pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL 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.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug: Daratumumab (Darzalex)

Submitted Funding Request:
In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy

Submitted by:
Janssen Inc.

Manufactured by:
Janssen Inc.

NOC Date:
April 13, 2017

Submission Date:
March 3, 2017

Initial Recommendation Issued:
August 3, 2017

Approximate per Patient Drug Costs, per Month (28 Days)
Submitted list price of $598.02 per 100 mg vial, and $2,392.08 per 400 mg vial

*Note: Costs are calculated based on an average weight of 70kg and BSA = 1.7m^2

Daratumumab-lenalidomide-dexamethasone regimen costs:
- cycles 1 and 2: $35,707.48 per 28-day course
- cycles 3 to 6: $22,311.83 per 28-day course
- cycles thereafter: $15,614.00 per 28-day course.

Daratumumab-bortezomib-dexamethasone regimen costs:
- cycles 1 to 3: $31,526.29 per 28-day course
- cycles 4 to 8: $13,665.43 per 28-day course
- cycles thereafter: $11,432.82 per 28-day course.

pERC RECOMMENDATION

pERC recommends the reimbursement of daratumumab (Darzalex) in combination with lenalidomide and dexamethasone (Len-dex) or bortezomib and dexamethasone (Bor-dex) for the treatment of patients with multiple myeloma with good performance status who have received at least one prior therapy, conditional on the cost-effectiveness being substantially improved and adoption feasibility being addressed.

pERC noted that treatment should be in combination with len-dex and bor-dex, as administered in the POLLUX and CASTOR trials, respectively. pERC also noted that daratumumab treatment should be continued until disease progression or unacceptable toxicity.

The Committee made this recommendation because daratumumab in combination with len-dex or bor-dex demonstrated a net clinical

	benefit when compared with either treatment without daratumumab, based on statistically significant and clinically meaningful improvements in progression-free survival, a trend toward an improvement in overall survival , and at least maintenance in patients' quality of life. The Committee acknowledged that daratumumab is associated with a manageable but not insignificant toxicity profile. The Committee was satisfied that daratumumab in combination with len-dex or bor-dex also aligned with patient values for an effective treatment option that provides disease control and improved survival. However, pERC noted that, at the submitted price and with the high level of uncertainty in the duration of treatment effect and the magnitude of overall survival benefit, daratumumab in combination with Len-dex or Bor-dex could not be considered cost-effective compared with Len-dex or Bor-dex alone. pERC also highlighted that the potential budget impact of daratumumab would be substantial due to the high cost of the triplet therapy and the large prevalent population for this treatment. pERC also had significant concerns about the capacity of jurisdictions to implement intravenous daratumumab in combination with Len-dex or Bor-dex 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 potentially long infusion times throughout the treatment course. All of these 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	**Pricing Arrangements to Improve Cost-Effectiveness** Given that pERC was satisfied that there is a net clinical benefit with daratumumab plus Len-dex or Bor-dex compared with Len-dex or Bor-dex alone, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness and budget impact of daratumumab to an acceptable level. Additionally, given the more frequent initial administration scheduleand pricing structure of daratumumab, pERC noted that innovative pricing agreements between between the manufacturer and provinces might be needed to ensure affordability and cost-effectiveness of daratumumab. **Factors Affecting Budget Impact and Adoption Feasibility** In considering the high cost of daratumumab, the large prevalent eligible population, and the unknown but potentially long duration of treatment, pERC concluded that a substantial reduction in the price of daratumumab would be required to improve affordability. **Time-Limited Need for Daratumumab** At the time of implementing a funding recommendation for daratumumab plus len-dex or bor-dex, jurisdictions may want to consider addressing the short-term, time-limited need for daratumumab plus len- or bor-dex for patients who are currently receiving len-dex or bor-dex alone as a second-line therapy and have not experienced disease progression or intolerance during second-line treatment. **Optimal Sequencing of Daratumumab Plus Len-Dex or Bor-Dex and Other Therapies Unknown** pERC concluded that the optimal sequencing of daratumumab plus Len-dex or Bor-dex and other treatments now available for the

treatment of multiple myeloma is currently unknown. However, pERC recognized that provinces would need to address this issue upon implementation of daratumumab reimbursement, and noted that collaboration among provinces to develop a common approach would be of value. pERC noted the opinion of the pCODR Clinical Guidance Panel that daratumumab in combination with Len-dex or Bor-dex may be a favourable second-line option over triplet therapy with carfilzomib; however, the Committee acknowledged that there is no direct evidence investigating the head-to-head efficacy and safety nor the appropriate treatment sequence for daratumumab and carfilzomib for the treatment of multiple myeloma after failure of one prior therapy. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments for relapsed or refractory multiple myeloma. However, pERC recognized that provinces would need to address this issue upon implementation of daratumumab reimbursement and noted that collaboration among provinces to develop a common approach would be of 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 which may be open for a maximum number of hours per day (e.g. 8-10 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).

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 which 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 impacts on available infrastructure, resources, and 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 prior to beginning treatment. Jurisdictions may want to consider liaising with Canadian Blood Services prior to implementation in order to identify potential barriers to implementation.

SUMMARY OF pERC DELIBERATIONS

Despite significant advancements in the treatment and life expectancy of patients with multiple myeloma, it remains an incurable disease, and most patients will relapse following initial therapy. Bortezomib-based or lenalidomide-based regimens are currently the standard treatment options in the second-line setting; however, the superiority of one regimen over the other has not been conclusively demonstrated. Additionally, pERC has issued a reimbursement recommendation for the use of carfilzomib in combination with lenalidomide and dexamethasone (Len-dex) as an additional second-line treatment option and for patients who are ineligible to receive the carfilzomib triplet therapy, carfizomib plus dexamethasone doublet therapy has been recommended for reimbursement by pERC. pERC noted that treatment options in multiple myeloma are changing rapidly as new agents are being introduced. 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 two open-label randomized controlled trials, CASTOR and POLLUX, which evaluated daratumumab-bor-dex compared with Bor-dex and daratumumab-len-dex compared with Len-dex, respectively, on efficacy and safety outcomes in patients with multiple myeloma who had disease progression after at least one prior therapy. pERC noted that there were statistically significant and clinically meaningful improvements in progression-free survival (PFS) in both POLLUX and CASTOR in favour of the daratumumab len-dex and daratumumab bor-dex groups, respectively. However, the Committee also noted that while the overall survival (OS) data were trending in favour of the daratumumab treatment arms, no differences have been reported. pERC discussed that both trials are continuing to collect data for the final OS analysis. The CGP noted that the depth of remission rates were unprecedented in myeloma, and pERC agreed with the CGP. pERC noted that the results of the quality of life measures from both trials were not yet published and that the available data are limited. However, the Committee noted that patients' health-related QoL was at least similar to that of patients receiving len-dex or bor-dex alone. pERC discussed the toxicity profile of daratumumab len-dex and daratumumab bor-dex and noted higher hematologic adverse events in patients treated with daratumumab, as well as higher infusion-related reactions with daratumumab. pERC also noted that the number of patients discontinuing treatment and the number of deaths related to treatment were similar in both arms in the two studies. pERC discussed that, while toxicities were increased with daratumumab, those toxicities were manageable.

pERC discussed the eligibility criteria for the treatment with daratumumab plus Len-dex or Bor-dex and agreed that if implemented, eligibility criteria for funding should be in line with the criteria from the CASTOR and POLLUX trials. pERC noted the Clinical Guidance Panel's (CGP's) conclusion that treatment decisions in current clinical practice are not made on performance status alone, but also consider the manageability of toxicities and whether the patient's performance status is influenced by myeloma-related factors. pERC agreed with the CGP's conclusion that patients with a reversible myeloma-related Eastern Cooperative Oncology Group Performance Status (ECOG PS) greater than 2 might benefit from treatment with daratumumab plus len-dex or bor-dex.

Overall, pERC concluded that there is a net clinical benefit with daratumumab plus len-dex and daratumumab plus bor-dex based upon statistically significant and clinically meaningful improvements in PFS, a manageable toxicity profile, and at least comparable quality of life (QoL) compared to len-dex or bor-dex alone.

pERC deliberated on patient advocacy group input and noted that patients value having access to effective treatment options that:

- provide disease control and prolong life
- provide a choice of therapy
- manage disease-related symptoms
- have fewer treatment- related symptoms.

pERC noted that the results of the CASTOR and POLLUX trials demonstrate that daratumumab plus len-dex or bor-dex provides improvement in PFS and at least maintenance in QoL. pERC noted that this aligned with patient values of having access to effective treatment options. pERC noted that the side effects of daratumumab were manageable, but not insignificant. pERC also noted that the variable, yet potentially long infusion, high rates of infusion-related reactions, and frequent dosing schedule could be a barrier to treatment accessibility for some patients. However, pERC discussed that submitted information from patients listed their experience with the administration of daratumumab as being neutral or no impact, long or time-consuming, having no effect or having a positive impact. Overall, pERC agreed that daratumumab plus len-dex or bor-dex aligned with patient values.

pERC deliberated upon the cost-effectiveness of daratumumab plus len-dex or bor-dex alone. pERC considered the uncertainties in the model inputs addressed by the pCODR Economic Guidance Panel (EGP) and agreed that the duration of the treatment effect is unknown, although it is unlikely to remain for the duration of the entire time horizon (i.e., 30 years). pERC also noted the relatively large gains in the post-progression health state and the extrapolation to a time horizon of 30 years, despite the relatively short duration of follow-up in the trials. pERC agreed with the EGP that the duration of the treatment effect is the largest effect driver of the incremental cost-effectiveness ratio (ICER) and that the cost of daratumumab is the largest cost driver impacting the ICER. pERC noted that the cost structure of daratumumab is front-loaded, with the greatest cost in the first two cycles for both the len-dex and bor-dex regimens. pERC noted that the model did not take into account the full administration costs of daratumumab. Specifically, the model underestimated costs related to preparation and administration of daratumumab doses and the potential need to divide the infusions over multiple days, depending on a patient's experience with treatment and the capacity of the treatment centre (i.e. hours of operation). pERC agreed with the EGP that the drug administration costs were grossly underestimated in the model; therefore, there is additional uncertainty in the incremental costs of daratumumab that is not accounted for in the submitted model. pERC agreed with the EGP that it is difficult to estimate the overall ICER for this patient population, given the two separate models for the two separate treatment regimens when, in reality, some patients may receive daratumumab-len-dex, others receive daratumumab-bor-dex, while yet others receive different treatments. pERC agreed that the true ICER is most likely at the higher end of the EGP's range of ICER estimates for both the daratumumab len-dex and daratumumab bor-dex regimens. Therefore, pERC concluded that daratumumab in combination with len-dex or bor-dex is not cost-effective. Furthermore, pERC noted that longer-term overall survival data will be required to reduce some of the uncertainty regarding cost-effectiveness. Additionally, pERC discussed that the submitted budget impact estimates do not fully convey the true budget impact of both treatment options being approved in a given market, which would impact the numbers significantly. pERC also considered the potential and significant opportunity costs associated with implementing daratumumab due to the substantial resource utilization related to the variable, yet potentially long infusion times and chair time, additional clinic visits for patients, as well as the need for additional pharmacy and nursing staff to administer and monitor the infusion over potentially two or three days. pERC concluded that the budget impact of daratumumab will be very high due to the high cost of daratumumab, resource-use costs, and treatment that continues until progression.

pERC considered the feasibility of implementing a reimbursement recommendation for daratumumab plus Len-dex or Bor-dex. Given that patients who were refractory to lenalidomide were excluded from treatment with daratumumab-len-dex in the POLLUX trial and patients who were refractory to bortezomib were excluded from treatment with daratumumab-bor-dex, the use of daratumumab in combination with Len-Dex or Bor-Dex would be limited in these patient populations, respectively. pERC also noted that daratumumab could be added onto treatment for patients already receiving Len-dex or Bor-dex as a second-line therapy in the event that disease progression or intolerance during treatment has not occurred. pERC noted the concern of pCODR's Provincial Advisory Group about the alternative dosing schedule of bortezomib in clinical practice versus the trial and concluded that the weekly schedule of bortezomib (versus the twice a week schedule) has lower toxicity and is, therefore, preferred. pERC also noted that the subcutaneous (SC) and intravenous (IV) routes of administration of bortezomib have been demonstrated to have noninferior efficacy in a randomized controlled trial; however, the SC route is associated with reduced toxicity. Therefore, it is anticipated that patients will predominantly receive bortezomib as an SC administration. pERC noted that if a patient experienced disease progression on daratumumab-len-dex,they were not be eligible for daratumumab bor-dex; vice versa for patients with disease progression on daratumumab-bor-dex. pERC noted that patients who progressed while on maintenance lenalidomide could be eligible for daratumumab bor-dex, but not for daratumumab with lenalidomide and dexamethasone.

pERC noted that red-cell phenotyping/genotyping should be performed prior to commencing daratumumab treatment since daratumumab interferes with blood compatibility testing. pERC noted that, upon implementation, a large number of patients would be eligible for treatment with daratumumab. Therefore, jurisdictions may want to consider liaising with Canadian Blood Services prior to implementation in order to inform them of the potential increase in volume of patients requiring red-cell phenotyping/gentoyping and to identify potential barriers to implementation.

pERC noted additional uncertainty regardingadoption feasibility with respect to infusion-related resource utilization and the duration, frequency, and changing patterns of dosing. pERC noted the potentially long, yet variable, infusion times for daratumumab would significantly increase resource use. In addition, administrations could pose difficulties for certain cancer centres open for a maximum number of hours per day (e.g. 8-10 hours) since longer infusion times and additional support medications may be required for some patients. These infusions could likely need to be split into multiple days, depending upon the specific patient and treatment centre.. pERC noted that this additional infusion time, as well as any infusion-related toxicities needing to be managed, would 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. pERC also noted the substantial incremental pharmacy, nursing, and chemotherapy suite resources required to prepare and administer daratumumab to patients. The Committee also noted that the infusion times and administration schedule for daratumumab were very intensive for pharmacy staff, nurses, and clinicians. The lengthy infusion time would increase pressure on health system resources and may place a substantial burden on patients and their caregivers. Therefore, pERC noted that jurisdictions will need to consider the significant impacts on available infrastructure, resources, and nursing and pharmacy staff when considering the feasibility of adoption.

At this time, pERC noted the lack of direct comparative evidence on the sequencing of daratumumab len-dex or bor-dex compared with carfilzomib len-dex. pERC discussed the limitations of an indirect treatment comparison provided by the submitter for daratumumab regimens and carfilzomib regimens. pERC noted that the overall conclusions of the network meta-analysis (NMA) were limited due to uncertainty in the estimates provided since there are differences in patient characteristics among the included studies. pERC noted the CGP's opinion that a possible sequence of treatment could be daratumumab len-dex or daratumumab-bor-dex after failure of one prior therapy and that a carfilzomib-containing regimen may be offered to eligible patients following failure of daratumumab-based therapy. The Committee acknowledged that there is no direct evidence investigating the appropriate treatment sequence or comparative benefit for daratumumab- and carfilzomib-basedtreatments for multiple myeloma after failure of one prior therapy. Therefore, pERC was unable to make an evidence-informed recommendation on sequencing of treatments for relapsed or refractory multiple myeloma. However, pERC recognized that provinces would need to address this issue upon implementation of daratumumab reimbursement, and noted that collaboration among provinces to develop a common approach would be of value.

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).

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of daratumumab in combination with lenalidomide-dexamethasone (len-dex) or bortezomib-dexamethasone (bor-dex) for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Studies included: Two randomized controlled trials and a network meta-analysis

The pCODR systematic review included two ongoing, open-label randomized phase III studies examining the use of daratumumab with Bor-dex versus Bor-dex alone (CASTOR) and daratumumab with Len-dex versus Len-dex alone (POLLUX) in patients with multiple myeloma who had received one or more previous lines of therapy. In both trials, the daratumumab regimen was given until disease progression or unacceptable toxicity. Patients in both trials were randomized 1:1 ratio and stratified by disease stage, number of previous lines of therapy, and whether they had previously been treated with bortezomib or lenalidomide. A total of 498 patients were randomized in the CASTOR trial, and 569 in the POLLUX trial. Both trials were superiority trials designed to demonstrate that the addition of daratumumab can reduce the risk of disease progression or death.

The pCODR review also provided a critical appraisal of a manufacturer-provided network meta-analysis (NMA) that evaluated the relative efficacy of daratumumab-based regimens versus carfilzomib-based regimens on outcomes such as progression-free survival (PFS) and overall survival in patients with multiple myeloma who had received at least one prior therapy. The overall conclusions of the NMA were limited because of substantial uncertainty in the estimates, given differences in patient characteristics among the included studies, notably the number of previous lines of therapy. Further, it was unknown how other treatment-effect modifiers, such as number of previous autologous stem cell transplants, affected the results as they were not reported. Although the results of the NMA presented demonstrated favourable results for daratumumab-based regimens, given the limitations and the lack of statistical adjustment to control for differences amongst studies the comparative efficacy of daratumumab-based regimens to carfilzomib-based regimens is uncertain. pERC therefore agreed that caution must be used in drawing conclusions from this indirect comparison.

Patient populations: Well balanced, younger than typical patients with multiple myeloma

Baseline characteristics were well balanced between the two trials. Patients must have received at least one prior line of therapy, defined as one of more cycles of a planned treatment program and have documented evidence of progressive disease as defined by the International Myeloma Working Group (IMWG) criteria. The median age for the CASTOR trial was 64 years in both the daratumumab arm and the control arm. Similarly, the median age in the POLLUX trial was 65 years for both groups. The median time from initial diagnosis of multiple myeloma was between 3.5 – 4 years for both studies. The majority of patients in both trials had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, while 4% to 8% of patients had an ECOG of 2 in the CASTOR and POLLUX trials, respectively.

pERC discussed the eligibility criteria of the trials and noted that there were minor exclusion criteria differences based on toxicity profiles of bortezomib or lenalidomide.

Key efficacy results: Clinically meaningful progression-free survival benefit

The key efficacy outcome deliberated on by pERC was progression-free survival (PFS) for both the CASTOR and POLLUX trials. pERC noted that there was a statistically significant and clinically meaningful improvement in PFS reported in favour of the daratumumab-len-dex and daratumumab-bor-dex groups. The POLLUX trial specifically reported a 63% reduction of the risk of disease progression in those who have received daratumumab-len-dex compared to Len-dex alone (hazard ratio [HR] 0.37; 95% confidence interval [CI], 0.27 to 0.52; $P < 0.001$). At the interim analysis, the median PFS for the treatment arm had not been reached compared with an estimated PFS of 18.4 months in patients who received len-dex alone. At the pre-specified interim analysis, the CASTOR trial demonstrated that the addition of daratumumab to bor-dex resulted in a significantly better median PFS compared with bor-dex alone (not estimable to 7.16 months; HR 0.39, $P < 0.0001$). The rate of PFS at 12 months was 60.7% in the daratumumab arm and 26.9% in the control arm. Median overall survival (OS) data were not available due to the short follow-up period. The rate of OS at 12-months was 85.5% for the daratumumab bor-dex arm compared to 79.9% in the bor-dex arm for the CASTOR trial and 92.2 % for the daratumumab len-dex arm and 87.0% for the len-dex arm in the POLLUX trial.

pERC noted that patients who have received Len-dex as their first-line treatment would be eligible for the daratumumab-bor-dex regimen in the second-line setting; vice versa, patients who have received a Bor-dex-basedregimen as first-line treatment would be eligible for the daratumumab len-dex regimen second line. pERC noted that based on the CGP opinion and favourable results of the CASTOR and POLLUX trials, daratumumab len-dex or bor-dex would be the more favoured choice in second-line treatment. It is important to note that, at this time, there are no data to support the use of daratumumab-len-dex or daratumumab-bor-dex in the first-line treatment of patients with multiple myeloma.

pERC also noted the pCODR Clinical Guidance Panel's (CGP's) conclusion that treatment decisions in current standard practice are not made on performance status alone, but also consider the manageability of toxicities and whether the patient's performance status is affected by myeloma-related factors. pERC therefore agreed with the CGP's conclusion that patients with potentially reversible myeloma-related ECOG PS greater than 2 may benefit from treatment with daratumumab plus Len-dex or Bor-dex.

Quality of life: At least similar QoL between treatment groups

The use of two outcome measures, the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core Module (QLQ-C30) and the five-level EuroQol 5-Dimensions Questionnaire (EQ-5D-5L), a generic measure of health status, was reported in both trials. To date, the results of these outcome measures have not yet been published; however, some preliminary results were provided by the submitter. In the CASTOR trial, the addition of daratumumab to Bor-dex maintained patients' quality of life. There were no significant differences in the mean scores over time on the Global Health Status, except at week 24, which favoured the daratumumab plus bor-dex treatment group. In the POLLUX trial, both groups noted an improvement in quality of life over time, with a statistically significant improvement seen at weeks 40 and 48 favouring the daratumumab- len-dex treatment group. pERC acknowledged that the available information on QoL favours triplet therapy of daratumumab in combination with Len-dex or Bor-dex over Len-dex or Bor-dex alone.

Safety: Concern for hematological events and Infusion-related reactions

pERC discussed the toxicity profile of daratumumab-len-dex and daratumumab-bor-dex and noted that the side-effects were generally manageable. The most commonly observed grade 3 or 4 events in the treatment and control groups in the CASTOR trial were thrombocytopenia (45.3% and 32.9%, respectively), anemia (14.4% and 16.0%, respectively), and neutropenia (12.8% to 4.2%, respectively). The most common grade 3 or 4 adverse events in the POLLUX trial included neutropenia in 51.9% of daratumumab patients and 37.0% of those in the control group, anemia (12.4% and 19.6%, respectively), and thrombocytopenia (12.7% and 13.5%, respectively).

pERC noted that almost half (45.3%) of patients receiving daratumumab in the CASTOR trial experienced an infusion-related reaction of any grade. For most of these patients (98.2%), infusion-related reactions occurred during the first infusion. The rate of infusion-related reactions in the POLLUX trial was similar to CASTOR, with 47.7% of patients receiving daratumumab experiencing an event of any grade. Again, most of these reactions (92%) took place during the first infusion. pERC therefore agreed that hematological events and infusion-related reactions may be of some concern in this population and would need to be monitored. Of note, according to the manufacturer's product monograph, occurrence of infusion-related

reactions of Grade 1 or higher impacts upon the infusion rates that are recommended for subsequent infusions of daratumumab, thus may lead to longer infusion times over the course of treatment for patients who experience infusion-related reactions during their first dose of daratumumab.

Need and burden of illness: Novel agents with improved survival

Approximately 2,700 patients are diagnosed with multiple myeloma annually. The median age at diagnosis is 69 years, and survival depends on stage, subtype, and cytogenetics. The five-year survival rate is estimated to be 48.5%. Despite significant advancements in the tresatment and life expectancy of patients with multiple myeloma, it still remains an incurable disease and patients will relapse following initial therapy. While bortezomib- or lenalidomide-based therapies are currently the standard treatment options in the second-line setting, superiority of one regimen over the other has not been conclusively demonstrated. Given that both options in the second-line setting have demonstrated an OS benefit, the choice of therapy largely depends on regimens used in the first line. Recently, carfilzomib in combination with Len-dex and and carfilzomib plus Dex have been approved for reimbursement in the relapsed setting based on an improvement in PFS and a trend toward improvements in OS. pERC noted thatthe use of daratumumab len-dex and daratumumab bor-dex in the second line setting will be an additional option for patients who have relapsed after one line of therapy.

Registered clinician input: Progression-free survival and manageable harms associated with daratumumab regimens

The clinicians providing input indicated that the current treatments for relapsed or refractory multiple myeloma include bortezomib, lenalidomide, pomalidomide, cyclophosphamide, and melphalan.
They also noted that overall, triplet combination therapy is superior to currently available therapies as triplet combination therapy provides a marked improvement in progression-free survival and likely an improvement in overall survival. Clinicians noted that daratumumab based regimens provided a deeper response, a higher response rate, and longer duration of response, and thus, would likely replace the current doublet combination therapies. pERC was in agreement with the clinicians that daratumumab regimens have a deeper response, higher response rate and longer duration of response.

Related to the sequencing of treatments, clinicians indicated that daratumumab-len-dex triple combinations should be used as second-line (and beyond) treatment for patients who have not had previous exposure to daratumumab but have relapsed following other treatments. The clinicians providing input felt that this triplet combination would replace the Len-dex doublet combination. For the daratumumab-bor-dex triplet combination, most clinicians providing input felt that this combination should be used as a second line (and beyond) treatment for patients who have not had previous exposure to daratumumab but have disease relapse following other treatments, including after first or second relapse. The clinicians felt that this triplet combination would replace Bor-dex combinations and other less effective regimens. pERC noted this input from the clinicians and was generally in agreement.

PATIENT-BASED VALUES

Values of patients with multiple myeloma: Disease- and treatment-related symptom control

pERC reviewed input from one patient advocacy group. The group indicated that the symptoms most important to control were infections, followed by kidney problems, mobility, pain, fatigue, neuropathy, and shortness of breath. Patients also reported that their disease most limited their ability to work, followed by their ability to travel, exercise, volunteer, conduct household chores, fulfill family obligations, and spend time with family.

Patients valued maintaining quality of life, managing or minimizing side effects, control of their disease, having access to effective treatments, control of symptoms, achieving or maintaining remission and prolonging survival. Patients' expectations of daratumumab, as per the combinations under review, were as follows: prolonged life, disease control, and remission. pERC noted these values and discussed that, based on the results of the CASTOR and POLLUX trials, daratumumab in combination with Len-dex or Bor-dex would align with patients values as it improves progression free survival and maintains quality of life.

Caregivers indicated that their ability to travel was most affected in their duties of caring for someone with myeloma. This was followed by their abilities to volunteer, spend time with family and friends, concentrate, fulfill family obligations, work, exercise, and conduct household chores.

Patient values on treatment: Disease control, remission, administration and fewer side effects than previous treatments

Of the 15 patients who used daratumumab as per the combinations under review, about half (5 of 11 respondents) said that daratumumab was managing their disease and two indicated the side effects were minimal. The patients who had negative side-effects with daratumumab listed long infusion times, lack of appetite, weight loss, some diarrhea and increased blood pressure after the first 2 infusions. The majority respondents who used daratumumab as per the combinations under review felt the effects they experienced were "extremely tolerable" (45.5%) or very tolerable (18.2%). Seven of 11 respondents rated their treatment as effective, very, or extremely effective, while one felt that the treatment was not effective. pERC noted these responses from patients and, based on the assessment of the patient respondents, pERC felt that daratumumab aligns with patient values.

pERC discussed whether the lengthy infusion time for daratumumab and the intensity of the administration could be a burden for patients and their caregivers, especially during the initial treatments. Patients noted that the administration of daratumumab was an important consideration. Of the 11 patients who responded to questions about the experience of administration, three reported daratumumab administration had neutral or no impact, two indicated that it was long or time-consuming, two responded it had no effect and two reported it had a positive impact. pERC acknowledged the length of infusion time associated with the daratumumab-len-dex or daratumumab-bor-dex regimens as a potential barrier to adoption feasibility and resource utilization.

ECONOMIC EVALUATION

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

The pCODR Economic Guidance Panel (EGP) assessed a cost-effectiveness analysis and cost-utility analysis comparing daratumumab plus Len-dex with Len-dex alone and daratumumab plus Bor-dex with Bor-dex alone for the treatment of patients with relapsed multiple myeloma who have received at least one prior therapy.

Basis of the economic model: Clinical and cost inputs

Costs considered in the analysis included drug acquisition, drug administration, routine follow-up care (pre- and post-progression), subsequent treatments, adverse event management, palliative care, and drug wastage.

The clinical effects considered in the analysis were based on PFS and OS estimates from the CASTOR and POLLUX trials. In addition, other clinical effects estimates considered include treatment duration, treatment duration of subsequent treatments, and adverse events.

Drug costs: High-cost drug combinations

At the list price, daratumumab costs $598.020 per 100 mg vial and $2,392.080 per 400 mg vial. Depending on the regimen, daratumumab is dosed differently. For the daratumumab plus len-dex regimen, daratumumab is given intravenously at a rate of 16 mg/kg weekly for eight weeks (cycles 1 to 2), then every two weeks for 16 weeks (cycles 3 to 6), then every four weeks thereafter. For the daratumumab plus bor-dex regimen, daratumumab is given intravenously at a rate of 16 mg/kg weekly (days 1, 8, and 15) during cycles 1 to 3, then every three weeks during cycles 4 to 8, then every four weeks thereafter.

- For the POLLUX trial, daratumumab cost $956.832 per day and $26,791.296 per 28-day course for cycles 1 and 2. For cycles 3 to 6, daratumumab cost $478.416 per day and $13,395.648 per 28-day course and, for the remaining cycles, daratumumab cost $239.208 per day and $6,697.824 per 28-day course.
- For the CASTOR trial, daratumumab cost $956.832 per day and $26,791.296 per 28-day course, for cycles 1 to 3. For cycles 4 to 8, daratumumab cost $318.944 per day and $8,930.430 28-day course. For each cycle thereafter, daratumumab cost $239.208 per day and $6,697.824 per 28-day course.

Based on a generic list price, bortezomib costs $1,402.420 per 3.5 mg vial. At a recommended dose of 1.3 mg/m^2 on days 1, 4, 8, and 11 of each 21-day cycle, bortezomib costs $168.670 per day and $4,722.820 per 28-day course.

At the list price, lenalidomide costs $340.00 per 5 mg, $361.00 per 10 mg, $382.00 per 15 mg, $403.00 per 20 mg, and $424.00 per 25 mg capsule. At the recommended dosage of 25 mg orally on days 1 to 21 per 28-day cycle, lenalidomide costs $318.00 per day and $8,904.00 per 28-day cycle.

At the list price, dexamethasone costs $3.00 per 40 mg orally. At the recommended dosage of 40 mg per day on days 1, 8, 15, and 22 of a 28-day cycle, dexamethasone costs $0.44 per day and $12.18 per 28 days.

At the list price, carfilzomib costs $1,533.33 per single-use vial of 60 mg.

- For cycle 1, at the recommended starting dosage of 20 mg/m^2 on days 1 and 2, and a target dosage of 27 mg/m^2 thereafter (days 8, 9, 15, and 16), carfilzomib costs $229.63 per day and $6,429.76 per 28 days. When wastage is considered, carfilzomib costs $273.81 per day and $7,666.65 per 28 days.
- For cycles 2 to 12, at the recommended dosage of 27 mg/m^2 on days 1, 2, 8, 9, 15, and 16, carfilzomib costs $251.36 per day and $7,037.98 per 28 days. When wastage is considered, carfilzomib costs $273.81 per day and $7,666.65 per 28 days.
- For cycles 13 to 18, at the recommended dosage of 27 mg/m^2 on days 1, 2, 15, and 16, carfilzomib costs $167.57 per day and $4,691.99 per 28 days. When wastage is considered, carfilzomib costs $219.05 per day and $6,133.32 per 28 days.

pERC discussed the cost of daratumumab and noted that jurisdictions will need to consider the budgetary impact of making this drug available. pERC noted that daratumumab is in combination with two already expensive regimens and agreed that a substantial reduction in the price of daratumumab is needed to manage the budgetary impact. pERC also noted that the cost of daratumumab is most impactful in the first cycles of use and, as such, innovative costing agreements between the provinces and manufacturers could help ease the budgetary barriers of implementing the use of daratumumab in all jurisdictions.

Clinical effect estimates: Duration of treatment and benefit post-progression

pERC discussed the several re-analyses conducted by the economic guidance panel (EGP) which looked at the factors affecting different clinically significant end points. pERC deliberated on the duration of treatment effect proposed by the submitter and on the EGP's reanalysis of a shorter duration of treatment effect. pERC agreed with the EGP that the duration of treatment effect submitted by the Submitter is not plausible, and agreed with the EGP reanalysis of exploring truncating the treatment effect to four years

Additionally, given the lack of clinical rationale to support the presence of a post-progression benefit in the daratumumab arm of both trials and the uncertainty of the ongoing relative benefit of daratumumab beyond the trial period, pERC agreed with the EGP in setting the duration of treatment effect to 94 months (instead of the submitted base case), which demonstrated no incremental gains in the post-progression state.

pERC also noted the EGP concern of the shape of the overall survival curve for daratumumab len-dex and that it did not reflect overall survival observed in clinical practice. pERC agreed with the EGP's approach to modify the shape of the curve through truncating the treatment effect at two years, which better reflects the survival of patients as observed in clinical practice.

Cost-effectiveness estimates: Not cost-effective by Economic Guidance Panel's estimates

pERC deliberated upon the cost-effectiveness of daratumumab-len-dex compared to Len-dex and daratumumab-bor-dex compared to Bor-dex alone, based on the submitted economic evaluation and reanalysis estimated provided by the EGP. Several uncertainties were highlighted by the EGP. The duration of treatment effect was noted as the single largest driver of cost and effect in the model. The EGP noted that, based on input from the CGP, it is unlikely that the treatment effect lasts for 30 years and examined truncating the treatment effect to two years, which is the end of the trial follow-up period. Consequently, this led to a significant increase in the incremental cost-effectiveness ratio (ICER) values. pERC agreed with this EGP reanalysis that the treatment effect is likely to be less than 30 years and noted that the resulting ICER would then lie closer to the upper bound of the EGP's reanalysis estimates, which were $594,144 per quality-adjusted life-year (QALY) for the daratumumab-len-dex regimen, and $195,399 per QALY for the daratumumab bor-dex regimen.

The EGP also noted that the modelling of the overall survival curves and post-progression benefits as not reflective of patients seen in the clinical setting. The EGP reanalysis truncated the OS treatment effect at two years and in order to show no incremental gains in the post-progression state, the duration of treatment effect was set to 8 years from 30 years. pERC, therefore concluded that due to the uncertainty in duration of treatment effect and the high cost of daratumumab, daratumumab plus Len-dex or Bor-dex could not be considered cost-effective.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Drug administration resource use and opportunity costs

pERC considered the feasibility of implementing a funding recommendation for daratumumab plus Len-dex and daratumumab plus Bor-dex. pERC noted that there may be a large prevalent population who could be eligible for treatment with daratumumab plus Len-dex or Bor-dex.

pERC discussed several barriers to accessibility that patients may experience with daratumumab. As an intravenous therapy, patients may have to travel to chemotherapy clinics or hospitals for treatment. The potentially long, patient specific infusion times may require patients to visit the chemotherapy clinic or hospitals multiple times within the same week. Due to the fact that many ambulatory clinics may have limited hours of operation (i.e. 8 – 10 daytime hours), , patients requiring longer infusion times may require treatment to be split over two or three days to accommodate their daratumumab infusions and support medications. pERC also noted that the frequent and complex dosing and administration schedule of daratumumab- len-dex or daratumumab- bor-dex poses significant challenges for scheduling chemotherapy chair time and potential challenges for certain patients needing to travel to receive therapy. In addition, daratumumab-based regimens would introduce an additional incremental workload for pharmacy, nursing, and chemotherapy suite resources required to prepare and administer daratumumab to patients.

pERC concluded that the budget impact of daratumumab will be very high due to the high cost of daratumumab, resource use costs, and treatment that continues until progression. pERC also considered the significant opportunity costs potentially present for daratumumab due to the very high potential budget impact, the increased resource utilization related to long, patient-specific infusion times, more frequent clinic visits and considerable impact on chair time available for all systemic therapies as well as the additional requirements of pharmacy and nursing staff to prepare, administer, and monitor daratumumab infusions required. Therefore, pERC noted that the administration of daratumumab is resource-intensive and that jurisdictions will need to consider the incremental costs to the health system required for the implementation of daratumumab due to the resource intensive nature of the preparation, administration, and monitoring.

pERC discussed the sequential use of daratumumab-len-dex or daratumumab- bor-dex in patients who have progressed on lenalidomide or bortezomib. pERC noted that patients with progressive disease on lenalidomide could be offered the daratumumab-bor-dex regimen and patients progressing on bortezomib would be given the daratumumab- len-dex regimen. pERC was unable to comment on patients who are refractory to lenalidomide or bortezomib as those patients were excluded from the POLLUX and CASTOR trials, respectively. pERC also noted that the optimal sequencing of daratumumab regimens compared with carfilzomib regimens is currently unknown. pERC was therefore unable to make an evidence-informed recommendation on sequencing. However, pERC recognized that provinces would need to address this issue upon implementation of daratumumab funding, and noted that collaboration among provinces to develop a common approach would be of value. pERC noted the CGP comments on sequencing depending on previous line of therapy, previous responses to lines of therapy, duration of response, side effects, patient factors, disease factors and access to medications. pERC acknowledged that these factors would be important in deciding the optimal sequencing for the treatment of patients with multiple myeloma who have received at least one prior therapy.

pERC also noted that, since daratumumab interferes with blood compatibility testing, there is a need for red blood–cell phenotyping (or genotyping) prior to initiating the administration of daratumumab.. Genotyping is predominately conducted by the Canadian Blood Services and would pose a significant resource use burden in light of the potential patient population eligible for daratumumab regimens.

Jurisdictions may want to consider liaising with Canadian Blood Services prior to implementation in order to identify potential barriers to implementation.

DRUG AND CONDITION INFORMATION

Drug Information	• IgG1κ human monoclonal antibody that targets the CD38 protein
	• Recommended dose, reviewed by pCODR, is 16 mg/kg of body weight, administered as an intravenous infusion as follows:
	  • for the daratumumab plus len-dex regimen, daratumumab is given intravenously at a rate of 16 mg/kg weekly for eight weeks (cycles 1 to 2), then every two weeks for 16 weeks (cycles 3 to 6), then every four weeks thereafter
	  • for the daratumumab plus bor-dex regimen, daratumumab is given intravenously at a rate of 16 mg/kg weekly (days 1, 8, 15) during cycles 1 to 3, then every three weeks during cycles 4 to 8, then every four weeks thereafter

Cancer Treated	• Multiple myeloma (relapsed or refractory to at least one prior line of therapy)
Burden of Illness	• It is estimated that, in 2016, 2,700 Canadians were diagnosed with multiple myeloma, and 1,450 patients died of this disease • Despite significant advancement, this remains an incurable disease
Current Standard Treatment	• Bortezomib-based regimen (bortezomib plus dexamethasone; cyclophosphamide plus bortezomib plus dexamethasone [CyBorD]) • Lenalidomide plus dexamethasone • Carfilzomib plus lenalidomide plus dexamethasone (recently recommended for reimbursement by pERC) • Carfilzomib plus dexamethasone (recently recommended for reimbursement by pERC)
Limitations of Current Therapy	• Life expectancy is limited with current therapies • There is a continued need for novel therapies that can improve life expectancy

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. Paul Hoskins, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Karen MacCurdy Thompson, Pharmacist
Valerie McDonald, Patient Member Alternate
Carole McMahon, Patient Member
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Dr. Marianne Taylor, Oncologist
Danica Wasney, Pharmacist

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

- Dr. Allan Grill, Dr. Scott Berry and Don Husereau, who were not present for the meeting
- Carole McMahon, who did not vote due to her role as a patient member alternate.

Avoidance of conflicts of interest

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

Information sources used

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

Consulting publicly disclosed information

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

Use of this Recommendation

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

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