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: Pomalidomide (Pomalyst)

Submitted Reimbursement Request:
In combination with dexamethasone and bortezomib for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

Submitted By: Celgene Inc.	**Manufactured By:** Celgene Inc.
NOC Date: July 02, 2019	**Submission Date:** March 15, 2019
Initial Recommendation: August 29, 2019	**Final Recommendation:** September 18, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	Pomalidomide costs $10,500.00 per 21-count blister pack: $500.00 per 1 mg, 2 mg, 3 mg, or 4 mg capsule. 4 mg (one capsule) once daily orally on days 1 to 14 of each 21-day cycle. Per 21-day cycle: $5,950.00 (no wastage). Per 21-day cycle: $7,000.00 (with wastage).

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 the reimbursement of pomalidomide (Pomalyst) in combination with dexamethasone and bortezomib (PVd) for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least one prior treatment regimen including lenalidomide, if the following condition is met:

- cost-effectiveness being improved to an acceptable level.

Patients should have a good performance status and treatment should be continued until disease progression or unacceptable toxicity.

pERC made this recommendation because it concluded that compared with bortezomib plus dexamethasone (Vd) there may be a net clinical benefit of PVd based on statistically significant and modest, though clinically meaningful, improvements in progression-free survival (PFS) and overall response rate (ORR), a manageable toxicity profile, and that it provides an additional treatment choice. However, pERC was unable to determine the magnitude of the clinical benefit of PVd compared with current standard care treatment options given the lack of robust comparative data on outcomes important to decision-making, such as overall survival (OS), PFS, and quality of life (QoL).

pERC agreed that PVd aligned with patient values because it delays disease progression, has manageable side effects, and offers an additional

	treatment choice. The Committee noted that there was considerable uncertainly in the cost-effectiveness estimates compared with available treatment options because of a lack of robust direct or indirect comparative clinical effectiveness data that informed the submitted economic evaluation.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness and Decrease Budget Impact** Given that pERC concluded that there may be a net clinical benefit of PVd compared with Vd in adult patients with RRMM who have received at least one prior treatment regimen including lenalidomide, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of pomalidomide to an acceptable level. **Optimal Sequencing of Pomalidomide in Combination With Dexamethasone and Bortezomib and Other Therapies Unknown** pERC concluded that the optimal sequencing of PVd and other treatments now available for the treatment of multiple myeloma is currently unknown. pERC was therefore unable to make an evidence-informed recommendation on sequencing. However, pERC recognized that provinces would need to address this issue upon implementation of pomalidomide reimbursement and noted that collaboration among provinces to develop a common approach would be of value. **Please note:** The Provincial Advisory Group's (PAG's) questions have been addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

Despite significant advancements in the treatment and life expectancy of patients with multiple myeloma, it remains an incurable disease, and most patients will relapse following initial therapy. Alkylators, proteasome inhibitors, immunomodulatory drugs, and corticosteroids have proven to be highly effective therapies for myeloma. There is no consensus with respect to the optimal sequencing or combination of drugs that should be used. Bortezomib- or lenalidomide-based therapies are currently the standard treatment options in the second-line setting. Patients who have been exposed to lenalidomide and are lenalidomide refractory will commonly be treated with bortezomib-based therapies, such as daratumumab plus bortezomib plus dexamethasone (DVd) or carfilzomib plus dexamethasone (Kd). pERC noted that some patients may not be eligible for certain therapies, as eligibility will depend on patients' age, prior treatments, comorbidities, tolerability, patient preferences, and jurisdictional reimbursement criteria. pERC therefore agreed that novel therapies that further improve survival and provide additional treatment choice are a continued need for these patients.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated on the results of one randomized, multi-centre, open-label, phase III trial (OPTIMISMM) that evaluated the efficacy and safety of pomalidomide in combination with bortezomib and dexamethasone (PVd) compared with bortezomib plus dexamethasone (Vd) in adult patients with relapsed or refractory multiple myeloma (RRMM) with previous exposure to one to three prior regimens, including at least two consecutive cycles of lenalidomide. pERC considered that the differences in PFS (the primary outcome) and ORR (a key secondary outcome) were statistically significant and clinically meaningful in favour of PVd. pERC noted that the results for OS, a secondary outcome, are immature and not statistically significant at present. pERC agreed with the pCODR Clinical Guidance Panel (CGP) that PFS is an appropriate and well agreed-upon primary end point in the setting of RRMM, as the heterogeneous disease biology as well as the application of further anti-myeloma therapies after progression may influence OS results. Given that a minimum improvement in median PFS of four to six months in this heavily pre-treated patient population has been identified in the clinical community as a clinically meaningful outcome, pERC concluded that a 4.1 month increase in median PFS for PVd over Vd is a modest but clinically meaningful result.

pERC deliberated on the toxicity profile of PVd and noted that there were more frequent toxicities compared with Vd, albeit in line with the known side effect profile of each individual drug. pERC discussed that the incidence of treatment-emergent adverse events (TEAEs) was higher for PVd, notably infections and infestations. In addition, more patients in the PVd arm experienced serious adverse events (SAE), especially pneumonia, as well as grade 3 or 4 TEAEs, including most commonly neutropenia and infections and infestations. While pERC acknowledged the increased risk of infections, the Committee agreed with the CGP that these toxicities are manageable in clinical practice. Overall, pERC concluded that the incidence and severity of adverse reactions seem consistent with the safety profile of pomalidomide when used in later lines of therapy, with no new safety signals identified, and side effects that can be managed with supportive care and dose adjustments.

pERC members discussed the available patient-reported outcomes data from the OPTIMISMM trial and noted that the QoL scores showed no clinically meaningful changes from baseline and no meaningful differences between treatment arms. However, the Committee noted that the number of patients providing QoL scores declined substantially over the course of the first year. pERC concluded that given the open-label design of the trial, the exploratory nature of the analysis, and the declining number of respondents, there is uncertainty in the QoL results.

Furthermore, pERC members discussed other currently relevant treatment options available for the requested patient population. While Vd may have been an appropriate comparator at the time of the OPTIMISMM trial design, pERC noted that DVd and Kd are currently relevant comparators. pERC agreed with the CGP and the registered clinicians providing input for this submission, that, rather than replacing alternative therapies, PVd would likely be used in case of contraindications or tolerability concerns with

treatments that are currently standard of care. pERC agreed that patients and clinicians place high value on additional treatment options to better tailor treatment to individual patient needs and preferences.

In the absence of a direct comparison of PVd with other relevant treatment options, pERC considered the results of a submitted indirect treatment comparison (ITC) that included comparisons of PVd against Vd, Kd, DVd, bortezomib plus cyclophosphamide plus dexamethasone (CyBorD), and panobinostat, bortezomib and dexamethasone (PanVd). pERC noted that PanVd was not a relevant comparator at the time of this pCODR review as it is currently not publicly funded in any participating jurisdiction, nor has it undergone pCODR review. pERC agreed with the pCODR Methods Team and the pCODR Economic Guidance Panel (EGP) that, given the presence of significant between-study heterogeneity (e.g., the proportion of patients with prior lenalidomide exposure, the number of prior lines of therapy, and the PFS definition across studies), limitations arising from the lack of closed loops in the network, the immaturity of OS data, and the absence of indirect comparisons for the QoL outcome, the comparative effectiveness of PVd versus Kd, DVd, and CyBorD remains uncertain.

pERC concluded that there may be a net clinical benefit to PVd compared with Vd in the treatment of adult patients with RRMM who have received at least one prior treatment regimen including lenalidomide. In making this conclusion, pERC considered the statistically significant and modest, though clinically meaningful improvements in PFS and ORR, a manageable toxicity profile, and the value of having an additional treatment choice. However, pERC was unable to determine the magnitude of clinical benefit of PVd compared with current standard care treatment options given the lack of robust comparative data on outcomes important to decision-making, such as OS, PFS, and QoL.

pERC deliberated on input from one patient advocacy group. pERC noted that few patients had direct experience using PVd. For those patients who had experience using PVd, most indicated that they achieved disease control. Half of the patients indicated that they experienced disease remission and fewer side effects than with other treatments. Less than half of the patients expressed that their QoL was fulfilled with PVd. Some patients deemed PVd's side effects, such as infections/pneumonia, pain, and diarrhea intolerable. Most patients believed that treatment choice based on side effects was highly important and almost all respondents considered access to effective treatments for multiple myeloma to be crucial. pERC considered that patients value having access to effective treatment options that offer disease control, have manageable side effects, improve QoL, and provide choice of drug treatments based on side effects and contraindications. In addition, pERC commented on the ease of taking pomalidomide orally versus having to go to the hospital for IV infusions. pERC concluded that PVd compared with Vd aligned with patient values in that it delays disease progression, has manageable side effects, and provides an additional treatment choice. However, the magnitude of the benefit of PVd is uncertain compared with currently available treatment options.

pERC deliberated upon the cost-effectiveness of PVd and concluded that it is not cost-effective when compared with Vd in adult patients with RRMM who have received at least one prior treatment regimen including lenalidomide. pERC noted that the submitter's base-case incremental cost-effectiveness ratio (ICER) was lower than the EGP's reanalyzed ICER estimate. The Committee noted that the EGP made the following changes to the model to address some of its limitations: (1) a shorter time horizon to address the uncertainty in survival estimates based on extrapolation of short-term trial data and to align the time horizon to previous pCODR reviews in the RRMM setting; (2) adjustment of the administration cost of bortezomib to reflect Canadian clinical practice instead of trial administration; (3) adjustment of the distribution of subsequent treatments to reflect CGP expert opinion instead of trial data; (4) assuming the full cost of the dispensed dose of pomalidomide instead of using the relative dose intensity from the trial to adjust the drug cost; and (5) calculating the cost of terminal care based on purchasing power parity. In addition, pERC deliberated on the cost-effectiveness of PVd compared with currently relevant comparators in Canadian clinical practice (e.g., DVd, Kd, and CyBorD). pERC agreed with the EGP that, given the limitations in the submitted ITC, the comparative effectiveness of PVd versus comparators other than Vd remains highly uncertain. Therefore, pERC concluded that PVd was not cost-effective at the submitted price compared with Vd and that there was considerable uncertainty in the cost-effectiveness estimates compared with DVd, Kd, and CyBorD because of the lack of robust direct or indirect comparative effectiveness data that informed the submitted economic evaluation.

pERC considered the feasibility of implementing a reimbursement recommendation for PVd in adult patients with RRMM who have received at least one prior treatment regimen including lenalidomide. pERC noted that the key factors influencing the incremental budget impact were the relative dose intensity of pomalidomide beyond week 25 of treatment, the second-line market share estimates for Kd in year 1, and

in year 2. pERC discussed that sequencing of treatments for this group of patients is rapidly evolving and dependent on jurisdictional access criteria to various anti-myeloma regimens and patient preferences. Further, pERC noted that drug wastage associated with dose modifications had not been accounted for in the submitted budget impact analysis, which likely resulted in an underestimate of the total budget impact associated with PVd reimbursement. pERC considered that dose reductions could potentially lead to drug wastage for patients who do not tolerate higher doses of medication and receive lower capsule strengths prior to finishing the amount of initially dispensed higher dose medication. In addition, pERC agreed with the EGP that although four different capsule strengths of pomalidomide are available, all capsule strengths have the same unit price, which may lead to increased expenditure in the case of dose modifications. The Committee members discussed that jurisdictions will need to consider the uncertainty in these factors upon implementation, and that the submitted Canada-wide budget impact is likely underestimated.

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 budget impact analysis
- 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:

- Registered clinician
- pCODR's Provincial Advisory Group (PAG)
- The submitter, Astellas Pharma Canada, Inc.

The pERC Initial Recommendation was to conditionally recommend the reimbursement of pomalidomide (Pomalyst) in combination with dexamethasone and bortezomib (PVd) for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least one prior treatment regimen including lenalidomide, if the following condition is met:

- cost-effectiveness being improved to an acceptable level.

Feedback on the pERC Initial Recommendation indicated that PAG, the submitter and the registered clinician agreed with the Initial Recommendation. All three stakeholders supported early conversion of the Initial Recommendation to a Final Recommendation. No feedback was received from patient groups.

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. Clarifications related to the feedback provided by stakeholders that reflected the initial deliberation by pERC were added to the Final Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the safety and efficacy of pomalidomide in combination with dexamethasone and bortezomib on patient outcomes in the treatment of adult patients with multiple myeloma following at least one prior treatment regimen including lenalidomide.

Studies included: One randomized phase III trial with an active comparator

The pCODR systematic review included one ongoing, international, multi-centre, open-label, randomized phase III trial: OPTIMISMM. The OPTIMISMM trial evaluated the efficacy and safety of pomalidomide in combination with bortezomib and dexamethasone (PVd) compared with Vd in adult patients with RRMM with previous exposure to one to three prior regimens, including lenalidomide.

A total of 559 patients were randomized, with 281 patients assigned to PVd and 278 assigned to Vd. Patients who were enrolled in the trial were treated with PVd (pomalidomide 4 mg orally on days 1 to 14 of each 21-day cycle; dexamethasone 20 mg orally [10 mg if over age 75] on days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day cycle [cycles 1 to 8], then on days 1, 2, 8, 9 of each 21-day cycle [cycle 9 onward]; bortezomib 1.3 mg/m^2 on days 1, 4, 8, 11 of each 21-day cycle [cycles 1 to 8], then days 1 and 8 of each 21-day cycle [cycle 9 onward]), or Vd (same doses). In both groups, study drugs were given until disease progression, withdrawal of consent, or occurrence of unacceptable toxic effects. Dose interruptions and reductions were permitted. Crossover was not permitted.

The median time on treatment was longer in the PVd arm than in the Vd arm: PVd = P: 8.7 months, V: 7.6 months, d: 7.8 months; Vd = V: 4.9 months and d: 4.9 months.

Patients were eligible for enrolment if they met the following criteria: older than 18 years, diagnosis of multiple myeloma and measurable disease, had received one to three prior regimens, including a lenalidomide-containing regimen for at least two consecutive cycles, and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2. Patients previously treated with bortezomib were permitted entry into the trial provided they did not have disease progression during treatment or within 60 days of the last dose of bortezomib. Patients who progressed on or within 60 days of a once-weekly bortezomib schedule or on a lower dose of bortezomib were included in the trial and were defined as the bortezomib-refractory patient population.

Patient population: Median age 67 years; 100% of patients had prior lenalidomide exposure; approximately 70% of patients had lenalidomide-refractory disease; median of two previous regimens

Baseline characteristics were generally well balanced between the two treatment arms, including age, ECOG PS, prior number of lines of therapy, high-risk genetic mutations and baseline International Staging System (ISS) stage III disease. The median age of patients in the OPTIMISMM study was 67 years in the PVd arm and 68 years in the Vd arm, and median time since diagnosis was 4.0 years in the PVd arm and 4.3 years in the Vd arm. A total of 270 out of 281 (96%) patients in the PVd arm and 256 out of 278 (92%) patients in the Vd arm had ECOG PS 0 or 1. Patients had received a median of two previous regimens prior to receiving the study drug. Induction with or without bone marrow transplant and with or without maintenance therapy was considered to be one regimen.

Refractoriness was defined as disease nonresponsive on therapy (failure to achieve minimal response or development of progressive disease) or disease progression within 60 days of the last dose (inclusive). Refractory meant refractory to the most recent time the medication was received. All patients had received prior lenalidomide (100%); 200 out of 281 (71.2%) patients in the PVd arm and 191 out of 278 (68.7%) patients in the Vd arm were lenalidomide refractory. A total of 201 out of 281 (71.5%) patients in the PVd arm and 203 (73%) patients in the Vd arm had received prior bortezomib; of these, 24 out of 281 (8.5%) in the PVd arm and 32 out of 278 (11.5%) in the Vd arm were bortezomib refractory. Most patients were refractory to the last previous regimen (196 out of 281 [69.8%] in the PVd arm and 184 out of 278 [66.2%] in the Vd arm). There were 64 out of 281 (22.8%) and 65 out of 278 (23.4%) patients in the PVd and Vd arms, respectively, who had received only one prior line of therapy and were identified as lenalidomide refractory.

A total of 161 out of 281 (57.3%) in the PVd arm and 163 out of 278 (58.6%) in the Vd arm had received a stem cell transplant.

Geographic region included the US: 53 out of 281 (18.9%) in the PVd arm and 69 out of 278 (24.8%) in the Vd arm, and other 228 out of 281 (81.1%) in the PVd arm and 209 out of 278 (75.2%) in the Vd arm.

Key efficacy results: Modest PFS benefit, OS immature, exploratory subgroup analyses reveal consistent PFS benefit for PVd

The primary outcome of OPTIMISMM was PFS, defined as the time from randomization to disease progression or death. The primary outcome was assessed by a blinded independent review adjudication committee (IRAC). The hypothesis of the trial was that PVd would increase PFS and would be superior compared with Vd alone. The estimated sample size requirements for the trial was 544 patients (320 PFS events) to provide 80% power and two-sided alpha of 0.05.

The pre-specified key secondary end points included OS (time from randomization until death from any cause) and ORR (partial response or better per International Myeloma Working Group [IMWG] criteria). These end points were included in the alpha spending function. Other pre-specified secondary end points included duration of response (defined as time of first documented response to confirmed progressive disease or death from any cause for all responders) and safety outcomes. These end points were not adjusted for multiplicity. Pre-specified exploratory end points included time to response, change in global health status, PFS after next line of therapy, and subgroup efficacy analyses. Subgroups included gender, age group ≤ 75 versus >75, race (white versus non-white), baseline ECOG PS (0 versus > 0), baseline cytogenetic categories (high risk versus not), number of prior myeloma regimens (1 versus > 1; 2 versus > 2), screening beta2-microglobulin level (< 3.5 mg/L versus ≥ 3.5 mg/L to ≤ 5.5 mg/L versus > 5.5 mg/L),

baseline albumin (< 3.5 g/dL versus ≥ 3.5 g/dL), ISS (I versus II versus III), baseline creatinine clearance (< 45 mL per minute versus ≥ 45 mL per minute; < 60 mL per minute versus ≥ 60 mL per minute), refractory to lenalidomide, refractory to last therapy for multiple myeloma, and prior exposure to proteasome inhibitors.

The study met its primary end point with a statistically significantly longer PFS in favour of the pomalidomide group. As of the protocol-defined final PFS analysis (data cut-off: October 26, 2017; median follow-up: 15.9 months), median PFS was 11.2 months versus 7.1 months in the PVd and Vd arms, respectively (hazard ratio [HR] = 0.61; 95% confidence interval [CI], 0.49 to 0.77; *P* = 0.0001).

The key secondary outcome, ORR (partial response or better according to IMWG criteria), was 82.2% and 50% in the PVd and Vd arms, respectively; odds ratio, 5.02 (95% CI, 3.35 to 7.52); *P* < 0.001. The OS analysis at the first interim analysis for OS (October 26, 2017, data cut-off) was immature and did not cross the pre-specified early stopping boundary for the interim analysis. The OS difference between treatment arms resulted in an HR of 0.98 (95% CI, 0.73 to 1.32); *P* = 0.89. As of an updated OS analysis at the September 15, 2018, data cut-off with a median follow-up of 26.2 months, a total of 242 OS events had occurred (43.3%). There were 116 out of 281 deaths with a median OS duration of 40.54 months (95% CI, 29.83 to not evaluable) in the PVd arm and 126 out of 278 deaths with a median OS of 30.46 months (95% CI, 24.61 to 35.94) in the Vd arm with an HR of 0.91 (95% CI, 0.70 to 1.18; two-sided *P* = 0.476).

Results from pre-specified yet exploratory subgroup analyses for PFS for lenalidomide refractory disease, age, and other demographic characteristics demonstrated a consistent benefit to PVd as compared with Vd.

Patient-reported outcomes: Quality of life (QoL) was maintained, no difference between treatment arms

The health-related quality of life (HRQoL) end points were exploratory and therefore the interpretation of this data is limited. The study measures were administered prior to the first day of every cycle (21 days) and at treatment discontinuation. The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core Module (QLQ-C30), the Multiple Myeloma Module (QLQ-MY20), and the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) were used to determine the impact of PVd on patient-reported outcomes as compared with Vd. A mixed-model repeated measures analysis was used to estimate overall least square means for change from baseline across all visits and least square means for change from baseline at day 1 of cycle 5,9,19, and 25 within each treatment group, and the difference between treatment groups. A clinically meaningful change (defined as a 10-point or more deterioration from baseline) was used for EORTC QLQ-C30 and EORTC QLQ-MY20. Compliance based on the number of subjects expected to complete the questionnaire at each visit was greater than 80% for both groups for most visits. However, the number of available patients providing data for the QoL measure (QLQ-C30) gradually declined with the number of responders decreasing to less than 50% at cycle 14. Response rates continued to decline thereafter with data available from 33 patients in the PVd group and 10 patients in the Vd group at cycle 26. The primary HRQoL end point in both arms, the global health status/QoL domain of the EORTC QLQ C30 instrument, did not change over time, or between arms at any point in time. The results for the secondary domain of interest (physical functioning, pain, and fatigue domains of the QLQ-C30; disease symptoms and side effects of treatment domains of the QLQ-MY20; and health utility of EQ-5D-3L) also showed no significant and clinically meaningful differences between the treatment groups.

Safety: Manageable toxicity profile

All patients who received at least one dose of the study treatment were included in the safety analyses, 278 patients in the PVd arm and 270 in the Vd arm. At least one treatment-emergent adverse event (TEAE) occurred in 277 out of 278 (99.6%) and 264 out of 270 (97.8%) of patients in the PVd and Vd arms, respectively. The most common TEAEs included infections and infestations (PVd versus Vd: 80.2 versus 64.8), general disorders and administration site conditions (PVd versus Vd: 76.6 versus 63.7), nervous system disorders (PVd versus Vd: 73.7 versus 60.4), gastrointestinal disorders (PVd versus Vd: 70.1 versus 62.2), blood and lymphatic system disorders (PVd versus Vd: 67.3 versus 53.0), and musculoskeletal and connective tissue disorders (PVd versus Vd: 61.5 versus 44.1).

More patients in the PVd arm experienced at least one grade 3 or 4 TEAE; 251 out of 278 (90.3%) in the PVd arm and 190 out of 270 (70.4%) in the Vd arm. Common grade 3 or 4 TEAEs included blood and lymphatic system disorders (PVd versus Vd: 55.4% versus 41.5%), infections and infestations (PVd versus Vd: 30.9% versus 17.8%), metabolism and nutrition disorders (PVd versus Vd: 25.5% versus 18.1%), nervous

system disorders (PVd versus Vd: 20.5% versus 11.9%), and general disorders and administration site conditions (PVd versus Vd: 18.0% versus 11.5%). There were 159 (57.2%) and 114 (42.2%) patients in the pomalidomide and control arms, respectively, who had at least one SAE. The most common SAE was pneumonia, which occurred in 32 (11.5%) patients in the pomalidomide arm and 17 (6.3%) patients in the control arm.

There were more TEAEs leading to dose reduction of any study drug in the PVd arm; 200 out of 278 (71.9%) compared with 139 out of 270 (51.5%) in the Vd arm, and TEAEs leading to interruption of any study drug (87.8% versus 67%). The proportions of patients with a least one TEAE leading to discontinuation of pomalidomide, in the PVd arm, and bortezomib, in the Vd arm, were 31 out of 278 (11.2%) and 50 out of 270 (18.5%), respectively.

In terms of TEAEs of interest, infections and infestations (all grades) occurred in 80.2% and 64.8% of patients in the PVd and Vd arms, respectively. Grade 3 or 4 infections and infestations occurred in 86 out of 278 (30.9%) of PVd patients, and 48 out of 270 (17.8%) of Vd patients. It was reported that those patients with infections did not have febrile neutropenia. The most common hematologic adverse event was neutropenia. All-grade neutropenia occurred in 130 out of 278 (46.7%) patients in the PVd arm and 29 out of 270 (10.8%) patients in the Vd arm. Grade 3 or 4 neutropenia occurred in 41.7% and 8.5% of patients in the PVd and Vd arms, respectively. Febrile neutropenia occurred in nine (3.2%) patients in the PVd arm, and zero patients in the Vd arm. All-grade thrombocytopenia occurred in 102 out of 278 (36.7%) patients in the PVd arm and 103 out of 270 (38.1%) patients in the Vd arm. Grade 3 or 4 thrombocytopenia occurred in 27.3% and 29.3% of patients in the PVd and Vd arms, respectively.

Twenty-seven (9.7%) patients in the pomalidomide arm and 12 patients (4.4%) in the control arm died during the treatment period or within 28 days after receiving the last dose of the study treatment.

Limitations: No direct comparative data to current standard care options

The submitter provided an ITC to evaluate the relative efficacy and safety of PVd in comparison with other treatment options among adult patients with RRMM. The following five therapies were included in the ITC: Vd, Kd, CyBorD, DVd, and PanVd. Although PanVd was included in the network meta-analysis, it was not identified as a relevant comparator for this pCODR review as it is currently not publicly funded in the target population, nor has it been reviewed by pCODR. Comparative PFS and OS estimates were included in the submitted economic analysis. The pCODR Methods Team performed a critical appraisal of the ITC and noted that due to concerns of a lack of risk of bias assessment performed, there may have been poor quality studies included. In addition, there was significant heterogeneity present on the ISS stage at baseline, the number of prior therapies, and PFS definition across studies. Also, the proportion of patients with prior exposure to lenalidomide varied across the included trials in the evidence network. Specifically, the OPTIMISM MM-007 trial included 100% of patients with prior lenalidomide exposure in comparison with the other trials that included a very small proportion of patients with lenalidomide exposure. Due to a lack of a closed loop in the evidence network, the consistency between direct and indirect comparisons could not be assessed. Data for OS was immature. Another outcome of interest, HRQoL, was not explored in the network meta-analysis. Based on these limitations, it was concluded that the comparative efficacy estimates may be biased, and the results reported for PFS and OS should be interpreted with caution.

Need and burden of illness: Need for treatments that improve survival and provide additional treatment choice

In 2016, it was estimated that 2,700 Canadians were diagnosed with myeloma, and 1,450 patients died of this disease. Despite significant advancements in the treatment and life expectancy of patients with multiple myeloma, it remains an incurable disease, and most patients will relapse following initial therapy. Alkylators (melphalan or cyclophosphamide), proteasome inhibitors (ixazomib, bortezomib, or carfilzomib), immunomodulatory drugs (thalidomide, pomalidomide, or lenalidomide), and corticosteroids (prednisone or dexamethasone) have proven to be highly effective therapies for myeloma. There is no consensus with respect to the optimal sequencing or combination of drugs that should be used. Bortezomib- or lenalidomide-based therapies are currently the standard treatment options in the second-line setting. Patients who have been exposed to lenalidomide and are lenalidomide refractory would commonly be treated with bortezomib-based therapies, such as DVd and Kd. pERC noted that some patients may not be eligible for certain therapies, as eligibility will depend on patients' age, prior treatments, comorbidities, tolerability, patient preferences, and jurisdictional reimbursement criteria.

pERC members' therefore agreed that novel therapies that further improve survival and provide additional treatment choice are a continued need for these patients.

Registered clinician input: PVd provides attractive additional treatment option; Kd and DVd relevant comparators; sequencing of alternative therapies remains unknown

There are several options for relapsing multiple myeloma patients, which introduces challenges in treatment selection but also provides opportunities for treatment personalization. Relevant comparators include Kd and DVd. Clinicians reported that PVd has several notable advantages compared with available treatments, including lower toxicity and easier administration, in addition to good progression-free survival benefits. In terms of sequencing, PVd could be given in the third-line setting after daratumumab-containing regimens, or second-line in patients who experience challenges with long-term IV therapies or have certain comorbidities or contraindications. Most clinicians believe that PVd would be an alternative treatment option and not a replacement for existing therapies.

PATIENT-BASED VALUES

Values of patients with RRMM: Improvement in QoL, disease control, enjoyment of a normal life, and disease remission

One patient input was provided to pCODR through a patient advocacy group submission from Myeloma Canada.

Patients expressed that multiple myeloma symptoms had a relatively high impact on daily life and most notably impacted patients' ability to work. Patients regarded the maintenance of QoL as the most desirable treatment goal, followed by management/minimization of side effects. According to patients, infections were the most important aspect of myeloma to control. Dexamethasone, bortezomib, and lenalidomide were the most frequently cited therapies used by patients. Frequent side effects included fatigue, neuropathy, insomnia, gastrointestinal problems, and shortness of breath. Patients had a generally positive outlook toward treatment with Vd and appreciated its effectiveness and low toxicity, allowing them to maintain a good QoL. Almost all respondents considered access to effective treatments for multiple myeloma to be crucial, and three-quarters did not report any issues with accessing treatment. Additionally, most patients believed treatment choice based on side effects was highly important. Most respondents had concerns about financial implications, with drug and parking costs being the most frequently cited.

In terms of expectations for alternative treatment options, focus was placed on improvement in QoL, disease control, enjoyment of a normal life, and disease remission.

Patient values on treatment: Disease control and remission; fewer side effects than with other treatments; some side effects deemed intolerable

Myeloma Canada provided the perspective of seven patients with experience with PVd. The majority of patients who had used PVd indicated that they achieved disease control. Half of the patients indicated that they experienced disease remission and fewer side effects than with other treatments. Less than half of these patients expressed that their QoL was fulfilled with PVd. Some patients deemed PVd's side effects, such as infections/pneumonia, pain, and diarrhea as intolerable.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility and cost-effectiveness analyses

The EGP assessed one cost-utility analysis (clinical effects measured by quality-adjusted life-years [QALYs] gained) and one cost-effectiveness analysis (clinical effects measured by life-years gained) of PVd compared with Vd for patients with RRMM who have had at least one prior treatment regimen including lenalidomide.

Basis of the economic model: Clinical and economic inputs

The key clinical outcomes considered in the cost-utility analysis were PFS, OS, time on treatment, and utilities.

Costs considered in the analysis included those related to drug acquisition and administration, monitoring care, health care resource utilization, subsequent treatment, and terminal care.

Drug costs: Treatment cost of pomalidomide, bortezomib, and dexamethasone

- Pomalidomide (oral) costs $10,500.00 per 21-count blister pack: $500.00 per 1 mg, 2 mg, 3 mg, or 4 mg capsule.
  Dosage schedule: One 4 mg capsule once daily on days 1 to 14 of each 21-day cycle.
  Cost per 21-day cycle: $5,950.00 (no wastage) or $7,000.00 (with wastage).
- Bortezomib (IV) costs $1,402.42 per 3.5 mg/13.5 mL vial (generic price).
  Dosage schedule: 1.3 mg/m^2 on days 1, 4, 8, 11 of each 21-day cycle (cycles 1 to 8), then days 1 and 8 of each 21-day cycle (cycle 9 onward).
  Cost per 21-day cycle: (Cycles 1 to 8): $3,895.49 (no wastage) or $5,609.68 (with wastage).
  (Cycles 9+): $1,947.75 (no wastage) or $2,804.84 (with wastage).

  Canadian clinical practice dose: 1.5 mg/m^2 once weekly for all cycles.
  Costs per 21-day cycle: $2,247.40 (no wastage) or $2,804.84 (with wastage).
- Dexamethasone (oral) costs $0.3046 per 4 mg tablet.
  Dosage schedule: 20 mg orally on days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day treatment cycle (cycles 1 to 8), then on days 1, 2, 8, 9 of each 21-day treatment cycle (cycle 9 onward).
  Cost per 21-day cycle: (Cycles 1 to 8): $9.75 (with or without wastage).
  (Cycles 9+): $4.87 (with or without wastage).

Cost-effectiveness estimates: Not cost-effective at the submitted price; uncertainty in comparative effect estimates derived from ITC

The submitter-provided economic analysis assessed the cost-effectiveness of PVd compared with Vd. The submitted base-case ICERs were lower than the EGP's lower-bound ICER estimates (submitted probabilistic ICER versus EGP's reanalyzed probabilistic ICER: $489,962.00 versus $580,444.00). The EGP made the following changes to the model to address some of the limitations:

- A shorter time horizon (15 years instead of 25 years) to address the uncertainty in survival estimates based on extrapolation of short-term trial data and to align the time horizon to previous pCODR reviews in the RRMM setting.
- Adjustment of the administration cost of bortezomib to reflect the once weekly dosing in Canadian clinical practice instead of trial administration, which was twice weekly dosing.
- Adjustment of the distribution of subsequent treatments to reflect CGP expert opinion instead of trial data.
- Assuming the full cost of the dispensed dose of pomalidomide instead of using the relative dose intensity from the trial to adjust the drug cost.
- Calculating the cost of terminal care based on purchasing power parity.

The EGP noted several limitations in the submitted analysis, particularly the uncertainty in the clinical comparative efficacy data. The submitter provided ITCs to present relative treatment effect estimates between comparators (Kd, DVd, CyBorD) in the absence of head-to-head data. The EGP noted that, given the limitations in the submitted ITC (for more details on the ITC see Limitations section), the comparative effectiveness of PVd versus comparators other than Vd remain uncertain. pERC concluded that PVd was not cost-effective at the submitted price compared with Vd and that there was considerable uncertainly in the cost-effectiveness estimates compared with treatments other than Vd because of a lack of robust direct or indirect comparative effectiveness data in the submitted economic evaluation.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact likely underestimated

The EGP noted that the key factors influencing the incremental budget impact were the relative dose intensity of pomalidomide beyond week 25 of treatment, the second-line market share estimates for Kd in year 1 and in year 2. The CGP noted that sequencing of treatments for this group of patients is rapidly evolving and depends on jurisdictional access criteria to various anti-myeloma regimens and patient preferences. The EGP noted that drug wastage associated with dose modifications had not been

accounted for in the submitted budget impact analysis, which likely resulted in an underestimate of the total budget impact associated with PVd reimbursement. pERC considered that dose reductions could potentially lead to drug wastage for patients who do not tolerate higher doses of the medication and receive lower capsule strengths prior to finishing the amount of initially dispensed higher-dose medication. In addition, although four different capsule strengths of pomalidomide are available, all capsule strengths have the same unit price, which may lead to increased expenditure in the case of dose modifications. The EGP indicated that the submitted Canada-wide budget impact is likely underestimated.

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, Oncologist
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. Henry Conter, Dr. Avram Denburg, and Dr. Christian Kollmannsberger, Dr. W. Dominika Wranik who were not present for the meeting.
- Daryl 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 pomalidomide in combination with dexamethasone and bortezomib for the treatment of adult patients with RRMM, through their declarations, two members had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, two of these members were 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*. There was no non-disclosable information in this Recommendation document.

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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information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report. This document is composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR document).

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 seeking information on whether comparison data is available comparing pomalidomide in combination with dexamethasone and bortezomib (PVd) to daratumumab plus bortezomib plus dexamethasone (DVd) or carfilzomib plus dexamethasone (Kd).	• pERC agreed with the pCODR Methods Team and the pCODR Economic Guidance Panel (EGP) that, given the presence of significant between-study heterogeneity (e.g., the proportion of patients with prior lenalidomide-exposure, the number of prior lines of therapy, and the PFS definition across studies), limitations arising from the lack of closed loops in the network, the immaturity of OS data, and the absence of indirect comparisons for the QoL outcome, the comparative effectiveness of PVd versus Kd, DVd, and bortezomib plus cyclophosphamide plus dexamethasone (CyBorD) remained uncertain.
• PAG is seeking clarity on whether or not the following patients would be eligible for treatment with pomalidomide in combination with dexamethasone and bortezomib (PVd): o patients who received more than 3 lines of prior therapy o patients with diagnosis of primary amyloidosis, as these patients were excluded from the MM-007 trial o patients who are on maintenance therapy with bortezomib or lenalidomide post autologous stem cell transplant (ASCT).	• pERC agreed with the pCODR Clinical Guidance Panel (CGP) that the benefit for patients with more than 3 lines of prior therapy cannot be concluded, based on the very small subgroup (i.e., only one patient per arm). Therefore, pERC concluded that the trial results cannot be generalized to patients with more than 3 prior lines of therapy. • pERC agreed with the CGP that there is insufficient evidence to determine the effectiveness of PVd in patients with primary amyloidosis. No evidence was identified within the current review to support the use of PVd in patients diagnosed with primary amyloidosis. • This study did include lenalidomide maintenance and the CGP agrees that the results of the OPTIMISMM trial are generalizable to patients who have received prior lenalidomide maintenance therapy post ASCT. There is insufficient data from OPTIMISMM to guide care in individuals who received bortezomib maintenance therapy post-transplant. However, in both transplant-eligible and transplant-ineligible settings, it is reasonable to apply the results of the OPTIMISMM study in bortezomib-exposed patients if patients are not refractory to bortezomib.
• PAG is seeking clarity on whether ASCT or maintenance lenalidomide would be considered as one line of prior therapy.	• pERC agreed with the CGP that ASCT with or without maintenance lenalidomide would be considered as one line of therapy.
• PAG is seeking guidance on the use of bortezomib and dexamethasone as standard of care in most Canadian jurisdictions (i.e., weekly subcutaneous bortezomib and dexamethasone on the same days). In the OPTIMISMM trial bortezomib is dosed at 1.3 mg/m^2 on days 1, 4, 8, 11 of each 21-day cycle (cycles 1 to 8), then days 1 and 8 of each 21-day cycle (cycle 9 onward), until disease progression. Dexamethasone is dosed at 20 mg orally on days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day cycle (cycles 1 to 8), then on days 1, 2, 8, 9 of each 21-day cycle (cycle	• pERC agreed with the CGP that the trial results can be generalized to patients who receive bortezomib and dexamethasone according to standard care dosing in most Canadian jurisdictions. Subcutaneous administration once weekly is currently used in Canada for many bortezomib-containing regimens. For example, for both bortezomib plus melphalan plus prednisone (VMP) and bortezomib plus cyclophosphamide plus dexamethasone (CyBorD), bortezomib is given once weekly for a duration defined by provincial funding.

9 onward). Some patients may not be able to tolerate the twice weekly bortezomib dose if PVd is recommended for reimbursement.	
• PAG is seeking guidance on the appropriate place in therapy of PVd and sequencing of all treatments available. In particular: ○ sequencing of first- and second-line therapies (e.g., carfilzomib-based, lenalidomide-based, daratumumab-based, and bortezomib-based regimens) for patients that are either eligible or ineligible for ASCT ○ preference for proteasome inhibitor (i.e., bortezomib, carfilzomib, or ixazomib), and whether they are considered interchangeable.	• pERC agreed with the CGP that the optimal sequencing of PVd and other treatments now available for the treatment of multiple myeloma is currently unknown. pERC was therefore unable to make an evidence-informed recommendation on sequencing. However, pERC recognized that provinces would need to address this issue upon implementation of pomalidomide reimbursement and noted that collaboration among provinces to develop a common approach would be of value. • pERC agreed with the CGP that generally, proteasome inhibitors can be used interchangeably. However, pERC also agreed with the CGP that treating clinicians would consider the following issues when choosing among proteasome inhibitors: From an efficacy perspective, carfilzomib would be considered superior to bortezomib and ixazomib, while bortezomib and ixazomib would be considered equivalent. Carfilzomib is considered to be more cardiotoxic compared with ixazomib and bortezomib; however, the toxicity profile is highly individualized. From a patient preference perspective, oral administration is preferred over subcutaneous (SC) and SC is preferred over intravenous administration. In addition, when choosing among proteasome inhibitors, clinicians will have to consider the different reimbursement criteria across jurisdictions.

PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.