pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

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
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation

Drug: **Daratumumab (Darzalex)** Submitted Reimbursement Request: **In combination with bortezomib, melphalan and prednisone, for the treatment of patients with newly diagnosed multiple myeloma who are not suitable for autologous stem-cell transplant**	
Submitted By: Janssen Inc.	Manufactured By: Janssen Inc.
NOC Date: November 27, 2018	Submission Date: January 4, 2019
Initial Recommendation: July 5, 2019	Final Recommendation: August 29, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	**Daratumumab combination with bortezomib, melphalan and prednisone (DVMP) cost breakdown** • Daratumumab costs $598.02 per 100 mg vial and $2,392.08 per 400 mg vial • Bortezomib costs $1,402.42 per 3.5 mg vial • Melphalan costs $1.7372 per unit (50-unit pack, 2 mg per unit) = $86.86 per pack • Prednisone costs $0.1735 per unit (100-unit pack, 50 mg per unit) = $17.35 per pack, or $0.0220 per unit (100-unit pack, 5 mg per unit) = $2.20 per pack 42-day cycle cost: • 1st 42-day cycle, total drug cost of DVMP is $43,939 • 2nd to 9th 42-day cycle, total drug cost of DVMP is $16,640 per cycle • 10th cycle until progression, average total drug cost of between $6,828 (1 daratumumab infusion), and $13,656 (2 daratumumab infusions) per 42-day cycle Calculated 28-day cycle cost • In first 42-day cycle average total cost of DVMP is $29,292.70 per 28-days • 2nd to 9th 42-day cycle, average total cost of DVMP is $11,093.40 per 28-day cycle 10th cycle until progression, total drug cost of DVMP is $6,828 per 28-day cycle (one daratumumab infusion per 4-week period [28-days])

pERC RECOMMENDATION ☐ **Reimburse** ☒ **Reimburse with**	pERC conditionally recommends to reimburse daratumumab in combination with bortezomib, melphalan, and prednisone (DVMP) for patients with newly diagnosed multiple myeloma who are not suitable for autologous stem-cell transplant if the following conditions are met: • Cost-effectiveness being improved to an acceptable level • Feasibility of adoption (budget impact) being addressed.

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.	Eligible patients include those with good performance status and treatment with the daratumumab component should continue until unacceptable toxicity or disease progression. pERC made this recommendation because it was satisfied that there is a net clinical benefit of DVMP compared with bortezomib, melphalan and prednisone (VMP) in this setting based on a statistically significant and clinically meaningful improvement in progression-free survival, and a trend to improved overall survival. In addition, DVMP had a manageable toxicity profile with no detriment to overall quality of life. pERC is also satisfied that DVMP aligns with patients' values of providing disease control, prolonged life, and no detriment to quality of life. pERC concluded that at the submitted price, DVMP could not be considered cost-effective compared with VMP. pERC also highlighted that the submitted budget impact of daratumumab is substantially underestimated and that the potential impact would be large due to the high cost of DVMP and the large prevalent population for this treatment in the upfront setting. pERC also had significant concerns about the capacity of jurisdictions to implement DVMP given the potentially large number of patients eligible for daratumumab and the administration schedule that includes frequent clinic visits and potential for infusion-related reactions that lead to long infusion times throughout the treatment course. All of these factors contribute to pERC's concern that implementation could lead to significantly increased resource utilization (e.g., nursing, pharmacy, clinic, and chemotherapy chair time).
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Price Arrangement to Improve Cost-Effectiveness and Affordability of Daratumumab** Given that pERC concluded that there is a net clinical benefit of DVMP compared with VMP in this setting, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness and affordability of daratumumab compared with other treatment options for multiple myeloma. **Factors Affecting Budget Impact and Adoption Feasibility** In considering the high cost of daratumumab, the large prevalent eligible population, the unknown but potentially long duration of treatment, and the broad impact of a complex administration schedule, pERC concluded that a substantial reduction in the price of daratumumab would be required to improve affordability. **Optimal Sequencing of Available Therapies After Progression on Daratumumab in Combination with Bortezomib, Melphalan, and Prednisone** pERC concluded that the optimal sequencing of therapies for patients with newly diagnosed multiple myeloma who are not suitable for autologous stem-cell transplant is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments. pERC recognizes that provinces will need to address this issue upon implementation of a reimbursement recommendation for daratumumab and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value.

Daratumumab in Combination with Cyclophosphamide, Bortezomib, and Dexamethasone
At the time of implementing a reimbursement recommendation for DVMP, jurisdictions may consider extending the reimbursement to daratumumab in combination with cyclophosphamide, bortezomib, and dexamethasone (DCyBorD) because pERC agreed with the registered clinician input and the Clinical Guidance Panel that DCyBorD would likely be equally effective as DVMP and possibly less toxic.

Time-Limited Need for Patients Who Have Recently Started Treatment with Bortezomib, Melphalan, and Prednisone or Cyclophosphamide, Bortezomib, and Dexamethasone
At the time of implementing a reimbursement recommendation for DVMP (or DCyBorD), jurisdictions may consider addressing the time-limited need of adding daratumumab to the treatment for patients who recently initiated VMP or for patients who recently initiated treatment with CyBorD. For patients who have recently completed first-line therapy with a non-daratumumab regimen (e.g., VMP; CyBorD; or lenalidomide and dexamethasone[Rd]) daratumumab would be reserved for the later line of treatment, rather than be added after the completion of the chemotherapy regimen.

Canadian Dosing of Bortezomib, Melphalan, and Prednisone Optional
pERC noted that jurisdictions may consider reimbursing the Canadian dosing of VMP in addition to the dosing of VMP used in the ALCYONE trial.

Different Frequency of Dosing Schedule of Daratumumab in Newly Diagnosed Patients and in Relapsed or Refractory Settings and Different Frequencies of Dosing/Scheduling for Bortezomib, Melphalan, and Prednisone Compared with Cyclophosphamide, Bortezomib, and Dexamethasone
pERC acknowledged that the recommended dosing schedule of daratumumab for newly diagnosed multiple myeloma differs from relapsed or refractory myeloma. As well, pERC noted that the frequency of dosing/scheduling for bortezomib, melphalan and prednisone are different compared with cyclophosphamide, bortezomib, and dexamethasone. As a result, these may lead to potential dosing errors. pERC recognized that centres have varying approaches for reducing potential dosing errors and noted that collaboration among provinces to develop a national, uniform approach to mitigate potential dosing errors would be of great value.

Resource Use and Adoption Feasibility
pERC noted that the administration of intravenous daratumumab is resource-intensive due to the duration, frequency, and changing pattern of dosing. pERC noted the potentially long infusion times for daratumumab could significantly increase resource use. In addition, administrations would pose difficulties for certain cancer centres that may only be open for a maximum number of hours per day (e.g., 8 to 10 hours) since longer infusion times and additional support medications may be required for some patients. There is a potential that daratumumab infusions may need to be split into multiple days, depending upon the requirements of the patient and treatment centre (e.g., prior infusion-related reaction, drug stability).

pERC also noted that i) variations in the lengths of infusion times, ii) a potentially high number of incident and prevalent patients eligible for this treatment, and iii) the potential management of any infusion-related reactions (that could lead to longer infusion times for subsequent doses) could significantly impact the availability of chemotherapy chair time for all patients requiring systemic therapy for all cancer indications. Therefore,

these represents a significant opportunity cost of implementing intravenous daratumumab-based treatment into the health system. pERC also noted the substantial incremental pharmacy and nursing resources required to prepare and administer daratumumab to patients. Therefore, pERC noted that jurisdictions will need to consider the significant impact on available infrastructure, resources, nursing, and pharmacy staff when considering the feasibility of adoption.

Potential Impact on Canadian Blood Services
pERC noted that, upon implementation, a large number of patients would be eligible for treatment with daratumumab and that, because daratumumab interferes with blood compatibility testing, those patients would require red cell phenotyping before beginning treatment. Jurisdictions may want to consider liaising with Canadian Blood Services before implementation in order to identify potential barriers to implementation.

Please note: Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

In Canada there were approximately 2,900 new myeloma cases in 2017. Of these, there were 1,700 in men, and 1,200 new cases of myeloma in women. There were 1,450 deaths from myeloma in 2017 accounting for approximately four deaths for every 100,000 people. The prevalence of myeloma is about 3.5 times the incidence. The median age for diagnosis of myeloma is 65 years. Front-line options currently include bortezomib, melphalan and prednisone; cyclophosphamide, bortezomib, and dexamethasone; or lenalidomide and dexamethasone. pERC noted that it recently made a recommendation for lenalidomide in combination with bortezomib and dexamethasone in a similar patient population; however, this combination is currently not funded in any Canadian jurisdiction. pERC acknowledged the need for more novel therapies with demonstrated improvements in overall survival 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

The pCODR systematic review included one, open-label, phase III, randomized controlled trial, ALCYONE, which examined the effect and safety of adding daratumumab to bortezomib, melphalan, and prednisone (DVMP) compared with bortezomib, melphalan, and prednisone (VMP) alone in patients with newly diagnosed multiple myeloma who were ineligible for autologous stem-cell transplantation. pERC recognized the importance of extending the first progression (i.e., delaying patient from progressing to second-line therapy) and noted that there was a statistically significant and clinically meaningful improvement in progression-free survival demonstrated in the trial. pERC discussed that the overall survival results based on updated (unpublished) longer follow-up data were more favourable for DVMP than the published results which were based on shorter follow-up data. pERC acknowledged that although the median overall survival was not reached, there appeared to be an early survival benefit with DVMP compared with VMP, and concluded that there was a trend to improved overall survival. As well, pERC discussed that patients in the ALCYONE trial were ineligible for transplant and would not have likely been eligible for transplant following treatment of DVMP; thus, pERC concluded that the additional observed benefit in the DVMP group was not attributed to transplant.

Moreover, pERC discussed that the most commonly reported grade 3 or 4 adverse events were neutropenia, anemia, and thrombocytopenia in both the DVMP and VMP groups. pERC noted a higher proportion of patients treated with DVMP reported infections and pneumonia. As well, pERC noted that daratumumab associated infusion-related reactions occurred in 27.7% of patients. pERC also noted that the number of patients discontinuing treatment and the number of deaths related to treatment were similar in both groups. pERC discussed that, while certain toxicities were increased with daratumumab, the toxicities were considered manageable. As well, pERC discussed the quality of life measurements and noted that apart from the observed improvement at the first time point for Global Health Status subscale and EQ5D VAS, there were no significant differences in quality of life at any other timepoints. Overall, pERC concluded that there is a net clinical benefit with DVMP based on a statistically significant and clinically meaningful improvement in progression-free survival, a trend to improved overall survival, manageable toxicity profile, and no detriment to overall quality of life.

pERC discussed the network meta-analysis used to inform the economic model that included a comparison with lenalidomide plus dexamethasone (Rd). pERC noted that DVMP was associated with a statistically significant reduction in risk of disease progression and death compared with VMP and non-statistically significant progression-free survival and overall survival compared with Rd-continuous. pERC acknowledged the limitations noted by the review team, shared their concerns regarding the heterogeneity across the study designs and populations, and concluded that results should be interpreted with caution. As well, pERC discussed the naive and match-adjusted indirect comparison demonstrating non-inferiority of VMP-modified regimens compared with VMP (VISTA registration) [redacted], and concluded that this was consistent with what clinicians expect since [redacted] were also noted by the Clinical Guidance Panel (CGP). (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.*)

pERC acknowledged that the registered clinicians expressed a preference to use DCyBorD over DVMP as a result of the better toxicity profile with CyBorD and more convenient bortezomib once weekly with CyBorD rather than twice weekly administration of bortezomib with DVMP, and the phase II evidence to support DCyBorD (LYRA study). Moreover, pERC discussed the extrapolation of the ALCYONE results to daratumumab + CyBorD and noted the CGP's conclusion that in the absence of a randomized clinical trial that compares DCyBorD with CyBorD, it is likely that a similar enhancement in efficacy will be seen by adding daratumumab to CyBorD. Therefore, pERC agreed that DCyBorD would likely be as equally effective as DVMP and possibly less toxic than DVMP. pERC acknowledged that the decision to extend the DVMP recommendation to DCyBorD was also supported by Myeloma Canada and the CGP. pERC also noted that the economic model assumed that efficacy for CyBorD was the same as the efficacy for VMP in the ALCYONE trial. As a result, pERC discussed the non-randomized cohort study identified by the submitter and the review team that evaluated the impact of different bortezomib-containing regimens including CyBorD, VMP, and bortezomib plus dexamethasone for the treatment of transplant-ineligible multiple myeloma patients. pERC acknowledged the CGP's assessment of the data and that CyBorD and VMP yield similar overall survival benefit and it was perceived that CyBorD offered a better toxicity profile compared with VMP. Based on patient input, clinical expectations, real-world evidence and phase II trial data highlighted by the registered clinicians, pERC agreed that VMP and CyBorD as well as DVMP and DCyBorD would have similar efficacy regardless of the backbone and perceived CyBorD and DCyBorD to be better tolerated than VMP and DVMP. As a result, pERC noted that at the time of implementing a reimbursement recommendation for daratumumab in combination with bortezomib, melphalan and prednisone, jurisdictions may consider extending the reimbursement to DCyBorD.

Upon reconsideration, pERC discussed the feedback on the Initial Recommendation from the registered clinician that red cell typing will need to be considered if daratumumab + VMP is to be implemented. pERC noted that the Economic Guidance Panel (EGP) indicated that the cost of red cell typing was not included in the pharmacoeconomic (PE) model and agreed with the CGP that the cost would not likely be significant. pERC acknowledged that red cell typing is currently being done, given the approvals for daratumumab in the relapsed setting; and reiterated that red cell phenotyping would be required before beginning treatment.

pERC deliberated on patient advocacy group input and noted that patients value remission, improved quality of life, disease control, prolonged life, fewer side effects than other treatments, and enjoying a normal life. pERC noted that patients felt CyBorD was a relevant comparator. As well, pERC acknowledged difficulties in recruiting patients who had direct experience with DVMP or DCyBorD. The Committee appreciated Myeloma Canada's efforts to highlight patient and caregiver expectations for DVMP or DCyBorD by drawing from previous submissions in multiple myeloma, focusing their input on VMP and CyBorD without daratumumab to illustrate patient experience with the comparative treatments, and citing real-world evidence to support their input. Overall, based on the clinical evidence discussed above and the patient input, pERC was satisfied that DVMP aligns with patients' values of having disease control, prolonged life, and no detriment to quality of life.

pERC deliberated upon the cost-effectiveness of DVMP compared with bortezomib, melphalan, and prednisone; cyclophosphamide, bortezomib, and dexamethasone; or lenalidomide and dexamethasone. pERC considered the uncertainties in the model inputs addressed by the pCODR EGP (i.e., time horizon, subsequent therapies, cost of bortezomib, wastage, and alternative parametric fitting VMP overall survival curves [upper bound only for DVMP versus VMP]).

According to the EGP, the uncertainty generated from the CyBorD efficacy assumption (i.e., efficacy equivalent to VMP, hazard ratio = 1) was not incorporated in the economic model, therefore there remains considerable uncertainty in relative efficacy between DVMP versus CyBorD. As a result of the lack of direct comparison of DVMP compared with CyBorD or Rd and limitations of the network meta-analysis, pERC noted the EGP's lower bound for the base-case estimate (which was higher than the submitter's base estimate) and their inability to calculate an upper bound for DVMP compared with CyBorD and DVMP compared with Rd due to uncertainty. pERC also noted for the Rd comparison, the utility values for both the progression-free and progressed disease state differed depending on the data source (ALCYONE trial versus FIRST trial) however this did not have a large impact on the incremental cost-utility ratio. Overall, pERC concluded that at the submitted price, DVMP could not be considered cost-effective compared with bortezomib, melphalan and prednisone; cyclophosphamide, bortezomib, and dexamethasone; or lenalidomide and dexamethasone.

Upon reconsideration, pERC discussed the submitter's feedback on the Initial Recommendation. Specifically, the submitter did not agree with the use of a 10-year time horizon in the reanalysis and noted that there have been previous pCODR submissions for multiple myeloma in which the EGP assumed a 20-year time horizon. While the EGP acknowledged that there have been previous pCODR submissions for multiple myeloma that assumed a 20-year time horizon in the reanalysis, the EGP maintained their reanalysis estimates for the lower and upper bound ICER estimates. Both the EGP and CGP acknowledged that some patients receiving DVMP may live up to or even longer than 10 years. However, given the relatively short follow-up in the ALCYONE trial (median follow-up of 27.8 months), with insufficient long-term follow-up data, both the CGP and EGP concluded that a time horizon of 10 years was appropriate. pERC agreed with the EGP and CGP that the 10-year time horizon was appropriate and appreciated the additional sensitivity analyses conducted by the EGP which explored the impact of the time horizon on the final EGP reanalysis (EGP's best-case estimate). pERC maintained that the daratumumab + VMP is not cost-effective compared with bortezomib, melphalan and prednisone; cyclophosphamide, bortezomib, and dexamethasone; or lenalidomide and dexamethasone.

pERC considered the feasibility of implementing a positive reimbursement recommendation for DVMP. Contrary to the submitter's budget impact, pERC discussed that the majority of patients would have DVMP in the first-line setting and that a minority of patients would have a non-daratumumab regimen in the first-line setting, and therefore disagreed with the market share proposed by the submitter in the DVMP reimbursed scenario of the budget impact analysis. In the DVMP reimbursed scenario of the budget impact analysis, it was unclear if and how the shift in market share from second-line daratumumab regimen to upfront daratumumab regimen was accounted for in the budget impact analysis, as pERC anticipates this shift to upfront daratumumab use to have a significant impact on the budget for the treatment of newly diagnosed multiple myeloma patients. Therefore, pERC concluded that the submitted budget impact of DVMP was substantially underestimated and that the potential budget impact would be substantial due to the high cost of DVMP and the large prevalent population for this treatment in the upfront setting. As a result, pERC concluded that a substantial reduction in the price of daratumumab would be required to improve affordability.

Upon reconsideration, pERC discussed that the submitter's disagreement with the EGP's statement that a key limitation of the budget impact analysis model was the inability to evaluate the impact of the third-line therapies. pERC discussed the CGP's comment that patients who relapse early may begin third-line therapy within the three-year budget impact time horizon; however, the EGP was unable to conduct an analysis on the impact of third-line therapies. pERC felt that this limitation (i.e. the inability to evaluate the impact of the third-line therapies) identified by EGP was reasonable and acknowledged that the number of patients who may progress onto third-line therapy during a three-year timeframe would be small. Nonetheless, pERC maintained that the submitted budget impact of DVMP was substantially underestimated and that the potential budget impact would be substantial due to the high cost of DVMP and the large prevalent population for this treatment in the upfront setting.

The Committee also discussed that while the submitter supported early conversion to Final Recommendation, the feedback received indicated that the submitter disagreed with the EGP's reanalysis of the ICER estimates and limitations of the BIA which required pERC to consider its recommendation. Although pERC recognized and discussed the concerns raised by the submitter, they also reflected on the impact this kind of feedback (with the support for early conversion) may have had on patients' timely access to treatments and expressed dismay. pERC acknowledged the importance of balancing the obligation of providing due process for substantive concerns raised by stakeholders with the goal of providing timely access to treatment for patients.

With respect to eligibility based on performance status, although the ALCYONE trial only included patients with an Eastern Cooperative Oncology Group Performance Status of 0 to 2, pERC noted that the decision to restrict treatment based on performance status should be left to the treating oncologist. Therefore, pERC concluded that patients with a good performance status should be eligible for DVMP. With respect to wastage, pERC acknowledged that wastage could be a potential concern in smaller centres and noted that the EGP's best-case estimates included wastage as opposed to the submitter's base case that did not include wastage. Refer to Appendix for additional PAG questions which are addressed in a summary table in Appendix 1.

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 two registered clinician groups, representing a total of eight clinicians: one joint submission on behalf of seven clinicians from the Myeloma Canada Research Network, and input from an individual clinician from Ontario.
- Input from pCODR's PAG.

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group, Myeloma Canada.
- One clinician from Ontario.
- The PAG.
- The submitter, Janssen.

The pERC Initial Recommendation was to reimburse DVMP for patients with newly diagnosed multiple myeloma who are not suitable for autologous stem-cell transplant if the following conditions are met:

- Cost-effectiveness being improved to an acceptable level.
- Feasibility of adoption (budget impact) being addressed.

Myeloma Canada, the clinician from Ontario, and PAG agreed with the Initial Recommendation and supported an early conversion to a Final Recommendation. The submitter agreed in part and supported an early conversion to a Final Recommendation. However, in its feedback, the submitter disagreed with the EGP's reanalysis estimates and limitation of the BIA for DVMP, which required pERC to reconsider its recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of DVMP compared with relevant comparators (VMP, CyBorD, and Rd) in patients with newly diagnosed multiple myeloma who are not suitable for autologous stem-cell transplant.

Studies included: ALCYONE: Randomized Controlled Trial of DVMP versus VMP alone

The pCODR systematic review includes one open-label, phase III, randomized controlled trial [ALCYONE] which aimed to examine the effect and safety of adding DVMP compared with VMP alone in patients with newly diagnosed multiple myeloma who were ineligible for autologous stem-cell transplantation.

The pCODR review team also provided contextual information on:

- A critical appraisal of a non-randomized cohort study identified by the submitter and the review team that evaluated the impact of different bortezomib-containing regimens including CyBorD, VMP and bortezomib plus dexamethasone for the treatment of transplant-ineligible multiple myeloma patients.
  - pERC acknowledged the review team's overall conclusion of the non-randomized cohort study: overall, the results of this non-randomized study are generally accepted and CGP's acceptance of the assumption that CyBorD is as effective as VMP.

- A critical appraisal of the naive and match-adjusted indirect comparison demonstrating non-inferiority of VMP-modified regimens compared with VMP (VISTA registration),
  - [redacted]pERC discussed the naive and match-adjusted indirect comparison demonstrating non-inferiority of VMP-modified regimens compared with VMP (VISTA registration) [redacted]

[redacted] and concluded that this was consistent with what clinicians expect since [redacted] were noted by the CGP. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.*)

- A critical appraisal of the submitter's network meta-analysis to compare the results of multiple randomized clinical trials, evaluating first-line therapy for transplant ineligible multiple myeloma.
  - pERC noted the review team's overall conclusion of the network meta-analysis: although the results showed that some Rd regimens had comparable efficacy to daratumumab + VMP, the other regimens evaluated had inferior progression-free survival and overall survival. However most of the regimens that were evaluated were not relevant to the Canadian setting (i.e., not used in Canada). In addition, the credible intervals were wide; making it necessary to interpret any conclusions with caution.

Patient populations: Transplant ineligible, median age 71
Key eligibility criteria included: newly diagnosed, documented multiple myeloma patients who were not eligible for stem-cell transplantation owing to coexisting conditions or an age of 65 years or older with an Eastern Cooperative Oncology Group Performance Status of 0 to 2. Patients with primary amyloidosis or monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma were excluded. The median age of patients was 71 years and between 15% to 17% of patients had myeloma with high-risk cytogenetic abnormalities.

Key efficacy results: Statistically significant and clinically meaningful improvement in progression-free survival and trend to improved overall survival
The key efficacy outcome deliberated on by pERC included progression-free survival and overall survival. There was a statistically significant and clinically meaningful improvement in progression-free survival. pERC discussed that the overall survival results based on updated longer follow-up data (median follow-up 27.8 months) were more favourable for DVMP than the results which were based on shorter follow-up data (16.5 months). pERC acknowledged that although the median overall survival was not reached, there appeared to be an early survival benefit with DVMP compared with VMP; and concluded that there was a trend to an improved overall survival.

Based on the median follow-up of 16.5 months' results, the risk of disease progression or death in the DVMP group was 50% lower compared with the VMP group (hazard ratio 0.50, 95% confidence interval [CI], 0.38 to 0.65; $P < 0.001$). Death was reported in 45 patients in the DVMP group and 48 patients in the VMP group; and the median overall survival was not reached (with the final overall survival analysis occurring after 330 deaths).

Based on the median follow-up of 27.8 months' results, the median PFS was not reached for DVMP group and was 19.1 months for the VMP group, with a hazard ratio of 0.43; 95% CI, 0.35-0.54; $P <0.0001$. Although the median overall survival was not reached, there appeared to be an early survival benefit with DVMP compared with VMP.

Patient-reported outcomes: No detriment to quality of life
Additional endpoints included patient-reported outcomes assessed using the European Organization for Research and Treatment of Cancer (EORTC) –QLQ-C30 questionnaire, EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L) questionnaire and health resource utilization. pERC discussed these quality of life measurements and noted that apart from the first time point where DVMP had a statistically significant improvement in Global Health Status subscale and EQ5D VAS compared with VMP, there was no significant difference in the quality of life measurements at any other time point. As a result, pERC concluded that compared with VMP, there was no detriment to quality of life.

Limitations: Unblinded trial, Immature overall survival data
pERC noted that the ALYCONE trial was not blinded and acknowledged that although the median overall survival was not reached (with the final overall survival analysis occurring after 330 deaths), there appeared to be an early survival benefit with DVMP compared with VMP. pERC also noted that the comparator was VMP, and no other RCTs comparing DVMP with other relevant interventions were

available; however, the submitter did include a network meta-analysis to address comparative efficacy of DVMP to other treatment options.

Safety: Increased infection and pneumonia in the DVMP group, but overall manageable toxicity profile
The most commonly reported adverse event of any grade (≥ 20% of the patients in either group) was neutropenia (in 49.7% of the patients in the daratumumab group and 52.5% of patients in the VMP group) followed by thrombocytopenia (48.8% and 53.7% in the DVMP and VMP group respectively). The most common grade 3 to 4 adverse events were neutropenia (39.9% and 38.7%), thrombocytopenia (34.4% and 37.6%), and anemia (15.9% and 19.8%). pERC noted a higher proportion of patients treated with DVMP reported infections and pneumonia. As well, pERC noted that daratumumab associated infusion-related reactions occurred in 27.7% of patients. pERC also noted that the number of patients discontinuing treatment and the number of deaths related to treatment were similar in both groups. pERC discussed that, while certain toxicities were increased with daratumumab, those toxicities were manageable and therefore, concluded that DVMP had a manageable toxicity profile.

Need and burden of illness: Need for more novel therapies with demonstrated improvements in overall survival.
In Canada there were approximately 2,900 new myeloma cases in 2017. Of these, there were 1,700 in men, and 1,200 new cases of myeloma in women. There were 1,450 deaths from myeloma in 2017 accounting for approximately four deaths for every 100,000 people. The prevalence of myeloma is about 3.5 times the incidence. The median age for diagnosis of myeloma is age 65. Front-line options include bortezomib, melphalan and prednisone; cyclophosphamide, bortezomib, and dexamethasone; or lenalidomide and dexamethasone. pERC noted that it recently made a recommendation for lenalidomide in combination with bortezomib and dexamethasone in a similar patient population; however, this combination is currently not funded in any Canadian jurisdiction. pERC acknowledged the need for more novel therapies with demonstrated improvements in overall survival for these patients.

Registered clinician input: Preference to use DCyBorD over DVMP
pERC acknowledged the registered clinicians' input, specifically: their conclusion that CyBorD was similar to VMP (which was supported by the non-randomized cohort study), their preference to use CyBorD over VMP (which was reflective of Canadian practice), their preference to use DCyBorD over DVMP (as a result of the better toxicity profile and more convenient bortezomib dose administration), and the phase II evidence to support DCyBorD [LYRA study]. pERC also noted the registered clinicians' sequencing of daratumumab in that it would be used first line to maximize the benefit in earlier treatment and that retreatment of daratumumab in later lines of therapy is not recommended (which was also supported by the CGP).

Upon reconsideration, pERC noted the feedback on the Initial Recommendation from the registered clinician that red cell typing will need to be considered if daratumumab + VMP is to be implemented. The EGP indicated in the Final Economic Guidance Report that the cost of red cell typing was not included in the pharmacoeconomic model; however, the CGP indicated that the cost would not be significant. The CGP noted that red cell typing was a logistical consideration and that it is currently being done, given the approvals for daratumumab in the relapsed setting.

PATIENT-BASED VALUES

Patients experience with multiple myeloma: symptoms of multiple myeloma that are important to control include infections, followed by kidney problems, mobility, pain, fatigue, neuropathy, and shortness of breath Patients also indicated their emotional well-being was impacted, and symptoms may fluctuate during their treatment journey. Most symptoms of myeloma have a neutral to significant impact on day-to-day activities and quality of life. Specifically, the ability to work was reported as the most affected, followed by the ability to travel, exercise, volunteer, conduct household chores, fulfill family obligations, and spend time with family and friends. Caregivers also experienced limitations in their daily life, with the ability to travel being rated as the most impacted, followed by ability to volunteer, spend time with family and friends, concentrate, fulfill family obligations, work, exercise, and conduct household chores.

Patient values on treatment: remission, improved quality of life, disease control, prolonged life, fewer side effects than other treatments, and enjoying a normal life
Patients value remission, improved quality of life, disease control, prolonged life, fewer side effects than other treatments, and enjoying a normal life. Patients' expectations for daratumumab include controlling symptoms such as infections, kidney problems, mobility, pain, fatigue, neuropathy, and shortness of breath. In addition, patients value a treatment option that would improve their ability to do day-to-day activities such as work, travel, conduct chores and fulfill family obligations.

Patients receiving VMP and CyBorD had differing expectations of their treatment. Patients who received VMP reported that their most important expectations of the treatment included improved quality of life and enjoying a normal life, whereas patients that received CyBorD ranked remission and disease control as their most important expectations of their treatment. Two-thirds (n = 2) of patients on VMP indicated prolonged life was an expectation that was met, and half of patients (n = 6) indicated CyBorD met their expectation of disease control. All patients receiving VMP (n = 3) rated their quality of life as poor or fair, whereas 58% (n=7) of CyBorD treated patients rated their quality of life as good, very good, or excellent. Overall, most patients on VMP and CyBorD thought their treatment was effective, with only one patient on CyBorD stating it was not effective in controlling multiple myeloma.

ECONOMIC EVALUATION

Economic model submitted: cost-effectiveness analysis and cost-utility analysis
The pCODR EGP assessed a cost-effectiveness analysis and cost-utility analysis comparing daratumumab, bortezomib, melphalan and prednisone (DVMP) to bortezomib, melphalan and prednisone (VMP); cyclophosphamide, bortezomib, and dexamethasone (CyBorD); or lenalidomide and dexamethasone (Rd) for the treatment of patients with newly diagnosed multiple myeloma who are not suitable for autologous stem-cell transplantation.

Basis of the economic model: partitioned-survival model
The partitioned-survival model was comprised of three health states (alive pre-progression, alive post-progression, and dead), and a cycle length of one week was used. The ALCYONE trial was used for efficacy and safety data for the comparison of DVMP with VMP. The model assumed that efficacy for CyBorD was the same as the efficacy for VMP in the ALCYONE trial. Progression-free survival for Rd was based on the FIRST trial and overall survival was based on a network meta-analysis. Safety outcomes were based on published trials for these regimens. Utility values used in the base case were derived from an analysis of EQ-5D-5L data from ALCYONE during the pre- and post-progression periods.

Drug costs: high cost of daratumumab

DVMP Cost breakdown
- Daratumumab costs $598.02 per 100 mg vial and $2,392.08 per 400 mg vial
- Bortezomib costs $1,402.42 per 3.5 mg vial
- Melphalan costs $1.7372 per unit (50-unit pack, 2 mg per unit) = $86.86 per pack
- Prednisone costs $0.1735 per unit (100-unit pack, 50 mg per unit) = $17.35 per pack, or $0.0220 per unit (100-unit pack, 5mg per unit) =$2.20 per pack

42-day cycle cost:
- 1st 42-day cycle, total drug cost of DVMP is $43,939
- 2nd to 9th 42-day cycle, total drug cost of DVMP is $16,640 per cycle
- 10th cycle until progression, average total drug cost of between $6,828 (1 daratumumab infusion), and $13,656 (2 daratumumab infusions) per 42-day cycle

Calculated 28-day cycle cost
- In first 42-day cycle average total cost of DVMP is $29,292.70 per 28-days
- 2nd to 9th 42-day cycle, average total cost of DVMP is $11,093.40 per 28-day cycle
- 10th cycle until progression, total drug cost of DVMP is $6,828 per 28-day cycle (one daratumumab infusion per 4-week period [28-days])

VMP Cost breakdown:
- Bortezomib costs $1,402.42 per 3.5mg vial

• Melphalan costs $1.7372 per unit (50-unit pack, 2mg per unit) = $86.86 per pack
• Prednisone costs $0.1735 per unit (100-unit pack, 50mg per unit) = $17.35 per pack, or $0.0220 per unit (100-unit pack, 5mg per unit) =$2.20 per pack

42-day cycle cost:
• 1st 42-day cycle, total drug cost of VMP is $7,031
• 2nd to 9th 42-day cycle, total drug cost of VMP is $3,278 per cycle
• 9th+ cycle until progression, total drug cost of VMP is $0 per cycle*

Calculated 28-day cycle cost:
• In first 42-day cycle, average total drug cost of VMP is $4,687.66 per 28-days
• 2nd to 9th cycle, average total drug cost of VMP is $2,185.07
• 9th cycle until progression, average total drug cost of VMP is $0 per 28-days*

CyBorD Cost breakdown:
• Bortezomib costs $1,402.42 per 3.5 mg vial
• Cyclophosphamide costs $0.4740 per unit (100-unit pack, 50 mg per unit)
• Dexamethasone costs $0.3046 per unit (100-unit pack, 4 mg per unit)
• Per 28-day cycle, at the doses included in the model, CyBorD costs $4,055

Rd Cost breakdown:
• Lenalidomide costs $424.00 per unit (21-unit pack, 25 mg per unit)
• Dexamethasone costs $0.3046 per unit (100-unit pack, 4mg per unit)
• Per 28-day cycle at the doses included in the model, Rd costs $8,916

*VMP was given up to nine cycles in DVMP and VMP regimens, therefore the cost of VMP beyond nine cycles is $0

Cost-effectiveness estimates: Not cost-effective compared with bortezomib, melphalan and prednisone; cyclophosphamide, bortezomib, and dexamethasone; or lenalidomide and dexamethasone
pERC considered the uncertainties in the model inputs addressed by the pCODR EGP (i.e., time horizon, subsequent therapies, cost of bortezomib, wastage, and alternative parametric fitting VMP overall survival curves [upper bound only for DVMP versus VMP]) and agreed with the EGP's reanalysis approach. pERC noted the EGP's lower bound for the base-case estimate (which was higher than the submitter's base estimate) and their inability to calculate an upper bound for DVMP compared with CyBorD and DVMP compared with Rd due to uncertainty in the results of the comparison from the NMA. The EGP's best estimate for DVMP compared with VMP ranged between $170,859/QALY and $389,092/QALY; whereas, the submitter's incremental cost-utility ratio (ICUR) was $145,207/QALY. The EGP's best estimate for DVMP compared with CyBorD ranged between $172,194/QALY and unknown (due to the uncertainty) and the submitter's ICUR was $144,171/QALY. The EGP's best estimate for DVMP compared with Rd ranged between $243,804/QALY and unknown (due to the uncertainty) and the submitter's ICUR was $155,180/QALY. pERC concluded that at the submitted price, daratumumab in combination with bortezomib, melphalan and prednisone could not be considered cost-effective compared with VMP, CyBorD, or Rd. Given that pERC concluded that there is a net clinical benefit of DVMP compared with VMP in this setting, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness and affordability of daratumumab compared with other treatment options for multiple myeloma.

Upon reconsideration, pERC discussed the submitter's feedback on the Initial Recommendation. Although the submitter supported early conversion, they disagreed with aspects of the EGP analysis and therefore, pERC was obliged to delay implementation of the recommendation to reconsider the recommendation. Specifically, the submitter did not agree with the use of a 10-year time horizon in the reanalysis and noted that there have been previous pCODR submissions for multiple myeloma in which the EGP assumed a 20-year time horizon. While the EGP acknowledged that there have been previous pCODR submissions for multiple myeloma that assumed a 20-year time horizon in the reanalysis, the EGP maintained their reanalysis estimates for the lower and upper bound ICER estimates. Both the EGP and CGP acknowledged that some patients receiving DVMP may live up to or even past 10 years. However, given the relatively short follow-up in the ALCYONE trial (median follow-up of 27.8 months), with insufficient long-term follow-up data, both the CGP and EGP concluded that a time horizon of 10 years was appropriate. The EGP conducted additional sensitivity analyses on the final EGP reanalysis (EGP's best-case estimate) for pERC to better

understand the impact of the time horizon. pERC maintained that the daratumumab + VMP is not cost-effective compared with bortezomib, melphalan and prednisone; cyclophosphamide, bortezomib, and dexamethasone; or lenalidomide and dexamethasone.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact substantially underestimated
The factors that most influence the budget impact analysis include population size, wastage cost, subsequent treatment cost, and market share. The EGP noted that it is difficult to determine how accurate the eligible population and market share are at this point in time. However, these parameters were able to be modified and a range of values were explored by the EGP.

Key limitations of the budget impact analysis model were the inability to evaluate the impact of the third-line therapies that were incorporated in the cost-effectiveness analysis model. The BIA only accounted for first-line and second-line therapies. This parameter was not modifiable and therefore not explored by the EGP, but there may potentially be a large overall budget impact. pERC noted that the majority of patients would have DVMP in the first-line setting and that a minority of patients would have a non-daratumumab regimen in the first-line setting, and as a result, pERC concluded that the submitted budget impact of DVMP was substantially underestimated and that the potential budget impact would be substantial due to the high cost of daratumumab in combination with bortezomib, melphalan and prednisone and the large prevalent population for this treatment in the upfront setting. In considering the high cost of daratumumab, the large prevalent eligible population, the unknown but potentially long duration of treatment, and the broad impact of a complex administration schedule, pERC concluded that a substantial reduction in the price of daratumumab would be required to improve affordability.

Upon reconsideration, pERC discussed that the submitter disagreed with the EGP's statement that a key limitation of the BIA model was the inability to evaluate the impact of the third-line therapies. Although the submitter supported early conversion, they disagreed with aspects of the EGP analysis and therefore, pERC was obliged to delay implementation of the recommendation to reconsider the recommendation. The submitter stated that treatment times in the reference scenario and new treatment scenario were long enough such that patients would not progress to a third-line treatment within the three-year time horizon, and that the inclusion of third-line therapies would increase the downstream cost of comparator regimens and decrease the overall incremental budget impact of funding daratumumab in the first-line setting. The EGP consulted with CGP and noted that patients who relapse early may be able to begin third-line therapy within the three-year time horizon. However, the EGP was unable to conduct an analysis on the impact of third-line therapies, and as a result, the impact of third-line therapies is unclear. pERC felt that this limitation was reasonable and acknowledged that the number of patients who may progress onto third-line therapy during a three-year time frame would be small. Nonetheless, pERC maintained that the submitted budget impact of DVMP was substantially underestimated and that the potential budget impact would be substantial due to the high cost of DVMP and the large prevalent population for this treatment in the upfront setting.

pERC concluded that the optimal sequencing of therapies for patients with newly diagnosed multiple myeloma who are not suitable for autologous stem-cell transplant is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments. pERC recognizes that provinces will need to address this issue upon implementation of a reimbursement recommendation for daratumumab and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value.

At the time of implementing a reimbursement recommendation for DVMP, jurisdictions may consider extending the reimbursement to daratumumab in combination with cyclophosphamide, bortezomib, and dexamethasone (DCyBorD) because pERC agreed with the registered clinician input and the CGP that DCyBorD would likely be equally effective as DVMP and possibly less toxic than DVMP given patient input, clinical history and expectations, real-world evidence, and registered clinician preference to use DCyBorD over DVMP due to possibly better toxicity profile and more convenient bortezomib administration. The decision to extend the DVMP recommendation to DCyBorD was also supported by Myeloma Canada and the CGP.

At the time of implementing a reimbursement recommendation for DVMP (or DCyBorD), jurisdictions may consider addressing the time-limited need of adding daratumumab to the treatment for patients who recently initiated VMP or for patients who recently initiated treatment with CyBorD. For patients who

have recently completed first-line therapy with a non-daratumumab regimen (e.g., VMP; CyBorD; or lenalidomide and dexamethasone[Rd]) daratumumab would be reserved for the later line of treatment, rather than be added after the completion of the chemotherapy regimen.

pERC noted that jurisdictions may consider reimbursing the Canadian dosing of VMP in addition to the dosing of VMP used in the ALCYONE trial.

pERC acknowledged that the recommended dosing schedule of daratumumab for newly diagnosed multiple myeloma differs from relapsed or refractory myeloma as well as the different frequency of dosing/scheduling for bortezomib, melphalan and prednisone compared with cyclophosphamide, bortezomib, and dexamethasone, and pERC noted that this may lead to potential dosing errors. pERC recognized that centres have varying approaches for reducing potential dosing errors and noted that collaboration among provinces to develop a national, uniform approach to mitigate potential dosing errors would be of great value.

pERC noted that the administration of intravenous daratumumab is resource-intensive due to the duration, frequency, and changing pattern of dosing. pERC noted the potentially long infusion times for daratumumab could significantly increase resource use. In addition, administrations would pose difficulties for certain cancer centres that may only be open for a maximum number of hours per day (e.g., 8 to 10 hours) since longer infusion times and additional support medications may be required for some patients. There is a potential that daratumumab infusions may need to be split into multiple days, depending upon the requirements of the patient and treatment centre (e.g., prior infusion-related reaction, drug stability).

pERC also noted that variations in the lengths of infusion times, a potentially high number of incident and prevalent patients eligible for this treatment, as well as the potential management of any infusion-related reactions that could lead to longer infusion times for subsequent doses, could significantly impact the availability of chemotherapy chair time for all patients requiring systemic therapy for all cancer indications, and therefore represents a significant opportunity cost of implementing intravenous daratumumab-based treatment into the health system. pERC also noted the substantial incremental pharmacy and nursing resources required to prepare and administer daratumumab to patients. Therefore, pERC noted that jurisdictions will need to consider the significant impact on available infrastructure, resources, nursing, and pharmacy staff when considering the feasibility of adoption.

pERC noted that, upon implementation, a large number of patients would be eligible for treatment with daratumumab and that, because daratumumab interferes with blood compatibility testing, those patients would require red cell phenotyping before beginning treatment. Jurisdictions may want to consider liaising with Canadian Blood Services before implementation in order to identify potential barriers to implementation.

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 who was not present for the meeting
- Daryl Bell who did not vote due to his role as a patient member alternate

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

- Dr. Henry Conter, Dr. Avram Denburg, Dr. Christian Kollmannsberger, and 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.

Avoidance of conflicts of interest

All members of the pERC 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 daratumumab+ VMP for MM for its Initial Recommendation, through their declarations, five members had a real, potential, or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, but none of these members was excluded from voting. For the review of daratumumab+ VMP for MM for its Final Recommendation, through their declarations, five members had a real, potential, or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, but none of these members was excluded from voting.

Information sources used

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

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. Janssen Canada Inc., as the primary data owner, did not agree to the disclosure of certain clinical information; therefore, this information has been redacted in the Recommendation and publicly available Clinical Guidance Report.

Use of this Recommendation

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

clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

Disclaimer

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

PAG Implementation Questions	pERC Recommendation
Currently Funded Treatments • Bortezomib/melphalan/prednisone (VMP), cyclophosphamide/bortezomib/dexamethasone (CyBorD), and lenalidomide/dexamethasone (Rd) are funded in all the provinces for patients with newly diagnosed multiple myeloma who are not suitable for autologous stem-cell transplant. • PAG noted that CyBorD is the current treatment of choice for patients with newly diagnosed multiple myeloma that are transplant ineligible. Although the comparator of VMP in the ALCYONE trial is a funded option, it is rarely used in this patient population. Therefore, PAG is seeking information on the use of daratumumab in combination with other bortezomib-based regimens (e.g., CyBorD or BMD).	**Currently Funded Treatments** • pERC noted the funded treatment options across Canada and acknowledged that although the comparator of VMP in the ALCYONE trial is a funded option, it is rarely used in this patient population. pERC noted that the CyBorD is the preferred regimen and is reflective of Canadian practice. • pERC acknowledged the LYRA trial highlighted by the registered clinicians which assessed DCyBorD and CGP's statement that no Phase III RCTs comparing DVMP with DCyBorD exist. pERC acknowledged that the registered clinicians expressed a preference to use DCyBorD over DVMP as a result of the better toxicity profile and more convenient bortezomib once weekly rather than twice weekly administration, and the phase II evidence to support DCyBorD (LYRA study in transplant eligible population). Moreover, pERC discussed the extrapolation of the ALCYONE results to daratumumab + CyBorD and noted the CGP's conclusion that in the absence of a randomized clinical trial that compares DCyBorD with CyBorD, it is likely that a similar enhancement in efficacy will be seen by adding daratumumab to CyBorD. Therefore, pERC agreed that DCyBorD would likely be as equally effective as DVMP and possibly less toxic than DVMP. pERC acknowledged that the decision to extend the DVMP recommendation to DCyBorD was also supported by Myeloma Canada and the CGP. As well, pERC acknowledged there are other ongoing daratumumab combination trials (e.g., MAIA).
Eligible Patient Population • PAG is seeking clarity that daratumumab + VMP (DVMP) would be limited to patients without primary amyloidosis or monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma. PAG is also seeking clarity on whether patients who receive urgent radiation prior to starting DVMP treatment, would be eligible. • If recommended for reimbursement, PAG noted the following groups of patients would need to be addressed on a time-limited basis: o Patients currently treated with VMP or other bortezomib-regimens for newly diagnosed multiple myeloma not eligible for transplant (e.g., CyBorD); o Patients who recently completely VMP and who have not yet experienced progression. • If switching to DVMP or adding daratumumab to VMP is appropriate in these patients, PAG is seeking guidance	**Eligible Patient Population** • pERC agreed with CGP in that it would not include MGUS, smoldering myeloma or amyloidosis without evidence of concomitant myeloma in the funding inclusion criteria, and that involved field radiation within 14 days of treatment with DVMP would likely be safe and acceptable (refer to generalizability table of the Clinical Guidance Report). • pERC noted that jurisdictions may consider addressing the time-limited need of adding daratumumab to the treatment for patients who recently initiated treatment with bortezomib, melphalan and prednisone or for patients who recently initiated treatment with cyclophosphamide, bortezomib, and dexamethasone. For patients who have recently completed first-line therapy with a non-daratumumab regimen (e.g., bortezomib,

on the dosing schedule administered and when in treatment daratumumab addition can be considered.	melphalan and prednisone; cyclophosphamide, bortezomib, and dexamethasone; or lenalidomide and dexamethasone) daratumumab would be reserved for later line of treatment. • pERC acknowledged that switching to DVMP or adding daratumumab to VMP is appropriate in these patients. With respect to guidance on dosing schedule administration and when in treatment addition can be considered, pERC noted that collaboration among provinces to develop a national, uniform approach to optimal dosing schedule will be needed upon implementation of the recommendation.
Implementation Factors • The recommended dosing/schedule for newly diagnosed multiple myeloma differs from relapsed or refractory myeloma and PAG noted this may lead to potential dosing errors. PAG noted that processes would need to be in place, prior to implementation of daratumumab, to minimize dosing errors and patient confusion. PAG is seeking guidance on the most appropriate dosing regimen for newly diagnosed, transplant-ineligible patients. • PAG is also seeking guidance on the use of a 90-minute daratumumab infusion beginning with the third dose, as this has been adopted in practice in the US to reduce chair time. • PAG noted 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) and is seeking guidance on the dose of bortezomib to be used when given in combination with daratumumab and the generalizability of the ALCYONE trial to Canadian practice. • PAG noted in the ALCYONE trial, there was a higher incidence of infections with DVMP. PAG is seeking guidance on the use of G-CSF with DVMP to minimize potential infections and neutropenia. • PAG has concerns for incremental costs due to drug wastage, specifically in centres where vial sharing would be difficult. Although there are two vial sizes available, dosage is based on weight and there will be some drug wastage as any unused portion would be discarded. PAG is seeking guidance on the use of dose rounding (e.g., round within 10% of calculated dose to nearest vial size) as this would minimize drug wastage.	**Implementation Factors** • pERC acknowledged that the recommended dosing/schedule for newly diagnosed multiple myeloma differs from relapsed or refractory myeloma and that this may lead to potential dosing errors. pERC also acknowledged the different frequency of dosing/scheduling for bortezomib, melphalan and prednisone compared with cyclophosphamide, bortezomib, and dexamethasone, and pERC noted that this may lead to potential dosing errors. pERC recognized that centres have varying approaches for reducing potential dosing errors and noted that collaboration among provinces to develop a national, uniform approach to mitigate potential dosing errors would be of great value. • pERC noted the adoption of a 90-minute daratumumab infusion beginning with the third dose in the USA to reduce chair time. To pERC's knowledge, this approach is not currently implemented in centres across Canada, and did not review evidence on the different infusion time, therefore pERC is unable to comment on the efficacy, safety or feasibility of a 90-minute daratumumab infusion. • pERC recognized the dose of bortezomib in the trial is different than the dose in Canadian practice and agreed with the CGP that it is unlikely that these variations will result in significantly different clinical and toxicity outcomes from that seen in the trial and therefore, agreed that the trial dosage was generalizable to the Canadian setting. As a result, pERC felt it was reasonable for jurisdictions to consider the dose of bortezomib in the ALCYONE trial as well as the dose of bortezomib in Canadian practice (once weekly schedule for all cycles) upon reimbursement of DVMP. • As noted above, pERC acknowledged that there was a higher incidence of infections with DVMP compared with VMP, however felt that other mechanisms to manage infection and neutropenia such as dose reduction and dose delay were widely considered and acknowledged that G-CSF is rarely used.

	• pERC acknowledged that wastage could be a potential concern in the smaller centres and noted that the EGP's best-case estimates included wastage as opposed to the submitter's base case that did not include wastage.

Sequencing and Priority of Treatments
• PAG is seeking guidance on the optimal sequencing of all available therapies for multiple myeloma. For patients who receive DVMP in the first-line setting and then progress,
  o What would be the best treatment after progression following DVMP?
  o Sequencing of subsequent second- and third-line therapies such as carfilzomib-based regimens (e.g., KRD), Rd, pomalidomide, retreatment with bortezomib-based regimens.
  o Clarity on whether patients would be ineligible for retreatment with daratumumab-based regimens in subsequent lines of therapy.
• PAG noted that daratumumab was reviewed for the treatment of patients with multiple myeloma who have received at least one prior therapy and is funded in many provinces. PAG is seeking guidance on the optimal use of daratumumab and preference to use daratumumab in the first-line setting or reserve daratumumab for relapsed or refractory disease.
• For patients who receive the nine cycles of daratumumab in combination with a bortezomib-based regimen and continue on daratumumab maintenance, PAG is seeking guidance on the appropriateness of adding a bortezomib-based regimen at relapse to daratumumab.
	Sequencing and Priority of Treatments
	• pERC concluded that the optimal sequencing of therapies for patients with newly diagnosed multiple myeloma who are not suitable for autologous stem-cell transplant is unknown. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments. pERC recognizes that provinces will need to address this issue upon implementation of a reimbursement recommendation for daratumumab and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value.
	• pERC acknowledged that a small portion of patients would choose lenalidomide plus dexamethasone first line, and for these patients and for patients who have recently completed first-line therapy with a non-daratumumab regimen (e.g., VMP; CyBorD; or Rd) daratumumab would be reserved for later line of treatment. Based on the clinician and CGP input, it is likely that for the majority of patients, DVMP or another daratumumab first-line regimen would be the preferred choice.
	• For patients who receive the nine cycles of daratumumab in combination with a bortezomib-based regimen and continue on daratumumab maintenance, pERC agreed with CGP in that retreatment of daratumumab regimen for these patients in relapsed setting would not be appropriate (i.e., if had daratumumab regimen in first line, it would not be appropriate to have daratumumab regimen in second-line or beyond).
	• With respect, to adding bortezomib-based regimen at relapse to daratumumab, pERC noted that DVMP is indicated for patients with newly diagnosed multiple myeloma who are not suitable for autologous stem- cell transplant, and is not indicated for the relapse setting.