom there is no intent for transplant.

pERC reviewed input from one patient advocacy group. pERC noted that patients value treatment options that can control their disease and disease related symptoms, have a more manageable toxicity profile, and improve their quality of life. Based on the statistically significant and clinically meaningful improvements in PFS and OS, and a manageable toxicity profile, pERC agreed that VLd aligns with patient values. Although quality of life was not measured on the SWOG-S0777 trial, among six patients who had experience with VLd, two of these patients indicated that VLd had improved their quality of life and allowed them to enjoy a normal life. While pERC recognizes the difficulty in identifying patients who have had experience with an agent under review, in the absence of QoL data from the trial, pERC was unclear how meaningful input from six patients were in determining whether or not VLd improved patients' quality of life. Patients also found VLd to be tolerable and that it improved their health and wellbeing. Overall pERC concluded that VLd aligns with patient values.

pERC deliberated upon the cost-effectiveness of VLd compared with Ld and CyBorD, both relevant comparators in the Canadian setting. For the comparison to Ld, pERC noted that the pCODR Economic Guidance Panel's (EGP) estimates were not vastly different from the submitter's estimates. The EGP made changes to the dose intensity (or the effect of dose intensity on the cost of lenalidomide), the time horizon, and end of life care costs. Given the small impact these inputs had on the incremental cost-effectiveness ratio (ICER), pERC concluded that VLd may be cost-effective, at the list price, compared with Ld. pERC further considered the comparison between VLd and CyBorD and was unable to make an informed recommendation on the cost-effectiveness of these two agents. Based on input from the CGP, registered clinicians and evidence from real-world data demonstrating similarity in efficacy between Ld and CyBorD, pERC was satisfied that there is likely a net clinical benefit of VLd compared with CyBorD. Despite this, in the absence of reliable cost-effectiveness estimates comparing VLd with CyBorD, the cost-effectiveness remains unknown.

pERC discussed the feasibility of implementing a funding recommendation for VLd. Both the CGP and registered clinicians agreed that patients may be deemed ineligible for transplant due to advanced age, comorbidities, or patient preference. pERC also noted that bortezomib was dosed twice weekly on the SWOG-S0777 trial but agreed with the CGP that in Canadian clinical practice, bortezomib would be administered as a once weekly subcutaneous dose. pERC further agreed that bortezomib is given up to a maximum of 8 cycles and the Committee does not anticipate that patients would have need to be treated beyond 8 cycles. However, pERC acknowledged that it is not able to make an evidence-informed recommendation on continuing bortezomib beyond 8 cycles. pERC considered a number of implementation questions related to sequencing of subsequent agents and noted possible algorithms suggested by registered clinicians. pERC agreed that sequencing of subsequent agents will be dependent on the treatment and responses that patients had to first-line therapy, as well as individual characteristics and comorbidities of patients. Based on input from registered clinicians pERC agreed that, generally, patients are likely to receive a daratumumab containing regimen in the second-line setting followed by pomalidomide- or carfilzomib-based treatments in the third line setting and beyond. Lastly, pERC agreed that depending on where the market share for VLd is taken from (Ld or CyBorD), if VLd is reimbursed, the BIA could be substantially underestimated as CyBorD is a less costly therapy than VLd.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review.
- Other literature in the Clinical Guidance Report that provided clinical context.
- An evaluation of the manufacturer's economic model and BIA.
- Guidance from the pCODR clinical and economic review panels.
- Input from one patient advocacy group (Myeloma Canada).
- Input from registered clinicians.
- Input from pCODR's PAG.

Feedback on the pERC Initial Recommendation was also provided by:

- One clinician group, (Cancer Care Ontario Hematology DAC)
- The PAG
- The submitter (Celgene Inc.)

The pERC Initial Recommendation was to reimburse lenalidomide (Revlimid) in combination with bortezomib and low-dose dexamethasone in patients with newly diagnosed multiple myeloma in whom stem cell transplantation is not intended. Feedback on the pERC Initial Recommendation indicated that the manufacturer, PAG, and registered clinician group agreed with the Initial Recommendation.

The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the efficacy and safety of lenalidomide (Revlimid) in combination with bortezomib and dexamethasone on patient outcomes compared with appropriate comparators in patients with newly diagnosed multiple myeloma (MM) for whom stem cell transplantation is not intended.

Studies included: One randomized controlled trial

The pCODR systematic review included one phase III randomized control trial (RCT), SWOG-S0777, comparing lenalidomide (Revlimid) in combination with bortezomib (Velcade) and low-dose dexamethasone (VLd) with lenalidomide in combination with low-dose dexamethasone (Ld). Three analyses were available of the SWOG-S0777 trial based on different data cuts and/or different sample sizes (due to differing censoring rules). The data published by Durie et al. 2017 was based on a November 5, 2015 data cutoff and included 470 patients. An abstract presented an updated analysis with a May 15, 2018 data cutoff and included 461 patients. The clinical study report (CSR) reported analyses based on November 5, 2015 and December 1, 2016 data cuts with sample sizes of 523 and 460, respectively.

In the absence of direct evidence to compare the efficacy and safety of VLd with cyclophosphamide, bortezomib, and dexamethasone (CyBorD), a relevant treatment option in the Canadian setting, the pCODR review also considered contextual information on evidence from two data sources comparing the efficacy of CyBorD to Ld. One source reported the findings of a RCT comparing CyBorD to Ld for the treatment of non-transplant eligible multiple myeloma patients in Alberta and a second (reported in an abstract and poster) was a retrospective cohort study for 423 transplant-ineligible MM patients treated with: cyclophosphamide, bortezomib, and prednisone (CyBorP)/CyBorD; 160 patients treated with Ld, 204 patients treated with bortezomib (Velcade), melphalan, and prednisone (VMP); and 55 patients treated with bortezomib (Velcade) and dexamethasone/prednisone (Vd/VP). Based on the records identified, CyBorD and Ld have similar clinical outcomes. pERC considered this information and agreed that the evidence from the SWOG-S0777 trial comparing VLd with Ld, can be generalized to the population of patients who may be treated with CyBorD. Given that VLd demonstrated a statistically significant and

clinically meaningful improvement in PFS and OS when compared with Ld, pERC concluded that VLd is also likely more effective than CyBorD.

Patient populations: Trial population generalizable to Canada

Key eligibility criteria included age ≥ 18 years, have newly diagnosed myeloma and presence of CRAB criteria (C = calcium, R = renal impairment, A = anemia, B = bone involvement). Baseline characteristics of patients enrolled were similar among the three sources reporting on the SWOG-S0777 trial. Based on the Durie 2017 publication the proportion of those older than 65 years was 38% and 48% in VLd and Ld, respectively. The median age was 63 years and 61 years, in VLd and Ld, respectively. The proportion of women in the VLd and Ld groups was 37% and 47%, respectively.

The majority of patients in the SWOG-S0777 trial were classified as having intent for transplant (69% and 68% in VLd and Ld groups, respectively). Based on the opinion of the CGP, intent to transplant may mean that the transplant was not planned as part of primary treatment but that transplant might be offered in the future, perhaps as part of primary treatment but more likely as treatment for relapse. pERC noted that Canadian patients are typically considered for transplant in first-line treatment while the SWOG-S077 trial reflected US clinical practice where patients may become eligible in subsequent lines of treatment. As a result, the majority of patients enrolled in the trial were classified as having intent for transplant although the intent may have been to proceed to transplant during subsequent lines of therapy. Based on this, pERC agreed with the CGP that the majority of patients in the SWOG-S0777 trial are representative of Canadian patients who would be deemed ineligible for transplant in first-line treatment.

Based on the SWOG S0777 trial, the induction regimen of lenalidomide is 25 mg orally once a day on days 1 to 14 plus bortezomib at 1.3 mg/m^2 intravenously on days 1, 4, 8, 11 plus 20 mg oral dexamethasone on days 1, 2, 4, 5, 8, 9, 11, and 12. Maintenance treatment included 25 mg oral lenalidomide once a day for 21 days plus 40 mg oral dexamethasone once a day for days 1, 8, 15, and 22 of each 28-day cycle. pERC noted that bortezomib was dosed twice weekly on the SWOG-S0777 trial but agreed with the CGP that in Canadian clinical practice, bortezomib would be administered as a once weekly subcutaneous dose.

Key efficacy results: Statistically significant and clinically meaningful improvement in progression-free survival and overall survival

The key efficacy outcome deliberated on by pERC included PFS, the primary outcome. Key secondary outcomes included OS and rate of overall response.

The median PFS for VLd and Ld was 43 and 30 months; respectively (HR = 0.712, 95% CI, 0.560 to 0.906, $P < 0.0018$). In the updated analysis, the median PFS for VLd and Ld was 41 and 29 months; respectively (HR = 0.742, 95% CI, 0.594 to 0.928, $P < 0.003$). The median OS for VLd and Ld was 75 and 64 months; respectively (HR = 0.709, 95% CI, 0.524 to 0.959, $P < 0.0125$). The median duration of response for VLd and Ld was 52 and 38 months; respectively (HR = 0.695, $P < 0.0133$). Results reported in the CSR were generally aligned with the Durie 2017 publication. In the 2018 update to the SWOG-S0777 data, the median OS for VLd was not reached and was 69 months for Ld; respectively (HR = 0.709, 95% CI, 0.543 to 0.926, $P < 0.0114$).

Based on these results, pERC agreed that VLd demonstrated a statistically significant and clinically meaningful improvement in PFS and OS when compared with Ld. pERC noted that OS is an end point that is often not achieved in myeloma studies and acknowledged the clinical significance of improvements in OS.

Patient-reported outcomes: Not measured in the SWOG-S0777 trial

Although quality of life was not measured in the SWOG-S0777 trial, patient input indicated that of the six patients who had experience with VLd, two thirds rated quality of life as good or excellent. While pERC recognizes the difficulty in identifying patients who have had experience with an agent under review, in the absence of QoL data from the trial, pERC was unclear how meaningful input from six patients were in determining whether or not VLd improved patients' quality of life.

Safety: Manageable toxicity profile

Adverse Events (AEs) of grade 3 or higher were more common in patients treated with VLd (82%), compared with Ld (75%). The most commonly reported grade 3 AE in the VLd group were hematological AE affecting the blood or bone marrow (73%), neurological (76%) and metabolic or laboratory results (53%), with two deaths reported as not directly attributable to treatment. Additionally, grade 3 pain, grade 3

constitutional symptoms and grade 3 gastrointestinal events occurred in 29%, 46% and 49% of patients, respectively. The most commonly reported grade 3 AEs in the Ld group were hematological AEs affecting the blood or bone marrow (70%), metabolic/laboratory results (51%) and constitutional symptoms (35%), with no deaths reported as an adverse event.

pERC discussed the toxicity profile of VLd and agreed with the CGP that toxicities were manageable. pERC further noted that the alternative mode of administration and dosing schedule of bortezomib that is used in Canada (subcutaneous dose given once weekly) compared with the twice weekly intravenous dosing of bortezomib in the SWOG-S0777 trial will substantially reduce toxicities associated with treatment, particularity neuropathy. pERC therefore agreed toxicities on the trial may have been overestimated.

Need and burden of illness: Myeloma will eventually relapse in all patients

Multiple myeloma is an incurable plasma cell neoplasm that represents 1.3% to 1.5% of all new cancers in Canada with an estimated 2,900 new cases annually with 1,450 patients dying from myeloma. The median age of diagnosis is 69 years with a five-year OS estimated at 48.5%. Without effective therapy, the illness results in a significant decrease in quality of life and is universally fatal.
The management of symptomatic myeloma is reliant on effective systemic chemotherapy and supportive measures. Patients with good performance status, preserved organ function and limited comorbidities are potentially eligible for high dose chemotherapy and autologous hematopoietic stem cell transplantation, which improves median survival by two to three years in comparison with conventional dose therapy. Approximately half of patients newly diagnosed will not be eligible for this treatment due to advanced age, comorbidities and/or impaired functional status. Choosing the appropriate patients for ASCT is at the discretion of the treating physician and approximately half of patients are transplant eligible.

Current standard frontline systemic therapy regimens in Canada for transplant-ineligible patients include combinations of bortezomib with an alkylating agent (melphalan or cyclophosphamide) and a corticosteroid; or lenalidomide and dexamethasone. Historically, stem cell transplant was an option for patients at the time of relapsed disease, and consequently, patients were assessed whether a transplant was intended in the first-line setting or not. Standard practice in Canada has evolved, and the current standard of practice is to determine eligibility for autologous stem cell transplantation at the time of diagnosis, and is generally only considered as part of first-line therapy. Regardless of the choice and duration of initial therapy, myeloma will eventually relapse in the vast majority and further therapy will be required.

Registered clinician input: Depth and duration of response with VLd are important

Input was received from one single clinician and one clinician group of five on behalf of the Myeloma Canada Cancer Research Network. Input from registered clinicians noted the following treatment options as being relevant comparators for the indication under review: Ld, CyBorD, bortezomib plus melphalan plus prednisone (VMP), and cyclophosphamide with bortezomib and prednisone (CyBorP). Clinicians agreed the most common treatments were CyBorD and Ld. One clinician stated that CyBorD and Ld are considered equivalent in terms of efficacy based on recent Canadian data. Although the toxicity profile favours Ld over CyBorD, this clinician stated that recent Canadian real-world data suggested an equivalency between CyBorD and Ld, but a slight superiority of Ld over CyBorD in regard to PFS in an unmatched population.

The joint clinician input identified unmet need for potent therapies resulting in long-term disease control. For patients who are fit enough for this triplet, one of the clinicians suggested VLd should be considered standard of care. Clinicians also noted that patients with standard and high risk of cytogenetic disease, would be a population of interest who would benefit from the VLd combination although patients who are considered frail would continue being offered Ld or CyBorD. Clinicians identified that patients may become ineligible for transplant due to age (older than 70 years of age), or presence of comorbidities. The single clinician input stated that inclusion and exclusion criteria from the trial were considered reasonable and applicable to clinical practice and stated that CRAB criteria could be used to identify eligible patients.

Clinicians noted that the depth and duration of response with VLd were important considerations for both long and short-term outcomes. Clinicians also indicated that VLd is well tolerated with no significant increases in toxicity compared with Ld and CyBorD. Clinicians further noted that they would prefer to use the best combinations as early as possible as the greatest benefit from treatment is usually observed in the first-line setting. It was also identified that VLd is important to have while clinicians wait for data on the efficacy and safety of monoclonal antibodies, such as daratumumab, to become available in this

setting. All clinicians agreed that cytogenetic testing is routinely conducted. Patients with high cytogenetic risk (mainly del17p) generally require greater oversight and would be treated with a bortezomib-based regimen.

Clinicians noted that VLd would be front line therapy for all patients who would be eligible for Ld or CyBorD. However, Ld and CyBorD would still have a role in treating frail patients with contraindications (small minority of patients). One clinician noted that having VLd as first-line treatment would help to ensure the best depth and duration of response, which would be difficult to achieve in later lines of therapy.

Although a number of potential sequences of treatment were suggested by registered clinicians, in general, daratumumab-based regimens were considered next choice for second-line treatment, if VLd were to be used as first-line therapy. Following lines of therapy included options involving pomalidomide or carfilzomib-based treatments.

PATIENT-BASED VALUES

Values of patients with Multiple Myeloma: Symptom and disease control, manageable toxicity profile

Input was received from Myeloma Canada and supplemented by reference to two prior Myeloma Canada submissions to pCODR for various lines of therapy. Patients providing input as part of the current submission identified that aspects of myeloma rated most important to control were infections, followed by kidney problems, mobility, pain, fatigue, neuropathy and shortness of breath. Patient respondents indicated that symptoms of myeloma affect their day-to-day activity and quality of life. Patients' ability to work was most affected, followed by the ability to exercise, travel, volunteer, concentrate, conduct household chores, fulfill family obligations, and spend time with family. Patients rated disease control as the most important expectation with current treatment. Among patients commenting on their current experiences with treatment, 10% and 11% of patients found diarrhea and constipation completely intolerable, respectively and 20% to 25% indicated that low blood counts, fatigue, dyspnea and infections were somewhat intolerable.

Patients described their experience of myeloma in the two prior pCODR submissions for myeloma in various lines of therapy. Among 294 patients responding, the majority rated access to effective treatments for myeloma (97%), ability of physicians to choose a treatment agent based on side effects profile (86%) and improvements in quality of life with treatment (89%) as very important. Among 202 patients responding, half (51%) noted financial implications related to drug cost, followed by travel costs (33%) and lost income due to work absence (32%). A quarter of patients (25%) responded that they had no financial implications related to treatment for myeloma. Among 155 patients responding, the majority (74%) indicated that they had not experienced financial difficulties accessing treatment. About a quarter (23%) indicated they had faced hardship including being denied treatment (6%), drug not covered (5%), limited to covered treatments (3%), travel to treatment (2%), cost of drugs (2%), access to physician (1%), access to available bed (1%), treatment not available (1%), and waited for treatment approval (1%).

A total of four caregivers provided input as part of the current review. When asked about the impact of caring for a loved one on their day-to-day activity and quality of life, three of the four caregivers rated the ability to concentrate as a 4 on a scale of 1 to 5 (1-not at all, and 5-highly affected), while 2 of 4 caregivers rated ability to work, travel and volunteer as highly affected (5). Among 123 caregivers responding in the prior pCODR reviews, 115-120 indicated that caring for someone with myeloma most impacted their ability to travel, followed by the ability to volunteer, spend time with family and friends, to concentrate, fulfill family obligations, to work, exercise, and to conduct household chores.

Patient values on treatment: Maintain quality of life, disease, and symptom control

Input received as part of prior pCODR submissions for myeloma in various lines of therapy showed that among 261 patients responding, patients valued the following outcomes when treating their myeloma: maintain quality of life or normal life (36%), manage/minimize side effects (20%), control the disease (19%), access to effective treatments (15%) and control symptoms (13%). Other aspects that were important included access to effective treatments (15%), achieve or maintain remission, prolong survival, access to a skilled medical team, to be cured, affordable treatments, disease status, maintain physical fitness, minimal use of drugs, and to feel hopeful.

Input was received from six patients through the Myeloma Canada survey for the current review. These patients had not had previous treatments and were not eligible for a stem cell transplant. When asked about expectations on the most import aspect of their disease to control, 40% of these respondents ranked disease control and prolonged life as the most important treatment expectations followed by fewer side effects and the ability to enjoy a normal life. The majority of patients (67%) indicated that VLd fulfilled their expectations for disease control while about a third of patients (33% each) noted VLd fulfilled the expectations for improved quality of life, remission, prolonged life, and enjoying a normal life. Of these six patients, 67% noted that VLd improved their health and wellbeing and 50% noted that it improved their long-term health outlook.

All six patients found the side effects of treatment with VLd to be tolerable or very tolerable. Among side effects experienced, the majority of respondents (50%) found diarrhea to be somewhat intolerable, followed by constipation (33%), and 20% each for fatigue, dyspnea, decreased appetite and headache. None of the respondents found the side effects completely intolerable. Most patients rated their quality of life as fair (33%) or good (50%) while 17% rated their quality of life as excellent while on VLd. Overall, five of the six patients indicated that VLd met their expectations.

Based on the statistically significant and clinically meaningful improvements in PFS and OS, and the manageable toxicity profile, pERC agreed that VLd aligns with patient values. Although quality of life was not measured on the SWOG-S0777 trial, input from six patients who had experience with VLd indicated that two of these patients had improved their quality of life and allowed them to enjoy a normal life. While pERC recognizes the difficulty in identifying patients who have had experience with an agent under review, in the absence of QoL data from the trial, pERC was unclear how meaningful input from six patients were in determining whether or not VLd improved patients' quality of life. Patients also found VLd to be tolerable and that it improved their health and wellbeing. Overall pERC agreed that VLd aligns with patient values.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness analysis

The pCODR EGP conducted a cost-effectiveness analysis of lenalidomide (Revlimid) in combination with bortezomib (Velcade) and dexamethasone (VLd) in adult patients with newly diagnosed multiple myeloma in whom transplant is not intended.

Basis of the economic model: Clinical and cost inputs

Costs considered in the analysis include drug acquisition, dose intensity, drug administration costs, AE costs, terminal care costs, stem cell transplant cost, subsequent therapy costs, and resource use costs.

The clinical effects considered in the analysis were PFS, OS and time on treatment based on the SWOG-S0777 trial. Other clinical effect estimates considered in the model include time to next treatment, and health related utilities.

Drug costs: ICER sensitive to the strength and combination of lenalidomide capsules

Lenalidomide costs $424.00 (25 mg), $403.00 (20 mg), $382.00 (15 mg), $361.00 (10mg), $340.00 (5 mg) per capsule.

Induction: 25 mg orally once a day on days 1 to 14 during cycles of a 21-day cycles (8 cycles maximum)

- $282.67 per day
- $7,914.67 per 28 day cycle

Maintenance (cycles 9 onward): 25 mg orally once a day on days 1 to 21 for a 28-day cycle (until progression)

- $424.00 per day
- $11,872.00 per 28 day cycle

Bortezomib costs $1,402.42 per 3.5mg vial. At the recommended dose, bortezomib is given at 1.3 mg/m^2 iv during cycles on days 1, 4, 8 and 11 for 21day cycles (8 cycles max). In Canadian clinical practice, bortezomib is given as 1.3 mg/m2 subcutaneously on days 1, 8, 15 and 22 for 21-day cycles (8 cycles max).

- $200.35 per day
- $5,609.68 per 28 day cycle

Dexamethasone costs $0.30 per 4 mg and $0.08 per 1mg tablet.

Induction: 20 mg taken orally on days 1, 2, 4, 5, 8, 9, 11 and 12 for 21 day cycles (8 cycles max)

- $0.57 per day
- $16.00 per 28 day cycle

Maintenance (cycles 9 onwards): 40mg taken orally on days 1, 8, 15 and 22 for 28 day cycles (until progression)

- $0.43 per day
- $12.00 per 28 day cycle

Cost-effectiveness estimates: Likely cost-effective compared with Ld, unknown cost-effectiveness compared with CyBorD

pERC deliberated upon the cost-effectiveness of VLd compared with Ld and CyBorD, both relevant comparators in the Canadian setting. For the comparison to Ld, pERC noted that the pCODR EGP estimates were not vastly different from the submitter's estimates.

pERC noted that the EGP's changes to how dose intensity is captured in the model had the largest impact on the ICER. In the model, the dose intensity observed in the SWOG S0777 trial was multiplied by the cost, to arrive at the expected cost for each agent. In EGP re-analysis, both the strength of each dose and the number of capsules were used to calculate the cost of lenalidomide. Furthermore, changes to the time horizon (reduced from 25 years in the base case to 15 years) were made to reflect a more plausible clinical course for the disease. Lastly, changes were made to the terminal care costs in the last 30 days of life to better reflect conversion from US dollars to Canadian dollars. When these changes were combined, the ICER changed from $49,484/QALY to $51,150/QALY-53,300/QALY. Given the small impact these inputs had on the ICER, pERC concluded that VLd may be cost-effective, at the list price, compared with Ld.

pERC further considered the comparison between VLd with CyBorD and was unable to make an informed recommendation on the cost-effectiveness of these two agents. pERC noted that the submitted model included a comparison of VLd to Ld and a comparison of VLd to VMP. Based on input from the CGP noting that VMP is not widely used in the Canadian setting, the VMP comparison was not considered further, however the submitted model did not include a comparison between VLd and CyBorD. Based on input from the CGP, registered clinicians, and evidence from real-world data demonstrating similarity in efficacy between Ld and CyBorD, pERC was satisfied that there is likely a net clinical benefit of VLd compared with CyBorD. Despite this, in the absence of cost-effectiveness estimates comparing VLd with CyBorD, the cost-effectiveness remains unknown.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Potential large budget impact

pERC discussed the feasibility of implementing a funding recommendation for VLd. Both the CGP and registered clinicians agreed that patients may be deemed ineligible for transplant due to advanced age, comorbidities or even patient preference. pERC also noted that bortezomib was dosed twice weekly on the SWOG-S0777 trial but agreed with the CGP that in Canadian clinical practice, bortezomib would be administered as a once weekly subcutaneous dose. pERC further agreed that bortezomib is given up to a maximum of eight cycles and pERC does not anticipate that patients would need to be treated beyond eight cycles. pERC considered a number of implementation questions related to sequencing of subsequent agents and noted possible algorithms suggested by registered clinicians. Although pERC agreed that sequencing of subsequent agents will be dependent on the treatment and responses that patients had to first-line therapy, as well as individual characteristics and comorbidities of patients, based on input from registered clinicians pERC agreed that generally patients are likely to receive a daratumumab containing regimen in the second-line setting followed by pomalidomide or carfilzomib-based treatments in the third line setting and beyond.

pERC noted that in the submitter's analysis, the market share for VLd in a scenario where VLd is reimbursed is taken from melphalan plus prednisone plus bortezomib (VMP), an regiment which is not reimbursed widely in the Canadian setting. pERC agreed that VLd will instead replace CyBorD or Ld. Depending on where the market share for VLd is taken from (Ld or CyBorD), pERC agreed that the BIA could be substantial as CyBorD is a significantly cheaper regimen. Other factors that most influenced the BIA were the size of the eligible population and drug acquisition costs.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Kelvin Chan and Dr. Anil Abraham Joy who were not present for the meeting
- Darryl Bell who did not vote due to his role as a patient member alternate

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of lenalidomide (Revlimid) plus bortezomib and low-dose dexamethasone for multiple myeloma, through their declarations, three members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

Disclaimer

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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
• PAG is also seeking information on comparative efficacy of lenalidomide/bortezomib/ dexamethasone (VLd) to CyBorD.	• In Canada, cyclophosphamide, bortezomib and dexamethasone (CyBorD) or Ld are the most commonly used current therapies in the first-line setting for transplant-ineligible patients. Although there are no data comparing VLd with CyBorD, the CGP agreed that using Ld is a reasonable and appropriate comparator. • Ld and CyBorD have previously been shown to have similar efficacy. Since VLd has demonstrated superiority over Ld, this can serve as an appropriate surrogate for Canadian patients. It is reasonable to believe that the magnitude of benefit would be similar if the comparator was CyBorD.
Eligible Patients • PAG is seeking guidance on determining patients who would not be eligible for SCT and therefore, could be eligible for treatment with VLd. • PAG is seeking clarity on whether patients with newly diagnosed amyloidosis who are transplant-ineligible, would be eligible for VLd in this setting. • PAG is seeking clarity on whether patients with newly diagnosed multiple myeloma that are transplant eligible, would be eligible for VLd in this setting.	• pERC noted input from registered clinicians and the CGP which indicated that eligibility for transplant will take into account the patients' age, comorbidities, and in other instances patient preference. • There is insufficient evidence to inform the benefit of VLd in patients with primary amyloidosis. However, for patients with myeloma and complications of amyloidosis as a consequence of the disease, VLd would be an appropriate first-line regimen if other inclusion criteria are met. • This study provides insufficient evidence to support or refute the use of VLd as an induction regimen prior to stem cell transplant.
• PAG noted patients currently treated with Ld for newly diagnosed multiple myeloma not eligible for transplant would need to be addressed on a time-limited basis (i.e., addition of bortezomib).	• At the time of implementing a reimbursement recommendation for VLd, jurisdictions may consider addressing the time-limited need of bortezomib (V) for patients who recently initiated treatment with Ld. However, pERC noted that this may not apply to patients who have been on Ld for a prolonged period of time and are responding well.
• There is a potential for indication creep to: other bortezomib-based regimens (i.e., addition of lenalidomide) in the first-line setting, maintenance treatment following transplant, and other lines of therapy.	• pERC noted the CGP's conclusions and input from registered clinicians and agreed that VLd is appropriate in the first-line setting. At the moment, there is no evidence to support its use in the second-line setting. pERC further noted that other multi-agent regimens containing novel agents such as daratumumab or carfilzomib may be appropriate at the time of relapse.
• PAG is seeking guidance on the use of bortezomib and dexamethasone as per standard of care (i.e., weekly subcutaneous bortezomib and dexamethasone on the same days). • PAG is also seeking guidance on whether there would be instances where patients should be given bortezomib beyond eight cycles (i.e., every two weeks as maintenance after cycle 8).	• In alignment with the CGP's conclusions, pERC agreed that the dosing of bortezomib and dexamethasone would remain consistent with the Canadian standard using once a week administration subcutaneously. • pERC is not able to make an evidence-informed recommendation on continuing bortezomib beyond 8 cycles however pERC noted that it is unlikely that patients would be treated beyond 8 cycles with bortezomib.
Sequencing • Treatments patients would be eligible for after progression on VLd in first-line; • Use of lenalidomide in second and	• pERC agreed with the CGP that the sequencing of subsequent agents is dependent on the treatment and responses that patients had to first-line therapy, as well as individual characteristics and comorbidities of

subsequent lines of therapy for relapsed/refractory multiple myeloma; • Sequencing of first and second-line therapies (e.g., carfilzomib-based, lenalidomide-based, daratumumab-based, bortezomib-based regimens, and pomalidomide-dexamethasone) for patients that are either eligible or ineligible for autologous stem cell transplant.	patients. Based on input from registered clinicians, pERC agreed that, generally, patients are likely to receive a daratumumab containing regimen in the second-line setting followed by pomalidomide or carfilzomib-based treatments in the third line setting and beyond. It is noted that lenalidomide-based regimens would not be provided to patients who are refractory to lenalidomide, unless lenalidomide was discontinued due to toxicity or patient preference.
• PAG is seeking guidance on whether cytogenetic testing is routinely conducted for patients with multiple myeloma, and if yes, how are results used to guide treatment options.	• Cytogenetic testing is routinely done for patients with myeloma, at the time of diagnosis. However, this testing would not likely impact the choice of therapy in first-line setting. The use of cytogenetic testing would remain the same as current standard practice.

CGP = Clinical Guidance Panel; CyBorD = cyclophosphamide plus bortezomib plus dexamethasone = VLd: lenalidomide/bortezomib/ dexamethasone; Ld = lenalidomide plus dexamethasone; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; SCT = stem cell transplant.