CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Pomalidomide (Pomalyst) Bortezomib for Multiple Myeloma

September 18, 2019

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1 ECONOMIC GUIDANCE IN BRIEF

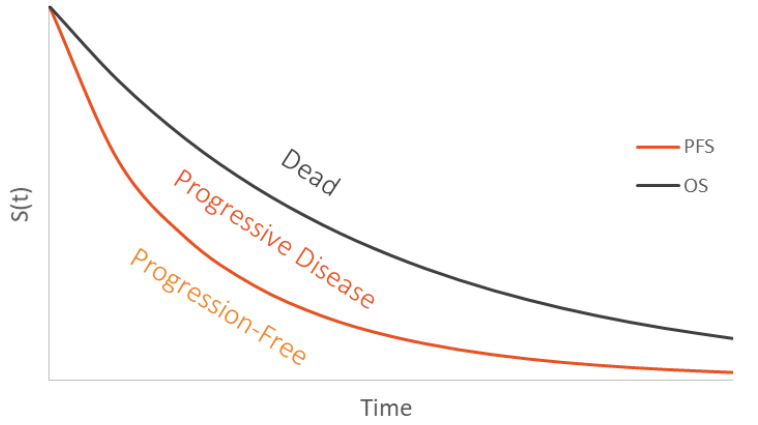
1.1 Submitted Economic Evaluation

The cost-utility analysis **submitted to pCODR by Celgene Inc.** compared pomalidomide (Pomalyst) in combination with bortezomib (generic) and dexamethasone (PVd) to bortezomib plus dexamethasone (Vd) for patients with relapsed or refractory multiple myeloma (RRMM) who have had at least one prior treatment regimen including lenalidomide (LEN).

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	Adult patients with RRMM who have received at least one prior treatment regimen, including LEN. The modelled population is consistent with the OPTIMISMM (MM-007) clinical trial and aligned with that of the funding request. The economic model presented one base case for the intention-to-treat (ITT) population of the OPTIMISMM trial (i.e., LEN-exposed patients with RRMM). Scenario analyses were conducted for the following patient subgroups from the OPTIMISMM trial: • Second-line LEN-exposed: RRMM patients who have received only one prior regimen, including LEN • Second-line LEN-refractory: RRMM patients who have received only one prior therapy regimen, and who are refractory to LEN
Type of Analysis	Cost-utility analysis and Cost-effectiveness analysis
Type of Model	Partitioned-survival model
Comparator(s)	Base case analysis (ITT population from OPTIMISMM trial) *and* scenario analyses in second-line only patients (LEN-exposed and LEN-refractory subgroups from OPTIMISMM trial): • Bortezomib in combination with dexamethasone (Vd) The effect estimates for the submitter's base case and scenarios are based on the OPTIMISMM trial data. The following comparators were included as part of an additional scenario analysis in LEN-exposed patients with RRMM (ITT population): • Bortezomib in combination with dexamethasone (Vd) • Daratumumab in combination with bortezomib and dexamethasone (DVd) • Carfilzomib in combination with dexamethasone (Kd) • Cyclophosphamide in combination with bortezomib and dexamethasone (CyBorD) Indirect comparison data from the submitter's NMA was used in this scenario analysis.
Year of costs	2018
Time Horizon	Lifetime (approximately 25 years)
Perspective	Canadian publicly funded health care payer
Cost of pomalidomide * *Price Source: pCODR submission*[1]	$10,500.00 per 21-count blister pack: $500.00 per 1 mg, 2 mg, 3 mg, or 4 mg capsule. At the recommended dose of 4 mg (one capsule) once

	daily taken orally on days 1 to 14 of each 21-day cycle, pomalidomide costs: • $283.33 per day and $5,950.00 per 21 days (no wastage) • $333.33 per day and $7,000.00 per 21 days (with wastage)
Cost of bortezomib ** Price Source:* IQVIA *Delta PA[2] accessed May 2019*	Based on a generic wholesale acquisition price, bortezomib costs $1,402.42 per 3.5 mg/13.5 mL vial. At a recommended dose of 1.3 mg/m^2 administered intravenously on days 1, 4, 8, and 11 of each 21-day cycle (cycles 1 to 8), then days 1 and 8 of each 21-day cycle (cycle 9 onwards), bortezomib costs: Cycles 1 to 8 • $185.50 per day and $3,895.49 per 21 days (no wastage) • $267.13 per day and $5,609.68 per 21 days (with wastage) Cycles 9+ • $92.75 per day and $1,947.75 per 21 days (no wastage) • $133.56 per day and $2,804.84 per 21 days (with wastage) At the recommended dose of 1.5 mg/m^2 administered once weekly in Canadian clinical practice for all cycles, bortezomib costs: • $107.02 per day and $2,247.40 per 21 days (no wastage) • $133.56 per day and $2,804.84 per 21 days (with wastage)
Cost of dexamethasone ** Price Source: Ontario Drug Benefit Formulary/Comparative Drug Index[3]*	Based on a list generic price, dexamethasone costs $0.3046 per 4 mg tablet. When combined with bortezomib at a recommended dose of 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 onwards), dexamethasone costs: Cycles 1 to 8 • $0.46 per day and $9.75 per 21 days (with or without wastage) Cycles 9+ • $0.23 per day and $4.87 per 21 days (with or without wastage)
Model Structure	A partitioned survival model was developed in Microsoft Excel that used an Area Under the Curve (AUC) approach. The proportion of patients who were progression-free, who experienced progressive disease, or who were dead at any time over the model time horizon was derived from non-mutually exclusive survival curves (**Figure 1**). Overall survival (OS) was partitioned to estimate the proportion of patients in the progression-free and progressive disease 'states'. Progressed disease was derived as the difference between the OS and progression-free survival (PFS) curves at each time point, representing the proportion of patients who are alive but not progression-free. Differences between interventions were modeled by using different PFS and OS curves for each treatment. Figure 1: Partitioned Survival Model Schematic

	 Source: pCODR submission.[1] PFS = progression-free survival; OS = overall survival; S(t) = survival function.
Key Data Sources	The clinical efficacy of PVd (measured in terms of PFS, OS, and time on treatment [TOT]) was sourced from a phase 3 multicenter, randomized, open-label study (OPTIMISMM trial, with data cut-off of September 15, 2018). The comparative efficacy of PVd and other comparator regimens (DVd, Kd, CyBorD) was obtained from an unpublished NMA commissioned by the submitter. The NMA data was used to derive relative OS, PFS, and TOT estimates. Health state utility values associated with pre-progression were sourced from the OPTIMISMM trial. Post-progression utility values were derived by applying a utility decrement to the pre-progression values from OPTIMISMM, based on a review of the literature. The drug cost for PVd was provided by the submitter. The submitter sourced drug acquisition costs for all other comparators from publicly-available sources, including the Ontario Drug Benefit Formulary/Comparative Drug Index. Costs associated with drug administration, monitoring care, health care resource utilization, subsequent treatment, and terminal care were obtained from Canadian publicly available sources. All costs were presented in 2018 Canadian dollars (CAD). Costs obtained from other years were inflated to 2018 CAD using the consumer price index from Statistics Canada. The choice of adverse events (AE) included in the model was based on grade 3 or 4 events occurring in at least 5% of patients in the OPTIMISMM trial. The proportion of AE for comparators included as part of scenario analyses were derived from the pivotal phase 3 trials of each of the relevant comparators using the same criteria as OPTIMISMM. The distribution of subsequent therapies in the third and fourth treatment lines (following second-line treatment failure) was based on clinical expert opinion.

CUA = cost-utility analysis; LEN = lenalidomide; PFS = progression-free survival; PVd = pomalidomide in combination with bortezomib and dexamethasone; OS = overall survival; RRMM = relapsed and/or refractory multiple myeloma; TOT = time-on-treatment

Notes: Costs are calculated using a body surface area (BSA) of 1.87m^2, sourced from the OPTIMISMM trial.

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), bortezomib in combination with dexamethasone (Vd) was previously considered to be standard care. However, the CGP and the provincial advisory group

(PAG) noted that in Canadian clinical practice bortezomib plus dexamethasone is no longer used as it has been replaced by more effective triplet therapies. DVd, Kd and CyBorD are more relevant comparators for patients who meet the pCODR requested reimbursement criteria for PVd. The submitter did include these comparisons in scenario analyses with comparative efficacy estimates informed by an NMA.

Relevant issues identified included:

- The CGP agreed that there may be a net clinical benefit to PVd compared with Vd in the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior treatment regimen including lenalidomide.
- PVd has a manageable toxicity profile and no obvious detrimental impact on HRQOL.
- Uncertainly about which line of therapy PVd would be used: with the assumed increasing use of monoclonal antibody therapy, daratumumab (D), there is uncertainly on where the regimen of PVd would fit; especially where none of the patients within the trial had previously received daratumumab. Additionally, daratumumab is currently only funded as part of combination therapy (DRd or DVd) but not otherwise which may influence the sequencing of therapy.
- No direct comparative evidence between PVd and standard care treatment options in Canada. A network meta-analyses (NMA) was submitted to address comparative effectiveness of PVd to DVd, Kd and CyBorD. However, the pCODR Methods Team noted several important shortcomings relating to the submitter's NMA. These included: a lack of risk of bias assessment for included studies; the presence of significant heterogeneity relating to the proportion of patients with prior exposure to lenalidomide at baseline, ISS stage at baseline, the number of prior therapies, and the PFS definition across studies; and, inability to assess consistency between direct and indirect comparisons due to the structure of the evidence network. As a result, the comparative efficacy estimates may be biased and certainty in the results reported for PFS and OS is limited and should be interpreted with caution.
- Within the Canadian context, the results from the OPTIMISMM study are especially relevant to patients whose disease is lenalidomide refractory. In Canadian clinical practice LEN treatment is usually prescribed until disease progression or intolerance. Therefore, patients who have received LEN and whose disease is LEN-refractory are a clinically relevant population. Patients who have received LEN and whose disease is considered non-refractory to LEN upon progression are likely to be few.
- If pomalidomide + bortezomib + dexamethasone are to become available, the CGP indicated that it would be valuable to have flexibility in the line of therapy that is selected given that line of therapy is dependent on provincial access to other active agents together with patient preferences.

Summary of registered clinician input relevant to the economic analysis

There are several options for patients with relapsing/refractory myeloma, which introduces challenges in treatment selection but also opportunities for treatment personalization. Relevant comparators include carfilzomib plus dexamethasone and the combination of daratumumab, bortezomib and dexamethasone. PVd has several notable advantages including lower toxicity and easier administration, in addition to good survival benefits. In terms of sequencing, PVd could be given in third-line 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 believed it would be an addition to and not a replacement for existing therapies.

- *The comparators Kd and DVd were incorporated in the submitted economic model as part of scenario analysis*
- *OS, PFS, and adverse events were incorporated in the submitted economic model.*
- *Subsequent lines of therapy were included in the submitted economic model by assuming a distribution of subsequent therapies according to line of treatment following progression with PVd.*

Summary of patient input relevant to the economic analysis
From a patient's perspective, infections were the most important aspect of myeloma to control dexamethasone, bortezomib and lenalidomide were the most frequently cited therapies experienced by patients. Frequent side effects included fatigue, neuropathy, insomnia, gastrointestinal problems and shortness of breath. Patients had a generally positive outlook towards treatment with Vd and appreciated its effectiveness and low toxicity, allowing them to maintain a good quality of life. Patients regarded the maintenance of quality of life as the most desirable treatment goal, followed by management/ minimization of side effects. Most patients believed treatment choice based on side effects was highly important. Additionally, most respondents had concerns about financial implications, with drug and parking costs being the most frequently cited.

A majority of patients that received PVd stated an improvement in disease control followed by remission and improved side effects whereas less than half expressed quality of life was fulfilled with PVd. Side effects deemed completely intolerable were infections/pneumonia, pain and diarrhea.

- *PFS, OS, and quality of life were incorporated into the model. Adverse events including pneumonia, fatigue, diarrhea, and neuropathic pain, among others, were also included.*
- *Patients' out-of-pocket-expenses, such as parking costs, were not considered in the economic analysis.*

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for pomalidomide in combination with bortezomib and dexamethasone, which are relevant to the economic analysis:

<u>Enablers</u>

- Pomalidomide is an oral medication that can be delivered to patients more easily and has lower administration costs than intravenous therapy in both rural and urban settings.
- Pomalidomide is an additional treatment option for patients with previously treated (relapsing) multiple myeloma.

<u>Barriers</u>

- Additional costs may be incurred for dose modifications due to flat pricing of pomalidomide (i.e., each pomalidomide tablet is priced equally regardless of strength). There are also concerns with the potential for drug wastage for patients who may be dispensed the 4mg capsules but do not tolerate and then have dose reduced 1mg, 2 mg or 3mg prior to finishing the amount of 4mg capsules dispensed.
    - *The EGP adjusted the cost of PVd medication by assuming dose intensity of 100%. EGP discussed possible implications of dose modifications in the limitations section (2.3).*

- Additional resources may be required to monitor and treat toxicities (e.g., neutropenia, thrombocytopenia, neuropathies).
    - The CGP noted that the resources required to monitor and treat toxicities would not be different from current clinical practice. It is important to recognize that if PVd is not used in earlier lines of therapy, Pd will be used later. The monitoring and treatments for side effects will be the same - now or later contingent on mortality.

- Some patients may require G-CSF while on pomalidomide combination therapy.
    - The CGP noted that the use of G-CSF largely depends on practice patterns and clinicians' beliefs. Therefore, it is difficult to know if G-CSF use would differ between PVd and its comparators. In the OPTIMISMM trial more

patients in the PVd arm than in the Vd arm received G-CSF (median overall treatment duration of PVd was longer than that of Vd: 38.3 months versus 21.4 months)
    - *G-CSF was not considered in the submitted economic model.*

- Pomalidomide is part of a controlled distribution program (RevAid); therefore, additional pharmacy resources may be required.
    - *Additional pharmacy resources have not been considered in the economic model. EGP discussed possible implications in the limitations section (2.3).*

- Number of prevalent patients with multiple myeloma who have received at least one prior therapy, including lenalidomide, is high and may result in a significant burden on the public payer's budget.
    - *An estimate of the number of prevalent patients with relapsed or refractory multiple myeloma who would quality for PVd treatment has been considered in the submitted budget impact model.*

- PAG noted that the cost of bortezomib has been significantly reduced with generic products being available and bortezomib re-treatment in second-line and beyond treatment settings would be an option in most provinces, particularly for patients who have already been previously treated with lenalidomide.
    - *The submitted economic model used the generic price for bortezomib.*

- The dose of bortezomib in the trial is different than the dose in Canadian practice (e.g., given on a once weekly schedule for all cycles). The trial dose is 1.3 mg/m^2 twice weekly and the dose used in Canadian clinical practice is 1.5 mg/m^2 once weekly.
    - *Costs associated with bortezomib administration were adjusted to account for the once weekly dosing of bortezomib in Canadian clinical practice, rather than the twice weekly dosing observed in clinical trial setting and modeled by the submitter.*

1.3 Submitted and EGP Reanalysis Estimates

The submitter's probabilistic base case analysis reported that PVd was associated with an incremental cost of $194,701 and generated, on average, an additional 0.40 QALYs compared to Vd over the modeled time horizon, resulting in a sequential ICUR of $489,962 per QALY gained compared to Vd.[1] The analysis was associated with a high degree of decision uncertainty as PVd had a 0.0% probability of being considered the most likely cost-effective intervention at a cost-effectiveness threshold up to $200,000 per QALY.

Based on reanalysis of the submitter's probabilistic base case, the EGP found that PVd was associated with an incremental cost of $214,708 and generated, on average, an additional 0.37 QALYs compared to Vd over the modeled time horizon, resulting in a sequential ICUR of $580,444 per QALY gained compared to Vd. EGP reanalysis further revealed that PVd was the optimal therapy at willingness-to-pay greater or equal to $580,444; if a decision maker's willingness-to-pay was less than $580,444, Vd was the optimal therapy. The probability that PVd was cost-effective assuming the threshold value for a QALY was $100,000 was 0%.

Table 2: Submitted and EGP Reanalysis Estimates for PVd versus Vd

Estimates (range/point)	Submitted	EGP Reanalysis
ΔE (LY)	0.50	0.46
Progression-free	0.67	0.66
Post-progression	-0.17	-0.19
ΔE (QALY)	0.40	0.37
Progression-free	0.53	0.52
Post-progression	-0.13	-0.14
ΔC ($)	194,701	214,708
ICER estimate ($/QALY)	489,962	580,444

EGP identified a number of limitations associated with the submitted economic evaluation:

- **Inappropriate choice of comparators in the base case analysis:** The total cost and QALYs associated with PVd were compared to Vd in the base case analysis of the submitted economic model[1]; however, feedback from the CGP indicated that Kd, DVd, and CyBorD would also be considered for use in patients who meet the pCODR requested reimbursement criteria for PVd. Therefore, Kd, DVd, and CyBorD were judged to be relevant comparators in Canadian clinical practice. While the submitter compared PVd with Kd, DVd, and CyBorD as part of a scenario analysis, these comparator regimens should have been included in the submitter's base case analysis. The submitter justified the exclusion of Kd, DVd, and CyBorD from their base case analysis based on significant uncertainty regarding their indirect treatment comparison estimates. The submitter and the pCODR Methods Team noted a number of important shortcomings relating to the submitter's NMA. These included: a lack of risk of bias assessment for included studies; the presence of significant heterogeneity relating to the proportion of patients with prior exposure to lenalidomide at baseline, ISS stage at baseline, the number of prior therapies, and the PFS definition across studies; immaturity of OS data, and inability to assess consistency between direct and indirect comparisons due to the structure of the evidence network. As a result, the comparative efficacy estimates may be biased and certainty in the results reported for PFS and OS is limited and should be interpreted with caution. Given the uncertainty in the submitter's NMA, Kd, DVd, and CyBorD were not considered in the EGP's best case analysis. Instead, an exploratory analysis was conducted to compare PVd with Vd, Kd, DVd, and CyBorD.
- **Uncertainty in the baseline distribution of patients according to line of therapy:** The submitted economic model assumed that 34.8% of patients would receive PVd in the second line, and that 40.3% and 24.9% would receive PVd in the third and fourth lines, respectively.[1] These proportions were sourced from the OPTIMISMM trial, and used to define a baseline distribution of patients, as well as to determine the number of patients who receive subsequent treatments in the third- and fourth-line setting following progression. Feedback from the CGP revealed that the use of PVd within the clinical trial is not likely to be reflective of its use in real world clinical practice and suggested that PVd use in second line would likely be much less than 34.8%. EGP considered this feedback in a scenario analysis and incorporated an alternative baseline distribution of patients in the EGP's best case analysis.
- **Time horizon does not reflect clinical course of disease**: A 25-year time horizon was used to model disease progression in the submitter's base case analysis.[1] In consultation with the CGP, this time horizon was deemed to be too long given that, in this indication, patients are pre-treated and the median age of the population in the OPTIMISMM trial was 68 years. Although previous pCODR reviews for relapsed multiple myeloma have used a time horizon of 10 years, patients in those reviews received two or more therapies. For this review, eligible patients included those who have received 1 or 2 or more prior therapies. Based on this, the EGP explored a time horizon of 15 years in scenario analysis and incorporated it in the EGP's best case analysis.
- **Uncertainty regarding long-term extrapolation:** The submitted economic model projects survival to 25 years based on short-term data (median follow-up of 26.2 months for OPTIMISMM trial).

Approximately 70% of the incremental benefits associated with PVd were accrued in the time period for which no clinical trial data are available. Accepting this extrapolation and the incremental QALY gain in the extrapolated period within the economic model assumes that the observed data from the OPTIMISMM clinical trial is sufficiently representative for long-term extrapolation.

- **Paucity of data on duration of treatment effect:** Given the immaturity of the clinical trial data, the duration of the treatment effect is unknown. The submitted economic model assumed that the effect of treatment with PVd was maintained over the model time horizon (25 years), which is not clinically plausible according to the CGP. EGP was not able to address this limitation in reanalysis due to the structure of the submitted model.
- **Dosing and administration of bortezomib does not reflect Canadian practice:** The administration of bortezomib in the submitter's economic model does not reflect Canadian clinical practice. Feedback from the CGP noted that bortezomib is administered once weekly at 1.5 mg/m2 in Canadian practice, rather than the 1.3 mg/m2 twice per week dosing schedule from the clinical trial. While once weekly dosing has not been assessed in clinical trials, CGP noted that there is no reason to believe that efficacy would differ between the two administration schedules. EGP therefore conducted a reanalysis using once weekly dosing for bortezomib for all cycles to improve the face validity of the submitted model and incorporated this dosing schedule in the EGP's best case analysis.
- **Inappropriate adjustment of pomalidomide cost according to dose intensity:** The submitted model adjusted drug costs proportionally to the dose received in clinical trials – the relative dose intensity (RDI).[1] While the impact of RDI on the costs for bortezomib or dexamethasone is expected to be minimal, given the possibility of vial sharing and the number of administrations would be the same, it is not appropriate to adjust the cost of pomalidomide based on RDI. Pomalidomide is likely to be dispensed to a patient by Canadian pharmacies for the full 21-day cycle (i.e., 14 days of drug administration) all at once, and the cost of medication is therefore independent of the dose administered. EGP assumed a RDI of 100% for pomalidomide in a scenario analysis and incorporated this adjustment in the EGP's best case analysis.
- **Implications of dose modifications associated with pomalidomide not considered**: Dose adjustment for pomalidomide is facilitated by the availability of four different strengths of medication. However, given that all capsule strengths have the same unit price, there is risk of increased expenditure associated with pomalidomide dose adjustments where patients who are initially dispensed a higher dosage strength and may subsequently need smaller capsule strengths to achieve therapeutic effect without neurotoxicity or other harmful effects or intolerance. For instance, a patient on a 4 mg daily dose may be dispensed smaller tablet strengths to allow for the possible need of dose reductions. Yet, this dispensing strategy would cost more than dispensing the 4 mg tablets. Dose reductions could also potentially lead to more drug wastage for patients who do not tolerate higher doses of medication and receive lower tablet strengths prior to finishing the amount of initially dispensed higher dose medication.
- **Underestimation of pomalidomide administration costs:** The submitted model assumed that there were no administration costs associated with pomalidomide.[1] However, pomalidomide administration and dispensing is very labour intensive in Canadian practice as all patients and prescribers must access this treatment through a controlled distribution program (RevAid) mandated by Health Canada, and only select pharmacies and pharmacists are permitted to dispense pomalidomide after getting certified through the RevAid program. Dispensing requirements for new patients and those associated with each refill also go above and beyond a regular prescription (e.g., review of contraception methods, pregnancy status for females of child-bearing potential). Therefore, costs associated with administration of pomalidomide were likely underestimated by the submitter.
- **Incorrect currency conversion of terminal care costs:** Terminal care costs were calculated to be $12,079.31 for the last 30 days of life in the submitted economic model and were sourced from a retrospective cohort study by Bekelman et al.[4] which reported costs associated with end-of-life

care among patients with cancer in 2010 US dollars. The preferred method of currency conversion is with purchasing power parity, which reflects the buying power of currency rather than the supply of currency in international markets at the time of conversion. This limitation is unlikely to significantly affect modelled outcomes and was tested in EGP re-analysis.

- **Increased uncertainty due to model structure:** While partitioned survival analysis (PartSA) is commonly used for economic modeling of treatments for advanced or metastatic cancers, the survival functions modelled through PartSA are considered structurally independent and thus fail to capture interdependency between the survival endpoints.[5] The PartSA approach can then lead to increased uncertainty on the long-term extrapolations since the hazard of death is based only on the time trend observed for the within-trial period, and it is difficult to assess the plausibility of extrapolations.[5] Moreover, results generated through PartSA can lead to a PFS curve that lies above the OS curve and then adjustment is needed.[5] Finally, it is difficult to reflect the correlation between survival curves in probabilistic analysis using the PartSA technique.[5]
- **Submitted model is complex and lacks transparency:** The submitted model lacked transparency and was unnecessarily complex. This made both the assessment of validity and the ability to conduct reanalysis challenging.

1.4 Detailed Highlights of the EGP Reanalysis

To address some of these limitations, the EGP made the following changes to the submitted economic model:

1. Time horizon was shortened from 25 years to 15 years to reduce uncertainty introduced by extrapolation of short-term outcomes over the time period for which no clinical trial data is available (i.e., long-term extrapolation) and the inability to vary the duration of treatment effect in the submitted model. This is consistent with previous pCODR reviews in the setting of relapsed or refractory multiple myeloma and a 15-year time horizon was supported by CGP expert opinion.
2. Costs associated with bortezomib administration were adjusted to account for the once weekly dosing of bortezomib in Canadian clinical practice, rather than the twice weekly dosing observed in clinical trial setting and modeled by the submitter.
3. The baseline distribution of patients according to the number of prior anti-myeloma regimens was reduced to 10% in the second line setting, and increased to 45% each in the third and fourth line settings. This is based on the expected use and place in therapy of PVd in Canadian practice according to the CGP.
4. Costs associated with pomalidomide were not adjusted based on relative dose intensity. Therefore, the full cost of the dispensed dose of pomalidomide was assumed and incorporated into the model.
5. Terminal care costs were recalculated using purchasing parity. The value in the manufacturer submitted model was $12,067.22, and the EGP re-calculated value was $15,172.27.

The EGP best case estimate was informed by all the above re-analyses (1 to 5).

Based on probabilistic analysis of the EGP best case analysis (**Table 3**), EGP found that PVd was associated with an additional benefit of 0.37 QALYs at an additional cost of $214,708 when compared to Vd, resulting in an ICUR of $580,444 per QALY gained. The overall QALY difference was small and can be interpreted as PVd producing, on average, an extra four months of perfect health over a patient's lifetime compared to Vd. The EGP's best case findings further revealed that PVd was the optimal therapy at willingness-to-pay greater or equal to $580,444; if a decision maker's willingness-to-pay was less than $580,444, Vd was the optimal therapy. The probability that PVd was cost-effective assuming the threshold value per QALY gained was $100,000 was 0%.

Table 3: EGP Best Case Estimate[a] – Overall Trial Population (LEN-exposed patients with RRMM)

	Scenario	Treatments	Total QALYs	Total Costs ($)	Sequential ICUR ($ per QALY)
	Submitter's base case	Vd	2.50	137,277	–
		PVd	2.90	331,978	489,962
1	Shortened time horizon to 15 years	Vd	2.46	135,554	–
		PVd	2.84	324,473	510,131
2	Adjusted bortezomib dosage and administration (1.5 mg/m^2 once weekly) based on use in Canadian practice	Vd	2.49	119,030	–
		PVd	2.89	312,390	480,717
3	Adjusted baseline distribution of patients based on expected place in therapy for PVd	Vd	2.50	123,114	–
		PVd	2.90	319,025	496,903
4	Assumed 100% relative dose intensity for pomalidomide	Vd	2.50	138,389	–
		PVd	2.90	360,581	563,634
5	Corrected terminal care costs based on purchasing power parity	Vd	2.51	140,395	–
		PVd	2.90	330,198	483,773
1 to 5	**EGP's Best Case Estimate**	**Vd**	**2.47**	**108,029**	–
		PVd	**2.84**	**322,736**	**580,444**

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year
[a] Total cost and QALYs are discounted probabilistic values, based on 5,000 Monte Carlo iterations.
Note: All costs are presented in 2018 Canadian dollars.

EGP undertook price-reduction analyses based on the submitter's base case and EGP's best case analyses, assuming proportional price reductions for pomalidomide (**Table 4**). Based on the EGP reanalysis, if a price reduction of 99% were obtained, the incremental cost per QALY gained for PVd versus Vd was $103,472.

Table 4: EGP Best Case Estimate Price Reduction Scenarios

Incremental Cost ($) per QALY Gained for PVd versus Vd		
Price	**Submitter's base-case analysis**	**Re-analysis by EGP**
Submitted	489,469	580,444
25% reduction	394,449	446,755
50% reduction	301,167	339,584
75% reduction	206,268	215,419
85% reduction	161,899	172,717
95% reduction	124,705	128,661

Incremental Cost ($) per QALY Gained for PVd versus Vd		
99% reduction	109,578	103,472

Note: All price reduction scenarios were based on probabilistic analysis using 5,000 Monte Carlo iterations.

EGP considered an exploratory analysis on the EGP best case estimate whereby PVd was compared to all relevant comparators identified by the CGP, including DVd, Kd, and CyBorD. The analysis was conducted over a 15-year time horizon using the submitter's NMA data, and results were presented sequentially through probabilistic analysis (**Table 5**). Findings of this exploratory analysis revealed that PVd was not a cost-effective treatment option for patients with RRMM when considering all available treatments, regardless of a decision-maker's willingness-to-pay threshold for a QALY gain. Sequential analysis further revealed that Vd was the optimal therapy at a willingness-to-pay threshold less than $454,251 per QALY gained. If a decision-maker's willingness-to-pay for a gain in QALY was greater or equal to $454,251, then Kd was the optimal therapy. All other treatment options were either dominated or subject to extended dominance. Results warrant careful interpretation in light of the limitations associated with the submitter's NMA.

Table 5: EGP Exploratory Analysis comparing PVd with all relevant comparators- Overall trial population; using 15-year time horizon

	Total Costs ($)	Total QALYs	ΔCost vs. Vd ($)	ΔQALYs vs. Vd	ICUR ($/QALY) vs. Vd	Sequential ICUR ($/QALY)
Non-dominated options						
Vd	108,091	2.47	–	–	–	–
Kd	364,700	3.04	256,610	0.56	454,251	454,251
Dominated options						
CyBorD	113,241	2.11	5,151	-0.36	Dominated by Vd	
DVd	288,566	2.63	180,475	0.16	Subject to extended dominance through Kd and Vd	
PVd	320,853	2.84	212,762	0.37	Subject to extended dominance through Kd and Vd	

Δ = Incremental; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year
Note: Total costs and QALYs are discounted probabilistic values, based on 5,000 Monte Carlo iterations.

The CGP indicated that in the Canadian context, the results from the OPTIMISMM study are especially relevant for patients who have LEN-refractory disease. In Canadian clinical practice LEN treatment is usually prescribed until disease progression or intolerance. Therefore, patients who have received LEN and who have LEN-refractory disease after at least one prior line of therapy are a clinically relevant population. If PVd was available, the CGP indicated that it would be valuable to have flexibility in the line of therapy that is selected given that line of therapy is dependent on provincial access to other active agents together with patient preferences. PVd could be administered in the second, third, or fourth line to LEN-refractory patients in Canada. Therefore, the EGP also considered a scenario analysis whereby PVd was compared to Vd in LEN-refractory patients who received two or more prior treatments. This scenario was not considered by the submitter, as subgroup analyses in the pCODR submission focused on LEN-exposed and LEN-refractory patients who received PVd in second-line only. For this EGP scenario analysis, it was assumed that PFS and OS hazard ratios from the submitter's NMA for the LEN-refractory population who received two or more prior treatments could be applied to the Vd

baseline survival trace for the second-line only LEN-refractory subgroup. Results of this scenario analysis were derived using probabilistic analysis conducted on the EGP best case analysis which adopted a 15-year time horizon (**Table 6**). Findings revealed that PVd was the optimal therapy if a decision-maker's willingness to pay for a QALY gain was greater or equal to $548,169. If a decision-maker's willingness-to-pay was less than $548,169, then Vd was the optimal therapy. These results should be carefully interpreted as the structure of the submitter's model only included survival information on patients with LEN-refractory disease who received PVd as second line therapy, while the NMA data was available for patients with LEN-refractory disease who received PVd in the second, third, or fourth line. The benefit associated with PVd is therefore likely overestimated in the EGP scenario and the ICUR of $548,169 per QALY gained is likely underestimated.

Table 6: EGP Scenario Analysis comparing PVd versus Vd in LEN-refractory population (second line and beyond) - 15 year time horizon

	Total Costs ($)	Total QALYs	ΔCost vs. Vd ($)	ΔQALYs vs. Vd	ICUR ($/QALY) vs. Vd	Sequential ICUR ($/QALY)
Vd	124,503	3.11	–	–	–	–
PVd	377,877	3.57	253,374	0.46	548,169	548,169

Δ = Incremental; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year
Note: Total costs and QALYs are discounted probabilistic values, based on 5,000 Monte Carlo iterations.

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include the size of the eligible patient population, the market share estimates for PVd and comparator regimens, the unit costs of comparator regimens, and the mean time on treatment for PVd and comparator regimens.

Key limitations of the BIA model included estimation of PVd-eligible patients using data from the RevAid controlled distribution program, which lacked transparency and could not be validated by the EGP. Specifically, it was not clear whether the reported number of users of LEN per quarter represented only new users per quarter, or if this were a combination of existing users and new users of LEN per quarter. Given that quarterly data were summed to arrive at the total number of PVd-eligible patients per year, there is a risk of double-counting of patients in the submitter's base case analysis. Another limitation of the BIA model was the adjustment of the cost of PVd using an 85% dose intensity, which likely resulted in an underestimate of the total expenditure associated with PVd, and in turn, an underestimate of the total budget impact associated with PVd reimbursement. This parameter was able to be modified by the EGP. The market uptake of PVd has a linear relationship with the net budget impact associated with PVd such that any percentage increase in the market uptake of PVd results in the same percentage increase in the net budget impact associated with PVd. Similarly, to the submitted economic model, the dosing and administration of bortezomib used in the BIA did not reflect Canadian clinical practice; this parameter was able to be modified by the EGP to the 1.5 mg/m^2 weekly dose used in Canada.

1.6 Conclusions

The EGP's best case estimate for PVd when compared to Vd is:

- $580,444 per QALY gained when the full, LEN-exposed trial population is considered; and,
- $548,169 per QALY gained when considering patients with LEN-refractory disease only.

Overall conclusions of the submitted model:

- *The submitted model was comprehensive and reflected current understanding of relapsed and refractory multiple myeloma patients treated with PVd compared to Vd. However, the model lacked transparency and was unnecessarily complex. Adjustments made to the model in EGP reanalysis did not significantly impact the expected survival benefit associated with PVd.*
- *The comparative cost-effectiveness of PVd versus all relevant comparators (DVd, Kd, CyBorD) is unknown. Exploratory analysis was conducted by the EGP to estimate cost-effectiveness of PVd compared to all relevant comparators; however, results warrant careful interpretation in light of the limitations associated with the submitter's NMA.*
- *The CGP indicated that in the Canadian context, the results from the OPTIMISMM study are especially relevant for patients who have LEN-refractory disease as LEN is currently given until progression or intolerance. Further the CGP indicated that it would be valuable to have flexibility in the line of therapy that is selected given that line of therapy is dependent on provincial access to other active agents together with patient preferences. Therefore, a scenario analysis was considered whereby PVd was compared to Vd in patients with LEN-refractory disease who received two or more prior treatments. Results of this scenario analysis should be carefully interpreted due to limitations regarding the model structure and the submitter's NMA data.*
- *Although the time horizon was shortened from 25 years to 15 years by the EGP to reduce the uncertainty associated with long-term extrapolation, this did not significantly impact the ICER associated with PVd compared to Vd as less than 3% of the modeled cohort was still alive at 15 years.*

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Lymphoma/Myeloma Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of pomalidomide (Pomalyst) in combination with bortezomib and dexamethasone for multiple myeloma. A full assessment of the clinical evidence of [drug name and indication] is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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