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 lenalidomide and dexamethasone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.	
Submitted By: **Janssen Inc.**	**Manufactured By:** **Janssen Inc.**
NOC Date: **October 25, 2019**	**Submission Date:** **July 17, 2019**
Initial Recommendation: **January 3, 2020**	**Final Recommendation:** **March 5, 2020**

Approximate per Patient Drug Costs, per Month (28 Days)	Dosing/Administrations (28-day cycle): • Daratumumab: • 16 mg/kg administered 4 times per cycle during cycle 1 to 2. • 16 mg/kg administered 2 times per cycle during cycle 3 to 6. • 16 mg/kg administered once per cycle afterwards until treatment discontinuation. • Lenalidomide: • 25 mg administered 21 times per cycle until progression. • Dexamethasone: 40 mg administered 4 times per cycle until progression. Unit costs: • Daratumumab: $598.02 per 100 mg vial. $2,392.03 per 400 mg vial. • Lenalidomide: $424.00 (21-unit pack, 25 mg per unit, $8,904 per pack). • Dexamethasone: $0.3046 (100-unit pack, 4 mg per unit, $30.46 per pack). Cycle cost (28-day cycle): • Cycle 1 and 2: $34,786.98 • Cycle 3 to 6: $23,085.00 • Maintenance: $16,028.60 Calculated per day cost: • During cycle 1 and 2: $1,242.39 • During cycle 3 to 6: $824.46 • Maintenance: $572.45

pERC RECOMMENDATION

☐ **Reimburse**

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

☐ **Do not reimburse**

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

pERC conditionally recommends to reimburse daratumumab in combination with lenalidomide and dexamethasone (DRd) 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.

Eligible patients include those with good performance status and treatment with DRd should continue until unacceptable toxicity or disease progression. pERC made this recommendation because it was satisfied that there is a net clinical benefit of DRd compared with lenalidomide and dexamethasone (Rd) in this setting based on a statistically significant and clinically meaningful improvement in progression-free survival (PFS). In addition, DRd had a manageable toxicity profile with no detriment to overall quality of life. pERC noted that DRd aligns with patients' values of providing disease control, the choice of treatment options, manageable side effects, and no detriment to quality of life.

pERC concluded that at the submitted price, DRd could not be considered cost-effective compared with Rd. 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 DRd and the large prevalent population for this treatment in the upfront setting.

pERC also had significant concerns about the capacity of jurisdictions to implement DRd given the potentially large number of patients eligible for daratumumab and the administration schedule that includes frequent clinic visits. 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 DRd compared with Rd 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 in the first-line setting.

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 reduction in the price of daratumumab would be required to improve affordability.

Optimal Sequencing of Available Therapies After Progression on Daratumumab in Combination with Lenalidomide and Dexamethasone
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 recognized that provinces will need to address this issue upon implementation of a reimbursement recommendation for DRd and noted that collaboration among provinces to develop a national, uniform approach to optimal sequencing would be of great value.

Time-Limited Need for Patients Who Have Recently Started Treatment with Lenalidomide and Dexamethasone
At the time of implementing a reimbursement recommendation for DRd, jurisdictions may consider addressing the time-limited need of adding daratumumab to the treatment for patients who recently initiated Rd. For patients who have recently completed first-line therapy with a non-daratumumab regimen (e.g., bortezomib, melphalan, and prednisone [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.

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, intravenous administrations would pose difficulties for certain cancer centres that may only be open for a limited number of hours per day (e.g., eight to 10 hours) since longer infusion times and additional support medications may be required for some patients. There is 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).

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: The 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 (VMP); cyclophosphamide, bortezomib, and dexamethasone (CyBorD); or lenalidomide and dexamethasone (Rd). pERC noted that it recently made a conditional recommendation for daratumumab in combination with bortezomib, melphalan and prednisone (DVMP) as well as lenalidomide in combination with bortezomib and dexamethasone (VRd) in a similar patient population; however, these combinations are 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, MAIA, that examined the effect and safety of adding daratumumab to lenalidomide and dexamethasone (DRd) compared with lenalidomide and dexamethasone (Rd) alone in patients with newly diagnosed multiple myeloma (NDMM) who were ineligible for autologous stem cell transplantation (ASCT). 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 PFS demonstrated in the trial. pERC acknowledged that the median overall survival was not reached for DRd or Rd in the trial and that additional follow-up with respect to survival is ongoing. pERC acknowledged that PFS is an important outcome in chronic diseases like myeloma and that it can be expected that the median overall survival was not reached in either arm as overall survival data collection is ongoing. pERC also commented that there were improvements in end points such as response rates and minimal residual disease (MRD) negativity.

pERC discussed that the most commonly reported grade 3 or 4 adverse events observed in the trial were neutropenia, anemia, lymphopenia, pneumonia, and leukopenia in both the DRd and Rd groups. pERC noted that a higher proportion of patients treated with DRd reported infections of any grade, fatigue, and diarrhea. 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 increased with daratumumab, the toxicities were considered manageable. In addition, pERC discussed the quality of life measurements and noted that apart from the observed improvement early on for Global Health Status (GHS) subscale and EQ5D Visual Analog Scale, there were no significant differences in quality of life at any other timepoints and it is uncertain if quality of life (QoL) improves over time. Overall, pERC concluded that there is a net clinical benefit with DRd based on a statistically significant and clinically meaningful improvement in PFS, manageable toxicity profile, and no detriment to overall QoL.

pERC discussed the network meta-analysis (NMA) used to inform the economic model that included a comparison with cyclophosphamide; bortezomib and dexamethasone (CyBorD); and bortezomib, melphalan, and prednisone (VMP). pERC acknowledged the review team's overall conclusion of the NMA that daratumumab-based regimens were more favourable with respect to overall survival (OS), PFS, and ORR. pERC acknowledged the limitations noted by the review team and agreed with their concerns regarding the heterogeneity across the study designs and populations, and the conclusion that results should be interpreted with caution.

pERC acknowledged that the registered clinicians expressed a preference to use DRd because it satisfied an unmet need for more effective treatment options with better toxicity profiles in the first-line setting. pERC also noted that registered clinicians supported the use of DRd early as a treatment regimen, as opposed to reserving it for later lines as it would optimize response rates and PFS in transplant ineligible patients. pERC noted that some registered clinicians were concerned that the trial inclusion criteria of

creatinine clearance that was of greater than 30 mL/min was too restrictive and DRd should be administered more broadly. However, pERC also agreed with the clinical guidance panel (CGP) that patients with pre-existing renal failure would be more effectively treated with a bortezomib-based regimen such as VMP. pERC noted there is a small minority of patients that may be treated with dose-reduced lenalidomide if there was a contraindication to the use of a proteasome inhibitor in patients with renal failure, and creatinine clearance less than 30 mL/min. pERC commented that often the creatinine clearance is a result of the myeloma and upon treatment for the disease patients' creatinine clearance may improve. pERC also agreed with the CGP and registered clinicians that the use of rapid infusion schedules for daratumumab may be an option for patients if the first infusion is tolerated. pERC also agreed with the CGP and registered clinicians that there is currently no evidence to inform reinitiating daratumumab after a treatment break due to a maximum response to daratumumab being reached, during which time Rd is continued. pERC noted the differing opinions in the registered clinician input on adding cyclophosphamide to DRd after biochemical progression. pERC commented that the decision to add cyclophosphamide is based on clinical judgment by the treating physician; however, there may be better second-line treatment options for patients once they progress.

pERC deliberated on one patient advocacy group input and noted that patients value remission, improved QoL, disease control, prolonged life, fewer side effects compared with other treatments, and enjoying a normal life. pERC noted that of the small number of patients, approximately half of the patients who had experience with DRd noted that expectations of improved QoL, disease control, remission, and prolonged life were fulfilled. In addition, pERC noted that patients who had experience with DRd reported that the common side effects of DRd were generally tolerated. pERC acknowledged comments from caregiver respondents that the treatment with DRd requires considerable time commitments. Based on the clinical evidence discussed above and the patient input, pERC agreed that DRd aligns with patients' values of having disease control, additional treatment options, a manageable side effect profile, and no detriment to QoL.

pERC deliberated upon the cost-effectiveness of DRd compared with Rd, CyBorD, and VMP. pERC considered the assumptions in the submitted economic model including the duration of treatment effect, extrapolation for OS, PFS and time to treatment discontinuation (TTD), and mortality estimates. pERC noted that the EGP made the following changes to the assumptions in submitted economic model in consultation with the CGP to address some of the limitations: The Statistics Canada estimate of mortality risk was increased to more accurately reflect the non-cancer mortality of the NDMM population; the best-fitting curve was selected for OS estimates for DRd; an alternate parametric curve was considered for the PFS of DRd; and an alternative parametric extrapolation for TTD to address estimated gaps between treatment discontinuation and progression. pERC agreed with the EGP that OS estimates in the DRd arm of the submitted economic model were unlikely to be plausible given the large benefits occurring post-progression. In addition, pERC considered that the OS benefit associated with second-line treatments was not considered in the submitted economic model. pERC also noted the uncertainty in the long-term survival estimates based on extrapolation of short-term trial data from the MAIA trial.

Upon reconsideration, pERC noted the sponsor's feedback on the Initial Recommendation that they were unable to replicate the results of the EGP's best-case estimates presented in the Economic Guidance Report. pERC discussed that the choice of the parametric curve in the EGP's best-case estimate was labelled incorrectly in the EGP report. pERC noted that the correction made for the choice of the parametric curve for TTD extrapolations did not change the EGP's best-case estimates. Therefore, pERC reiterated that the DRd regimen was still not cost-effective at the submitted price.

Furthermore, pERC deliberated on the cost-effectiveness of DRd compared with CyBorD and VMP. pERC noted that due to the lack of a direct comparison of DRd compared with CyBorD or VMP, the relative effectiveness of VMP to DRd was sourced from the sponsor's NMA. pERC noted that the economic model assumed that the efficacy of CyBorD was the same as the efficacy of VMP relative to CyBorD based on clinical expert opinion. pERC agreed with the EGP that given the limitations in the submitted NMA, the comparative effectiveness of DRd compared with CyBorD and VMP remains uncertain.
In addition, pERC discussed that the EGP conducted price reduction analyses to assess the impact of a price reduction of daratumumab on the incremental cost-utility ratio. From these analyses, it was concluded that an incremental cost-effective review (ICER) around $100,000 QALY could not be achieved even with a price reduction of 95%. pERC noted that this was most likely a result of the high cost of daratumumab as well as the use of daratumumab regimens in subsequent lines of treatment in the comparator arms. pERC noted the EGP's lower and upper bounds for the best-case estimate which were about three times higher than the sponsor's submitted ICER. pERC concluded that at the submitted price

DRd could not be considered cost-effective compared with VMP, CyBorD, or Rd. Given that pERC concluded that there is a net clinical benefit of DRd compared with Rd 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 sponsor's feedback on the Initial Recommendation noting that a price reduction analysis should be done evaluating the reduction of all the treatments in the DRd regimen, including lenalidomide. The sponsor noted that the DRd regimen is driven by the cost of daratumumab and of lenalidomide, highlighting that over the median duration of therapy extrapolated for DRd in the reanalysis, the cost of lenalidomide exceeds that of daratumumab. pERC agreed with the EGP that in the price reduction scenarios, the drug acquisition cost of daratumumab was reduced while keeping the drug acquisition cost of other drugs and administration costs constant for the DRd regimen, which is consistent with the appraisal of the sponsor's reimbursement request for the submitted product under review. pERC also noted that the limited effect of price reduction on the ICER of daratumumab is due to the fact that daratumumab can be given in the second line with or after Rd, VMP, and CyBorD. While a reduction in the price of daratumumab reduces first-line treatment costs for DRd, it also reduces the cost in subsequent line treatments with Rd, VMP, and CyBorD. In the PE model, daratumumab is not available for second-line treatment of DRd patients.

pERC considered the feasibility of implementing a positive reimbursement recommendation for DRd. pERC discussed that the majority of patients would have DRd in the first-line setting and that a minority of patients would have a non-daratumumab regimen in the first-line setting, increasing the market share proposed by the sponsor. pERC noted that it was unclear if and how the shift in market share from a second-line daratumumab regimen to an upfront daratumumab regimen was accounted for in the submitted budget impact analysis, as pERC anticipates this shift to upfront daratumumab to have a significant impact on the budget for the treatment of NDMM patients due to an anticipated longer duration of therapy. Therefore, pERC concluded that the submitted budget impact of DRd was substantially underestimated and that the potential budget impact would be substantial due to the high cost of DRd and the large prevalent population for this treatment in the upfront setting. As a result, pERC concluded that a reduction in the price of daratumumab would be required to improve affordability. With respect to eligibility based on performance status, although the MAIA 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. With respect to wastage, pERC acknowledged that wastage could be a potential concern in smaller centres and noted that the EGP's scenario analysis included wastage. pERC also discussed PAG's request for clarity on the eligible patient population, specifically regarding the time-limited need for those patients currently treated with Rd, CyBorD, and VMP. pERC also discussed the PAG's request for clarity on implementation factors, including the adoption of a 90-minute infusion to reduce chair time, incremental costs due to drug wastage, as well as PAG's request on sequencing and priority of treatments including which treatment option would be best suited and preferred for the first-line and second-line treatment for multiple myeloma. pERC addressed these implementation questions from PAG that are outlined 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 registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One clinician group, (CCO Hematology Drug Advisory Committee)
- The PAG
- The sponsor Janssen Inc.

The pERC Initial Recommendation was to recommend reimbursing daratumumab in combination with DRd for patients with NDMM who are not suitable for autologous stem cell transplant.
Feedback on the pERC Initial Recommendation indicated that the PAG and registered clinician group agreed while the sponsor agreed in part with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of DRd compared with relevant comparators (Rd, CyBorD, and VMP) in patients with NDMM who are ineligible for ASCT.

Studies included: MAIA — Randomized controlled trial of DRd versus Rd alone

The pCODR systematic review included one open-label, phase III, randomized controlled trial [MAIA] which evaluated the efficacy and safety of daratumumab in combination with lenalidomide and dexamethasone for the treatment of patients with NDMM who are ineligible for ASCT.

The pCODR review also provided contextual information on a critical appraisal of the sponsor's NMA comparing daratumumab-based regimens with other pharmacological interventions for patients with NDMM who are ineligible for ASCT. In addition, a critical appraisal of the sensitivity analysis of the sponsor's submitted NMA for the addition of bortezomib-lenalidomide-dexamethasone (VRd) was provided. The results of this NMA were used to inform the sponsors economic evaluation, with respect to the comparisons with CyBorD and VMP.

Patient populations: Patient population: Transplant ineligible, median age 73

Key eligibility criteria included patients with NDMM who were ineligible for high-dose chemotherapy with stem cell transplantation due to age (≥ 65 years) or the presence of coexisting conditions that were likely to result in the development of unacceptable side effects were randomized into the study. Specifically, patients had documented multiple myeloma satisfying CRAB criteria (calcium elevation, renal insufficiency, anemia, and bone abnormalities), had bone marrow with at least 10% plasma cells or a biopsy proven plasmacytoma, and had evidence of measurable secretory disease. Enrolment was limited to patients who did not receive prior therapy for multiple myeloma and who were not considered candidates for HDT and ASCT. Patients with a poor Eastern Cooperative Oncology Group (ECOG) performance status (PS) score (i.e., ECOG PS score of 3 or worse) or with a creatinine clearance < 30 mL/min were excluded for safety reasons, as this population of patients generally has a greater risk for toxicity. The majority of patients were ≥ 75 years (DRd 43.5% versus Rd – 43.6%) with an ECOG PS of 0 or 1. An ECOG PS score of ≥ 2 at baseline was reported in 17.1% and 16.0% of patients in the DRd and Rd treatment groups, respectively. It was noted that patients with monoclonal gammopathy of undetermined significance or smoldering multiple myeloma, primary amyloidosis, plasma cell leukemia or POEMS syndrome were excluded from the trial.

Key efficacy results: Statistically significant and clinically meaningful improvement in PFS Immature OS data

The key efficacy outcomes deliberated on by pERC included PFS and OS. The trial met its primary outcome (crossed the pre-specified boundary for superiority) and demonstrated a statistically significant improvement in PFS (investigator assessed) such that the combination of DRd significantly prolonged PFS compared with Rd alone, HR 0.56 (95% CI, 0.43 to 0.73, *P* < 0.001). As of the primary analysis pre-defined cut-off date of September 24, 2018, and a median follow-up of 28.0 months (range 0 to 41.4), disease progression or death had occurred in 26.4% (97/368) of patients in the DRd group and 38.8% (143/369) of patients in the Rd group. The Kaplan–Meier estimate of the percentage of patients who were alive without disease progression at 30 months was 70.6% (95% confidence interval [CI], 65.0 to 75.4) in the DRd group and 55.6% (95% CI, 49.5 to 61.3) in the Rd group. The median PFS was not reached in the DRd group and was 31.9 months (95% CI, 28.9 to not reached) in the Rd group. At the latest data cut off, OS data remained immature with 138 patients who had died, 62 (16.8%) in the DRd group and 76 (20.6%) in the Rd group, which is consistent with the expectation in newly diagnosed patient populations. The median OS was not reached in either group, and follow-up for long-term survival is ongoing. The hazard ratio was 0.78 (95% CI, 0.56 to 1.10).

pERC also noted secondary end points including complete response and MRD negativity. The percentage of patients with complete response (CR) or better in the intention-to-treat (ITT) population was significantly higher in the DRd groups than in the Rd group (47.6% versus 24.9%), as was the percentage with very good partial or better response (79.3% versus 53.1%) (*P* < 0.001 for both comparisons). A total 92.9% of patients in the DRd group and 81.3% in the Rd group had an overall response. Among the patients who had a response (partial response or better), 80.3% (95% CI, 75.1 to 84.5) in the DRd group and 65.7% (95% CI, 58.6 to 71.8) in the Rd group sustained the response for 30 months. The median time to the first response was 1.05 months in both groups, and the median time to a CR or better was 10.4 months in the DRd group and 11.2 months in the Rd group. pERC acknowledged the improvement in response rates for patients treated with DRd versus Rd.

Based on the ITT population, the DRd group demonstrated a greater rate of MRD negativity compared with the Rd group. The MRD negativity rate, at a threshold of 1 tumour cell per 10^5 white cells, was more than three-fold higher in the DRd group compared with the Rd group (DRd: 24.2%, Rd: 7.3%). pERC noted the improvement in MRD negativity rate with DRd versus Rd.

Patient-reported outcomes: No detriment to QoL

The QoL data reported from patient-reported end points, including the EORTC QLQ-C30 and EQ-5D-5L, indicated improvements in health-related quality of life for both treatment arms, with high compliance rates. Clinically meaningful benefit in GHS was observed for patients between cycles 9 to 12. Additional QoL data after cycle 12 was not available. From the EORTC QLQ-C30, GHS improved in both treatment groups across all time points, with significantly greater improvement from baseline to cycle 3 in the DRd group versus the Rd group (least squares [LS] mean change from baseline: DRd, 4.5 [95% CI, 2.4 to 6.6] versus Rd, 1.5 [95% CI, –0.7 to 3.7]; between-arm difference in LS mean change from baseline: 3.0 [95% CI, 0.1 to 5.9]; P = 0.0454). In the DRd group, a clinically meaningful benefit was observed for GHS starting in cycle 9 and sustained through cycle 12. The mean change from baseline in the GHS score did not meet the Minimally Important Differences (MID) threshold at any time for the Rd group. From the EuroQol EQ-5D-5L, VAS score improved from baseline to cycle 12 for both treatment groups, with significantly greater improvement in the DRd group compared with the Rd group at cycle 12 (LS mean change from baseline: DRd, 10.1 [95% CI, 8.1 to 12.1] versus Rd, 4.9 [95% CI, 2.8 to 7.0]; between-arm difference in LS mean change from baseline: 5.2 [95% CI, 2.4 to 8.0]; P = 0.0002). In the DRd group, the VAS score had clinically meaningful improvement from baseline starting at cycle 3 and sustained through cycle 12; the Rd group crossed the MID threshold of clinically meaningful benefit at cycle 9, but this was not sustained through cycle 12. The median time to worsening of the EQ-5D-5L VAS score was 10 months longer in the DRd group compared with the Rd group (32.2 months versus 22.1 months, respectively), although this difference was not statistically significant and the upper bound was not evaluable at the clinical cut off.

Limitations: Unblinded trial, Immature OS data, lack of head-to-head data for relevant comparators

The review team noted that overall, the MAIA trial was well conducted. pERC did note that the trial was not blinded and acknowledged that at the time of the data analysis, OS data were immature (median overall survival was not reached in either group) making the actual degree of long-term benefit of DRd compared with Rd unknown. Follow-up for long-term survival data from the MAIA trial is ongoing.

A number of relevant comparators were noted by the CGP and PAG, including DVMP and VRd. There were no head-to-head trials identified in the systematic review that evaluated DRd with these comparators. The comparison for DVMP was provided as part of the NMA submitted by the sponsor; however, a comparison with VRd was not included in the NMA. Therefore, the review team requested the sponsor to provide an updated indirect treatment comparison for the comparison of DRd with these relevant comparators. To address this request, the sponsor provided a sensitivity analysis that included VRd in the NMA. pERC discussed the sensitivity analysis of the submitted NMA that included VRd. pERC agreed with the review team's assessment that the violation of the similarity assumption and that the interpretation of results from the comparison were limited. pERC acknowledged that the choice of treatment with daratumumab-based regimens would be dependent on individual patient disposition and characteristics.

Safety: Increased infection and pneumonia in the DRd group, but overall manageable toxicity profile
A total of 364 patients in the DRd group and 365 patients in the Rd group received at least one dose of study treatment and were included in the safety analysis. With a median treatment duration of 25.3 months in the DRd treatment group and 21.3 months in the Rd treatment group, daratumumab in combination with Rd resulted in higher incidences of any grade and grade 3 or 4 neutropenia and pneumonia in patients with NDMM not eligible for stem cell transplant. The most common adverse events of grade 3 or 4 were neutropenia (50.0% in the DRd group and 35.3% in the Rd group), anemia (11.8% and 19.7%), lymphopenia (15.1% and 10.7%), pneumonia (13.7% and 7.9%), and leukopenia (11.0% and 4.9%).The incidence of infections of any grade was 86.3% in the DRd group and 73.4% in the Rd group; the incidence of grade 3 or 4 infections was 32.1% in the DRd group and 23.3% in the Rd group. Serious treatment-emergent adverse events were reported at comparable incidences in the DRd and Rd groups.

Of the 364 patients who received daratumumab, 40.9% experienced an infusion-related reaction (IRR). IRRs usually occurred during administration of the first dose (in 98.0% of the patients who had such reactions), and only one patient (with grade 4 hypertension) discontinued daratumumab treatment due to an IRR.

Need and burden of illness: Need for more novel therapies with demonstrated improvements in OS.
Front-line options include bortezomib, melphalan, and prednisone (VMP); cyclophosphamide, bortezomib, and dexamethasone (cyBorD); or lenalidomide and dexamethasone (Rd). pERC noted that it recently made a conditional recommendation for daratumumab in combination with bortezomib, melphalan, and prednisone (DVMP) as well as lenalidomide in combination with bortezomib and dexamethasone (VRd) in a similar patient population; however, these combinations are not currently funded in any Canadian jurisdiction. pERC acknowledged the need for more novel therapies with demonstrated improvements in OS for these patients.

Registered clinician input: Preference to use Daratumumab containing regimen first-line
pERC noted that the registered clinicians reported improvements of treatment tolerability, safety, and effectiveness with DRd compared with currently available therapies. Overall, clinicians were satisfied with the results from the phase III randomized, open-label, active-controlled clinical trial (MAIA). Namely, a superior PFS and minimal toxicity were highlighted as key benefits of the treatment combination. In addition, the clinicians noted that the discontinuation rate due to toxicity of DRd was reported to be lower compared with other treatments such as lenalidomide/ bortezomib/ dexamethasone (VRd). pERC noted the registered clinicians' opinion that daratumumab 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).

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
For patients with multiple myeloma, symptoms that are important to control include infections, followed by kidney problems, mobility, pain, fatigue, neuropathy (pain, numbness, tingling, swelling, or muscle weakness), and shortness of breath. Overall, six respondents reported that the common side effects of daratumumab and Rd were generally tolerated. Among the side effects associated with currently

available treatments, pain was most commonly rated (24%) as "most important to avoid;" alternatively, shortness of breath was most commonly rated (21%) as "least important to avoid."
Patient values on treatment: remission, improved QoL, disease control, prolonged life, fewer side effects than other treatments, and enjoying a normal life.

Patients value remission, improved QoL, 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.

The input provided by caregivers on the impact of multiple myeloma and current therapies noted that caregivers are most significantly affected by the ability to travel and conduct daily activities. Caregivers noted that the treatment itself is time-consuming and caregivers often accompany patients receiving treatments.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness analysis and cost-utility analysis (CUA)

The sponsor submitted a cost-effectiveness and cost-utility analysis for daratumumab in combination with lenalidomide and dexamethasone for patients with NDMM who are ineligible for ASCT. The comparators in the economic model were lenalidomide and dexamethasone (Rd); Cyclophosphamide, bortezomib, and dexamethasone (CyBorD); and bortezomib, melphalan, and prednisone (VMP).

Basis of the economic model: partitioned-survival model

The economic analysis used a partitioned-survival model to estimate health and cost outcomes. The partitioned-survival model allocated a cohort of patients across three health states: pre-progression, post-progression, and death. At model start, the whole cohort is in the pre-progression health state. Over time the cohort transitions to either disease progression or to a death state. Individual parametric distributions were fitted to the data from the MAIA trial to estimate long-term OS, PFS, and TTD for the DRd and Rd arms. Curves were selected based on AIC, BIC, individual fit, and clinical guidance. For the VMP comparison, OS and PFS estimates were generated using hazard ratios relative to the Rd arm and sourced from the NMA provided by the sponsor. CyBorD was assumed to have the same clinical effectiveness as VMP.

Drug costs: high cost of daratumumab

DRd Cost Breakdown:

Daratumumab costs $598.02 per 100 mg vial and $2,392.03 per 400 mg vial.
Lenalidomide costs $424.00 (21-unit pack, 25 mg per unit, $8,904 per pack).
Dexamethasone costs $0.3046 (100-unit pack, 4 mg per unit, $30.46 per pack).

Cycle cost (28-day cycle):
In cycle 1 and 2 the total cost for a 28-day cycle is $34,786.98
In cycle 3 to 6, the total cost for a 28-day cycle is $23,085.00
In the remaining cycles, the cost for maintenance is $16,028.60

Rd Cost Breakdown:

- Lenalidomide:
  $424.00 (21-unit pack, 25 mg per unit, $8,904 per pack)
- Dexamethasone:
  $0.3046 (100-unit pack, 4 mg per unit, $30.46 per pack)

- Rd Cycle cost (28-day cycle):
  All cycles: $8,914.97

VMP Cost Breakdown

- Bortezomib:
  $1,402.42 per 3.5 mg vial

- Melphalan:
  $1.7614 per unit (50-unit pack, 2 mg per unit, $88.07 per pack)
- Prednisone:
  $0.1735 (100-unit pack, 50 mg per unit, $17.35 per pack).
  $0.0220 (100-unit pack, 5 mg per unit, $2.20 per pack).

VMP Cycle cost (42-day cycle):
- Cycle 1: $ 7,266.04
- Cycle 2 to 9: $3,386.33

VMP Calculated 28-day cycle cost:
- During cycle 1: $ 4,844.027
- During cycle 2 to 9: $2,257.55

CyBorD Unit Costs

- Bortezomib:
  $1,402.42 per 3.5 mg vial
- Dexamethasone:
  $0.3046 (100-unit pack, 4 mg per unit, $30.46 per pack)
- Cyclophosphamide:
- $0.4740 (100-unit pack, 50 mg per unit, $47.40 per pack)

Cycle cost (28-day cycle)
- During cycles 1-9: 3908.94

Clinical effect estimates: Efficacy data obtained from the MAIA trial and Sponsor's NMA
Parameters related to the efficacy of DRd and Rd were informed by the MAIA trial. Relative efficacy for VMP was sourced from sponsor's NMA. Efficacy of CyBorD was assumed to be the same as VMP. Utility values were sourced from the MAIA trial. Adverse event frequency and resource utilization was sourced from the MAIA trial, previous trials, and clinical input.

Cost-effectiveness estimates: Not cost-effective compared with lenalidomide and dexamethasone; bortezomib, melphalan, and prednisone; or cyclophosphamide, bortezomib, and dexamethasone
pERC considered the uncertainties in the model inputs addressed by the EGP and noted that based on 2,500 iterations, the EGP's probabilistic estimate of the ICER of DRd versus CyBorD is between $267,388/QALY and $799,051/QALY, with a best estimate of $498,339 /QALY that differed from the sponsor's best estimate of $220,588/QALY. The EGP made the following changes to the model to address some of its limitations: the Statistics Canada mortality hazard of the general population was increased to more accurately reflect the non-cancer mortality of the NDMM population; the best-fitting curve was selected for OS estimates for DRd as they resulted in the reduction of post-progression survival benefits in the DRd arm; an alternate parametric curve was considered for the PFS of DRd which reduced the portion of the effectiveness benefit of DRd which occurred post-progression; and an alternative parametric extrapolation for TTD using the Weibull distribution was selected to address estimated gaps between treatment discontinuation and progression. The EGP conducted price reduction scenarios to assess the impact of a change of daratumumab price on the incremental cost-utility ratio. From these analyses, it was concluded that an ICER around $100,000 QALY could not be achieved even with a price reduction of 95%.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget Impact is underestimated
The factors that most influence the budget impact analysis include population size, wastage cost, subsequent treatment cost, and market share. Key limitations to the budget impact analysis model were the assumed market share of Rd and VMP in the listing scenario. These parameters were modified and explored by the EGP resulting in a 6% over-estimation of the net-budget impact. pERC noted that the majority of patients would have DRd 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 DRd was substantially underestimated and that the potential budget impact would be substantially higher than the sponsor's estimate due to the high cost of daratumumab in combination with lenalidomide and dexamethasone 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.

pERC concluded that the optimal sequencing of therapies for patients with NDMM who are not suitable for ASCT 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 DRd, jurisdictions may consider addressing the time-limited need of adding daratumumab to the treatment for patients who recently initiated Rd. For patients who have recently completed first-line therapy with a non-daratumumab regimen (e.g., Rd; VMP; or CyBorD); daratumumab would be reserved for the later line of treatment, rather than be added after the completion of the chemotherapy regimen.

pERC acknowledged that the recommended dosing schedule of daratumumab for NDMM differs from the DVMP dosing schedule for front-line therapy recently reviewed by pCODR. pERC noted that the DRd dosing schedule for newly diagnosed patients is the same as relapsed or refractory myeloma. 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., eight 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 IRR, 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 IRRs 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. However, pERC commented that shorter infusion times and the ability to better manage IRRs will assist in decreasing the overall resources used for administration.

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 implementing the treatment, in order to identify potential barriers.

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
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, 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. Avram Denburg and Dr. Anil Joy who were 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. Maureen Trudeau who did not vote due to her role as the pERC Chair

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 in combination with Rd for NDMM, through their declarations, no members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, and none of the members were excluded from voting. For the Final Recommendation, no members had a real, potential, or perceived conflict, and based on application of the pCODR Conflict of Interest Guidelines, none of the members were excluded from voting.

Information sources used

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

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

Use of this recommendation

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

Disclaimer

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APPENDIX 1: CADTH pERC RESPONSES TO PAG IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
Currently Funded Treatments • Lenalidomide plus dexamethasone (Rd), cyclophosphamide/bortezomib/dexamethasone (CyBorD), bortezomib/melphalan/prednisone (VMP) are funded in almost all provinces for the treatment of patients with NDMM who are not eligible for ASCT. • Lenalidomide/bortezomib/dexamethasone (VRd) and Daratumumab/bortezomib/melphalan/prednisone (DVMP-VMP) were recently reviewed by pCODR and both received a positive conditional reimbursement recommendation. • PAG noted that Rd and CyBorD are current treatments of choice for patients with NDMM that are transplant ineligible. Although the comparator of Rd in the MAIA trial is a funded option, PAG is also seeking comparative information on DRd compared with CyBorD.	pERC noted the funded treatment options across Canada and acknowledged the recent pCODR recommendations for VRd and DVMP-VMP. pERC also noted that CyBorD is the preferred regimen and would be reflective of Canadian practice. pERC commented that the submitted NMA from the sponsor demonstrated daratumumab-based regimens as more favourable with respect to PFS and response rates. However, pERC also recognized the differences in the populations and that results are to be interpreted with caution.
Eligible Patient Population • PAG is seeking clarity that daratumumab + RD (DRd) 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 DRd treatment, and patients who present with renal failure would be eligible for treatment with DRd. • PAG is seeking guidance on the definition of "transplant ineligible" as they may vary (e.g., different age cut-offs). If recommended for reimbursement, PAG noted the following groups of patients would need to be addressed on a time-limited basis: • patients currently treated for NDMM not eligible for transplant (e.g., Rd, CyBorD, or VMP) • patients who recently completely Rd and who have not yet experienced progression. If switching to DRd or adding daratumumab to Rd is appropriate in these patients, PAG is seeking guidance on the dosing schedule administered and when in treatment daratumumab addition can be considered.	pERC agreed with the CGP that the results of this trial are not generalizable to patients with MGUS, smoldering myeloma, or amyloidosis. Patients treated with radiation would not impact patient eligibility for this regimen, and a 14-day post-treatment window would not impact choice of regimen used (refer to generalizability table of the Clinical Guidance Report). pERC noted that the definition of "transplant ineligible" is to be dependent on jurisdictional guidelines. pERC agreed with the CGP that patients with renal failure would use a bortezomib-based regimen such as daratumumab/bortezomib/dexamethasone. There is a small minority of patients who may be treated with dose-reduced lenalidomide if there was a contraindication to the use of a proteasome inhibitor in patients with renal failure, and creatinine clearance less than 30 mL/min. pERC noted that jurisdictions may consider addressing the time-limited need of adding daratumumab to the treatment for patients who recently initiated treatment with Rd. For patients who have recently completed first-line therapy with a non-daratumumab regimen (e.g., bortezomib, melphalan, and prednisone; cyclophosphamide, bortezomib, and dexamethasone; or lenalidomide and dexamethasone) daratumumab would be reserved for a later line of treatment. • pERC acknowledged that switching to DRd or adding daratumumab to Rd 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 administered will be needed upon implementation of the recommendation.
Implementation Factors • The recommended dosing/schedule for DRd in this setting differs from other daratumumab-based regimens for multiple myeloma (e.g., D-CyBorD, DVMP or DRd), and may lead to potential dosing errors. PAG noted that processes would need to be in place, before implementation of daratumumab in this setting, to minimize dosing errors and patient confusion. • PAG is seeking guidance on whether clinicians would support the adoption of a 90-minute daratumumab infusion to reduce chair time. • PAG is also seeking guidance on whether clinicians would add cyclophosphamide to DRd upon biochemical progression. Also, if there is evidence to inform whether patients could have a treatment break from daratumumab after a maximum response is achieved, then continue on Rd Maintenance, and re-initiate daratumumab at the time of disease progression on Rd. • PAG is seeking guidance on treatment duration and discontinuation criteria. • Additional resources will be required for pre-medication, drug preparation, administration time, and close monitoring for multiple severe adverse effects including infusion reactions. PAG noted that the significantly increased chair time compared with current treatment is a barrier to implementation, given the additional resources needed as well as slower infusion time to reduce the risk of infusion reactions with daratumumab. Additional hospital resources may be required if patients have an IRR that requires inpatient hospital admission for management/monitoring or to complete the reminder of the infusion post reaction (infusion time beyond hours of operation of ambulatory chemotherapy suite). • 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, daratumumab 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 DRd in NDMM differs from DVMP in the first-line setting. 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. However, pERC also noted that the dosing schedule for DRd in the newly diagnosed setting is the same as the dosing schedule in the relapsed/refractory setting. • pERC also noted that variations in the lengths of infusion times, a potentially high number of incident and prevalent patients eligible for this treatment, and the potential management of any IRRs (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 represent 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 the adoption of a 90-minute daratumumab infusion beginning with the third dose in the US 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 noted that at this time there is no evidence to support adding cyclophosphamide beyond progression. • As noted above, pERC acknowledged that there was a higher incidence of infections with DRd compared with Rd, 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 noted that the criteria for treatment duration and discontinuation from the MAIA trial is acceptable. • 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 sponsor'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 DRd in the first-line setting and then progress:
  • What would be the best treatment after progression following DRd?
  • Sequencing of subsequent second- and third-line therapies such as carfilzomib-based regimens (e.g., KRd), bortezomib-based regimens, pomalidomide, and retreatment with lenalidomide-based regimens
  • Clarity on whether patients would be ineligible for retreatment with daratumumab-based regimens in subsequent lines of therapy.
• PAG is seeking guidance on the preferred first-line treatment option in this setting (e.g., Rd, VRd, CyBorD, DVMP-VMP, D-CyBorD, or DRd). In what clinical scenarios would DRd be the preferred first-line setting and in what clinical scenarios would DRd not be used in the first-line setting?
• PAG noted that daratumumab for the treatment of patients with multiple myeloma who have received at least one prior therapy, is funded in many jurisdictions or is under provincial consideration. PAG is seeking guidance on the optimal use of daratumumab and preference to use daratumumab in the first-line setting or reserve daratumumab for downstream treatment.
• Daratumumab in combination with VMP, for the treatment of patients with NDMM who are not suitable for ASCT, was recently reviewed and received a positive conditional recommendation at pCODR. PAG is seeking guidance on preference for daratumumab in combination with Rd or VMP.
	• pERC concluded that the optimal sequencing of therapies for patients with NDMM who are not suitable for ASCT 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 agreed with the CGP that treatment after progression on a daratumumab containing regimen would be a carfilzomib containing regimen.
	• Upon reconsideration, pERC discussed PAG's feedback and agreed with the registered clinician input and also the CGP that data on retreatment of patients with daratumumab-based regimens in subsequent lines of treatment were not available at the time of the review and therefore retreatment with daratumumab in later lines of therapy is not recommended.
	• pERC agreed with the registered clinicians and the CGP that daratumumab-based regimens would be offered in the first-line setting.
	• pERC noted the data from the submitted NMA and agreed with the CGP that treatment with either DRd or DVMP will be individualized to the patient's circumstances.

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