pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC) FINAL RECOMMENDATION

The 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 pCODR Expert Review Committee (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 Funding Request:** For the treatment of patients with multiple myeloma who 1) have received at least three prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD); *or* 2) have failed or are intolerant to a PI and who have failed or are intolerant to an IMiD.	
Submitted By: Janssen Canada Inc.	**Manufactured By:** Janssen Canada Inc.
NOC Date: June 29, 2016	**Submission Date:** April 21, 2016
Initial Recommendation: September 29, 2016	**Final Recommendation:** December 1, 2016

pERC RECOMMENDATION	pERC does not recommend reimbursement of daratumumab for the treatment of patients with multiple myeloma who 1) have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD); *or* 2) have failed or are intolerant to a PI and who have failed or are intolerant to an IMiD. The Committee made this recommendation because it was unable to conclude that, based on the available evidence, there is a net clinical benefit of daratumumab compared with other treatments. While pERC noted that there is a need for effective treatments in this setting and that daratumumab produces anti-tumour activity, the Committee concluded that there was considerable uncertainty in the evidence available on outcomes important to decision-making, such as overall survival (OS), progression-free survival (PFS), and quality of life (QoL). pERC also concluded that daratumumab partially aligned with patient values based on its anti-tumour activity and therapeutic intent. The Committee noted that, based on the high level of uncertainty in the available clinical data, there was a high degree of uncertainty in the cost-effectiveness estimates for daratumumab; thus, pERC concluded that there is a low probability that daratumumab would be cost-effective in this population compared with other available treatments.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS	No next steps were identified.

SUMMARY OF pERC DELIBERATIONS

In 2015, an estimated 2,700 new cases of multiple myeloma were diagnosed in Canada, with an average age at diagnosis of 62 years. Multiple myeloma is incurable and an estimated 1,400 deaths were attributable to the disease in 2015. Despite the improvement in clinical outcomes with the use of PIs and IMiDs, patients eventually become resistant to these agents. The prognosis for these patients is poor and treatment options, other than supportive care, are limited. Therefore, pERC agreed with the pCODR Clinical Guidance Panel (CGP) that there is a need for effective treatment options for patients with relapsed and/or refractory multiple myeloma who have progressed following treatment with a PI and an IMiD, and had also received at least three prior therapies. Upon reconsideration, the Committee acknowledged and also agreed with the patient advocacy group's feedback that there is need for effective treatment options.

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

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberated on the results of two single-arm, open-label studies (MMY2002 and GEN501) that evaluated daratumumab monotherapy in patients with multiple myeloma who were previously treated with at least three lines of therapy (including a PI and an IMiD), or were refractory to both a PI and an IMiD. pERC noted that the sample size of both studies was small, and that while the limited overall response rate data indicated some activity of daratumumab in this patient population, without comparative data it was not possible for the Committee to assess the magnitude of effect compared with other available therapies. pERC was also concerned that the results to date of the two trials are immature and place emphasis on the results of the patients with early responses, rather than providing evidence of the results of the complete sample of patients over a course of time.

pERC noted that, in the absence of comparative data, the submitter provided a propensity score matching analysis utilizing patient data from a retrospective chart review as the control arm population. pERC agreed with the CGP that there were substantial limitations in the propensity score matching analysis, including that some prognostically important variables were missing from matching, such as staging, cytogenetics, and time since diagnosis, and that the groups were not balanced with respect to the proportion of patients who were double refractory to both a PI and an IMiD. The effect of these limitations on the magnitude of the difference in outcomes between daratumumab and other available treatments is uncertain, and could under- or overestimate the true difference. Therefore, the Committee did not have confidence in the results of the analysis. Upon reconsideration, the Committee noted the submitter's feedback related to the methodology of the submitter's propensity score matching analysis. pERC agreed with the CGP's response that staging and time since diagnosis are important to consider in this setting. In addition, pERC felt that the inability to control for unknown confounding variables increases the uncertainty in the results of the submitter's analysis.

Additionally, given the prevalence of patients with multiple myeloma who are double refractory to a PI and an IMiD, pERC felt that a phase 3 randomized trial could have been conducted in this population to determine the comparative efficacy of daratumumab in relation to available treatment options or best supportive care. Upon reconsideration, pERC noted the feedback from stakeholders regarding the feasibility of a randomized controlled trial (RCT) and acknowledged the CGP's response to the stakeholders' feedback indicating the CGP's opinion that a trial comparing daratumumab to best supportive care is not feasible for pragmatic reasons. The Committee reiterated that a phase 3 randomized trial could have been conducted in this population, given the prevalence of patients with

multiple myeloma who are double refractory to a PI and an IMiD. pERC also reiterated that in this setting there was clinical equipoise and therefore, an RCT would have been justified.

pERC also noted that neither the MMY2002 study nor the GEN501 study collected data on health-related QoL. pERC agreed with the CGP that QoL data in these patients, who have received several treatments for multiple myeloma, are essential to understand the patient experience with daratumumab. The submitter provided unpublished QoL data from another ongoing study of patients receiving daratumumab; however, the details of this additional study and the QoL data provided were limited, and pERC therefore did not have confidence in the results. pERC also deliberated on the toxicity of daratumumab and noted that infusion reactions are common with the initial dosing of daratumumab and that they decrease with subsequent exposures; however, overall, the toxicity profile was manageable. Therefore, due to the limitations in the evidence from the two studies discussed, pERC was unable to conclude that there is a net clinical benefit of daratumumab compared with other treatments. While pERC acknowledged that daratumumab produces anti-tumour activity, the Committee concluded that there was considerable uncertainty in the evidence available on outcomes important to decision-making, such as OS, PFS, and QoL.

pERC deliberated upon input from one patient advocacy group and input from registered clinicians regarding the use of daratumumab in patients with multiple myeloma. pERC noted that both the patient advocacy group and the registered clinicians noted that daratumumab provides another therapeutic option with a mechanism of action different from currently available treatments for patients who are double refractory to a PI and an IMiD. The patient advocacy group also noted that patients value having treatment options that prolong survival and improve QoL. pERC discussed the fact that there were no QoL data reported in the two non-comparative trials on daratumumab in this population, and they also noted the uncertainty in the effectiveness of daratumumab on PFS and OS compared with other therapeutic options. In addition, pERC noted the lengthy infusion time for daratumumab and the intensity of the administration schedule. The Committee felt that the long infusion time and frequency of administration could be a burden on patients and their caregivers. Therefore, pERC concluded that daratumumab partially aligned with patient values. During the reconsideration process, pERC discussed feedback on the Initial Recommendation from the patient advocacy group related to the administration of daratumumab. pERC acknowledged that although there exists a considerable time commitment (infusion time, frequency of administration, travel to treatment centre) associated with the use of daratumumab, which may pose a challenge to some, but not all, patients and their caregivers. The Committee also noted that the feedback from the patient advocacy group regarding discussions and negotiations related to the pan-Canadian Pharmaceutical Alliance (pCPA) and for the procurement of additional resources in order to implement new cancer therapies are beyond the scope of the pCODR review process.

pERC deliberated on the cost-effectiveness of daratumumab compared with the following treatments: high dose dexamethasone; bortezomib, cyclophosphamide and dexamethasone; and pomalidomide and dexamethasone. pERC concluded that, at the submitted price, it was highly unlikely that daratumumab was cost-effective. pERC accepted that the pCODR Economic Guidance Panel (EGP) could not provide an estimate of the upper bound for the incremental cost-effectiveness ratio (ICER) because of the uncertainty in the clinical data available, and agreed with the EGP that the true ICER was not near the lower bound. pERC noted several limitations in the submitted economic model, mostly due to the lack of direct comparative evidence and lack of data with long-term follow-up. In reviewing the economic model provided by the submitter, pERC noted the inconsistency in the survival curve for PFS compared with the curve for OS. Furthermore, the Committee noted that the majority of the clinical benefit derived in the model submitted by the manufacturer occurred in the post-progression state. In other words, accepting the model would require an assumption that patients derived the majority of the benefit of the treatment after they had stopped receiving the treatment. pERC agreed with the EGP and CGP that the clinical plausibility of this assumption was difficult to accept. Upon reconsideration, the Committee noted the submitter's feedback on pERC's Initial Recommendation regarding the continuation of benefit after treatment ends. pERC felt that the submitter's feedback did not fully address the continued

benefit after treatment ends. The Committee, however, agreed with the CGP's response to this feedback that the possible assumptions that may explain the amount of clinical benefit derived after progression may be that the drug is not actually stopped on progression, and rather additional agents are added; or, the progression is biochemical and the drug is continued.

pERC also noted that the submitter included the effect of downstream treatments in the model; however, the costs of downstream treatments were not included, and thus the ICER was underestimated.

pERC discussed the feasibility of implementing a reimbursement recommendation for daratumumab for the treatment of double-refractory multiple myeloma. pERC agreed with the Provincial Advisory Group (PAG) that this would be an add-on therapy, and not a replacement therapy, therefore increasing the budget impact of daratumumab. As well, they 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 resources, and could place a substantial burden on patients and their caregivers. After discussing feedback from the patient advocacy group related to the administration of daratumumab, pERC acknowledged that although there exists a time commitment (infusion time, frequency of administration, travel to treatment centre) associated with the use of daratumumab, which may pose a challenge to some, but not all, patients and their caregivers. pERC discussed the potential place in therapy for daratumumab and whether it would be considered a last treatment option for patients. pERC agreed that for some patients, daratumumab may be the last treatment option, but based on the good performance status of patients included in the non-comparative studies, and the fact that patients received subsequent therapy in the non-comparative trials, pERC concluded that for many patients, daratumumab would not replace end of line treatment; rather, daratumumab would be an add on therapy. In addition, pERC recognized that additional downstream resources and costs would be incurred due to the interference of daratumumab with blood compatibility testing. Upon reconsideration, pERC acknowledged that in their feedback, the registered clinicians felt that additional downstream resources and interference with compatibility testing would be minimal. The Committee also discussed that CGP's opinion that daratumumab is more work from a blood bank perspective; however, this work is relatively easy to manage. The Committee acknowledged that the CGP believes that the costs would be minimal from a blood bank perspective, as the infrastructure is already set up for this aspect in other clinical contexts. pERC also noted the CGP's proposed method of managing the impact. However, the Committee still felt that daratumumab may have an impact on blood compatibility testing and require additional downstream resources exists. pERC also recognized that the registered clinicians also highlighted that there were few options for double refractory patients and that the response rates in these patients (and also in triple/quadruple refractory patients) was unprecedented. However, the Committee noted that there was no evidence available for triple/quadruple refractory patients.

The Committee also noted that there would likely be substantial wastage associated with daratumumab due to the weight-based dosing. In addition, it noted the extremely high cost of daratumumab, and that it was one of the most expensive drugs ever considered by the Committee, based on the drug cost alone. pERC noted that, in addition to the high drug costs, there would also be considerably high administrative costs associated with daratumumab due to the long preparation and intensive infusions required. Upon reconsideration, the Committee acknowledged the feedback from PAG related to the lack of enthusiasm over daratumumab/dexamethasone combination therapy and the issues regarding infusion times. pERC discussed the CGP's response to PAG's feedback and agreed with the CGP that the feedback regarding triplet therapy is out of scope for this review. Moreover, pERC recognized that although there exists a time commitment (infusion time, frequency of administration, travel to treatment centre) associated with the use of daratumumab, which may pose a challenge to some, but not all patients and their caregivers.

pERC acknowledged the clarification provided by the submitter and the EGP regarding the attenuating cost of daratumumab over time as dosing becomes less frequent with subsequent cycles. In addition, the

Committee noted the two errors and corrected ICERs provided by the EGP and agreed with the EGP that the errors have little impact on the reanalysis estimates of the incremental cost-effectiveness.

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 provide clinical context
- An evaluation of the submitter's economic model and budget impact analysis
- Guidance from pCODR clinical and economic review panels
- Input from one patient advocacy group: Myeloma Canada
- Input from registered clinicians in a joint submission
- Input from pCODR's Provincial Advisory Group (PAG).

The pERC Initial Recommendation was not to fund daratumumab for the treatment of patients with multiple myeloma who 1) have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD); or 2) have failed or are intolerant to a PI and who have failed or are intolerant to an IMiD.

Feedback on the pERC Initial Recommendation indicated that PAG agreed, while the registered clinicians, patient advocacy group and submitter disagreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the safety and efficacy of daratumumab (Darzalex) on patient outcomes for the treatment of patients with multiple myeloma who 1) have received at least three prior lines of therapy including a PI and an IMiD; *or* 2) have failed or are intolerant to a PI and who have failed or are intolerant to an IMiD.

Studies included: Single-arm, phase 2 (MMY2002) and phase 1/2 (GEN501) open-label studies

The pCODR systematic review included two single-arm, open-label, phase 2 (MMY2002) and phase 1/2 (GEN501) studies that evaluated daratumumab monotherapy in patients with multiple myeloma.

MMY2002

MMY2002 included patients with multiple myeloma who received at least three prior lines of therapy (including PIs and IMiDs) or whose disease was refractory to both PIs and IMiDs. Patients received daratumumab intravenously at 16 mg/kg per week for eight weeks, then every two weeks for 16 weeks, and then every four weeks thereafter. Patients received therapy until disease progression or until an unmanageable level of toxic events occurred. Eligibility criteria included Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 2. Key exclusion criteria include clinically significant cardiovascular and respiratory conditions.

The primary end point was overall response rate (ORR) and secondary end points included duration of response (DoR), progression-free survival (PFS), overall survival (OS), and clinical benefit rate.

GEN501

GEN501 included patients with multiple myeloma who required systemic therapy and whose disease was relapsed or refractory to at least two prior lines of therapy. Patients received daratumumab intravenously at 16 mg/kg once weekly (eight doses; after the first dose, a three-week washout period occurred and then weekly doses were resumed), then twice monthly (eight doses), and then monthly for up to 24 months. Patients received therapy until disease progression or until an unmanageable level of toxic events occurred. Eligibility criteria included ECOG PS 0 to 2. Key exclusion criteria include clinically significant cardiovascular and respiratory conditions. The primary end point was safety, and secondary end points included pharmacokinetics, objective response according to the International Myeloma

Working Group (IMWG) uniform response criteria for myeloma, time to disease progression, DoR, PFS, and OS.

The pCODR review also provided contextual information on a propensity score matched comparison of the MMY2002/GEN501 studies with an International Myeloma Foundation Medical Chart Review. This analysis was used to provide comparative effect estimates of daratumumab versus other treatment options in patients with multiple myeloma who were highly pre-treated and highly refractory to available treatment.

Patient populations: Heavily pre-treated, double refractory to a proteasome inhibitor and an immunomodulatory agent, most with performance status 0 to 1

MMY2002

The median age was approximately 64 years. A total of 36 (34%) patients were 65 to 74 years and 12 (11%) were 75 years or older. Most patients were ECOG PS 0 or 1, with 8% of patients being ECOG PS of 2. The median number of prior lines of therapy was five; most patients had had more than three prior lines of therapy (82%). According to the pCODR Clinical Guidance panel (CGP), the treatment duration of daratumumab in this clinical setting is not clearly known. However, as reported by the MMY2002 study, the median DoR was 7.4 months with a PFS of 3.6 months. Therefore, the CGP speculates that the duration of therapy may be between three and eight months, depending on individual cases.

GEN501

The median age was 64 years. A total of 16 (38%) patients were 65 to 74 years and 4 (10%) were 75 years or older. Most patients were ECOG PS 0 or 1, with 5% of patients being ECOG PS of 2. The median number of prior lines of therapy was four; 62% of patients had had more than three prior lines of therapy.

Overall, in MMY2002 and GEN501, the majority of patients had received previous PIs (99% with bortezomib, 50% with carfilzomib), IMiDs (99% with lenalidomide, 63% with pomalidomide, and 44% with thalidomide), or allogeneic stem cell transplant (80%). Almost all patients (97%) were refractory to their last line of therapy and (95%) refractory to both a PI and an IMiD. A proportion of patients were refractory to bortezomib + lenalidomide + carfilzomib + pomalidomide (31%).

Key efficacy results: Active treatment, unclear magnitude of effect

The key efficacy outcomes deliberated on by pERC were ORR (primary end point for MMY2002), DoR, PFS, and OS.

MMY2002

Response was seen in 31 patients (29.6%). The median time to response was 0.9 months. The DoR was 7.4 months. Responses were seen irrespective of previous lines of therapy and refractory status. The clinical cut-off date was January 9, 2015, 7.7 months after the last person had received first dose (median follow-up was 9.3 months). The median PFS was 3.7 months. The 12-month OS rate was 64.8% and at the updated analysis (June 30, 2015 data cut-off), the median OS was 17.5 months.

GEN501

Response was seen in 15 patients (36%). The median time to response was one month. The DoR was not reached. pERC acknowledged that the primary end point in GEN501 was safety and that efficacy outcomes were secondary end points. Responses were exploratory outcomes and were seen irrespective of previous lines of therapy and refractory status. The median PFS was 5.6 months. The 12-month OS rate was 77%.

Overall, pERC noted that it was not possible to assess the magnitude of benefit of daratumumab in the absence of a comparative trial. And while pERC acknowledged the use of a propensity score matching analysis, it concluded that there were several limitations associated with the analysis that limited the Committee's confidence in the results of the analysis.

Quality of life: No data collected

The Committee noted that studies MMY2002 and GEN501 did not collect quality of life (QoL) data. pERC noted that the submitter provided unpublished QoL data from another ongoing study of patients receiving daratumumab. However, the details of this additional study and the QoL data provided were limited; therefore, pERC did not have confidence in the results.

Safety: Frequent infusion reactions, manageable toxicity profile

MMY2002

The most common treatment emergent adverse events (TEAEs) of any grade (≥ 20%) were fatigue (40%), anemia (33%), nausea (29%), thrombocytopenia (25%), neutropenia (23%), back pain (22%), and cough (21%). Grade 3 or higher anemia and thrombocytopenia occurred more frequently in responders than non-responders. No patients discontinued daratumumab because of drug-related TEAEs, infusion-related reactions, or death. Thirty per cent of patients had a serious TEAE and 23% had grade 3/4 serious TEAE. Infusion-related reactions occurred in 42% of patients (none of grade 4); the most common (≥ 5%) were nasal congestion (12%), throat irritation (7%), and cough, dyspnea, chills, and vomiting (6% each). Five patients (5%) discontinued treatment due to a TEAE; this, however, was not drug-related. A total of 31 (29%) patients died after treatment: 29 (27%) patients died because of progressive disease and two (2%) patients died because of an adverse event.

GEN501

The Committee noted that the primary end point in GEN501 was safety. The most common adverse events (≥ 25%) were fatigue, allergic rhinitis, and pyrexia. A total of 26% of patients had a grade 3/4 adverse event. Serious adverse events were reported in 33% of patients who received 16 mg/kg. Seventy-one per cent of patients had an infusion-related reaction.

Overall, pERC noted that in both MMY2002 and GEN501, no patients discontinued treatment with daratumumab due to an infusion-related reaction. Infusion-related reactions were managed by administering pre-infusion medications including antihistamines, antipyretics, and corticosteroids. Grade ≥ 3 infusion-related reactions in GEN501/MMY2002 were uncommon; only one patient in both studies experienced grade ≥ 3 dyspnea infusion-related reaction.

Limitations: Small, non-comparative studies

The main limitations of MMY2002 and GEN501 were their non-comparative study designs (phase 1/2, single-arm, open-label, non-randomized). No health-related QoL data were collected for MMY2001 and GEN501. In addition, the propensity score matching analysis provided by the submitter had limitations, such as the omission of some prognostically important variables from matching (including staging and time since diagnosis, and the groups were not balanced in double-refractory status. pERC noted that the effect of these limitations on outcomes in terms of over- or underestimation of true difference is uncertain. In their feedback, the submitter commented on the pERC's conclusion related to the propensity score matching analysis and that a clinical expert consulted by the submitter was of the opinion that staging and time since diagnosis may not be as important as other variables in the propensity score matching analysis. pERC noted that the CGP reiterated that staging and time since diagnosis have value and, moreover, staging and time since diagnosis may be more salient given the absence of an RCT. Upon reconsideration, the Committee agreed with the CGP's response that staging and time since diagnosis are important to consider in this setting. pERC members also emphasized the potential importance of cytogenetics as another variable to be considered within the PSM. In addition, pERC also felt that the inability to control for unknown confounding variables increases the uncertainty in the results of the submitter's analysis. In addition to the known missing variables, pERC also felt that unknown variables likely contribute to the uncertainty.

In response to the feedback related to the feasibility of an RCT from the stakeholders, pERC noted that the CGP clarified that a trial comparing daratumumab to best supportive care is not feasible for pragmatic reasons. The Committee reiterated that a phase 3 randomized trial could have been conducted in this population given the prevalence of patients with multiple myeloma who are double refractory to a

PI and an IMiD. pERC also reiterated that in this setting there was clinical equipoise and therefore, an RCT would have been justified.

Need: Incurable disease with more effective treatment options required

In 2015, an estimated 2,700 new cases of multiple myeloma were diagnosed in Canada, with an average age at diagnosis of 62 years. Multiple myeloma is incurable and an estimated 1,400 deaths were attributable to the disease in 2015. Despite the improvement in clinical outcomes with the use of PIs and IMiDs, patients eventually become resistant to these agents. The pCODR Clinical Guidance Panel (CGP) stated that given the dismal prognosis of patients refractory to a PI and an IMiD, there is a clear need for novel non-cross-resistant modalities of treatment that overcome the tumour microenvironment-mediated drug resistance and genetic instability of the disease.

Registered clinicians: Another therapeutic option

The registered clinicians providing input stated that daratumumab provides another therapeutic option with a mechanism of action different from current treatments for patients who are refractory to a PI and an IMiD. They reported that daratumumab demonstrates better activity in the heavily pre-treated and refractory patients and noted that there are currently no approved therapy that provides such response with such favourable toxicity profile.

In their feedback, registered clinicians commented on their clinical experience related to interference with blood compatibility testing and additional downstream resources. pERC noted that the CGP felt that daratumumab is more work from a blood bank perspective, but this work is relatively easy to manage. The Committee also acknowledged that the CGP believe that the costs would be minimal from a blood bank perspective because the infrastructure is already set up to support other clinical contexts. pERC also noted the CGP's proposed methods of managing the impact. However, the Committee still felt that daratumumab may have an impact on blood compatibility testing and require additional downstream resources exists.

PATIENT-BASED VALUES

Values of patients with multiple myeloma: Control symptoms of disease

The most important aspect of myeloma to control is infection, followed by kidney problems, pain, mobility, neuropathy, fatigue, and shortness of breath. Respondents indicated that symptoms associated with myeloma most affected their ability to work, followed by the ability to travel, exercise, volunteer, conduct household chores, fulfill family obligations, and spend time with their family. Most respondents experienced fatigue with their treatment for myeloma; other treatment side effects included neuropathy, pain, insomnia, stomach issues, nausea, shortness of breath, confusion, diarrhea, constipation, and skin rashes.

Patient values regarding treatment: Seeking improvement in survival and quality of life

pERC noted that the majority of respondents indicated that it was important that new treatments bring about improvement in their physical condition and that the expected benefit would be a lack of disease progression. pERC discussed the lack of QoL data reported in the two non-comparative trials on daratumumab in this population, and the Committee also noted the uncertainty in the effectiveness of daratumumab on PFS and OS compared with other therapeutic options. In contrast, pERC noted that six out of the seven respondents who were interviewed indicated that daratumumab has met their expectations, in that they are responding to the treatment and that it has improved their QoL. pERC also discussed the lengthy infusion times, and acknowledged that some respondents accepted the infusion times because the infusion frequency is reduced over time. However, 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. Upon reconsideration, pERC discussed feedback on the initial recommendation from the patient advocacy group related to the administration of daratumumab. pERC recognized that although there exists a time commitment (infusion time, frequency of administration, travel to treatment centre) associated with the use of daratumumab, which may pose a challenge to some, but not all patients and their caregivers. The Committee noted that the feedback

from the patient advocacy group regarding discussions and negotiations related to the pan-Canadian Pharmaceutical Alliance (pCPA) are beyond the scope of the pCODR review process. Moreover, pERC discussed the patient advocacy group's feedback related to the quality of life. pERC noted that the patient group surveyed and interviewed respondents about their experience of daratumumab. Six out of the seven respondents who were interviewed indicated that daratumumab has met their expectations, in that they are responding to the treatment and that it has improved their QoL. However, pERC had concerns that daratumumab possibly adversely affects QoL given the intensity of the treatment (both related to time and safety) and, without a comparator, pERC was unable to conclude the real effect on QoL for a group of patients with multiply refractory advanced disease.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness analysis using partitioned-survival model

The pCODR Economic Guidance Panel (EGP) assessed a cost-effectiveness and cost-utility analysis submitted to pCODR by Janssen Inc. that compared daratumumab to Canadian average current care (patients receiving pomalidomide/dexamethasone, bortezomib/dexamethasone/cyclophosphamide, or high-dose dexamethasone) as defined by Canadian clinical experts for patients with multiple myeloma who have received at least three prior lines of therapy including a PI and an IMiD, or who have failed or are intolerant to a PI and an IMiD.

Upon reconsideration, two errors (related to the median survival time of 20.1 months instead of 20.7 months and selection of distribution) were noted in the report and therefore were corrected. EGP noted that these errors, however, have little impact on their initial reanalysis estimates. The Committee noted these errors and corrected incremental cost-effectiveness ratios (ICERs), and agreed with the EGP that the errors have little impact on the EGP's reanalysis estimates.

Basis of the economic model: Pooled data from GEN501/MMY2002, indirect comparison

The pharmacoeconomic model was based on an indirect comparison. The effectiveness input parameters, the OS and PFS, and the cost input parameters of daratumumab came from the combined patient sample from the GEN501 and MMY2002 studies with patients taking a 16 mg/kg dose of daratumumab. The estimates for the average current care came from a recent analysis using international chart review data. The relative efficacy of daratumumab compared with the average current care was obtained using propensity score matching.

Drug costs: Intensity of intravenous injection varies over time, and high drug costs

The list price for daratumumab is $598.02 per 100 mg/5 mL vial and $2,392.08 per 400 mg/20 mL vial. The intensity of intravenous injection is variable over time: four injections per month for the first two months; two injections per month from three to six months, and one injection per month from seven months. The cost per cycle (28-day course) for Cycles 1 and 2 (with four injections) would be $28,705 (or $7,176.25/week or $1,025.18/day); for Cycles 3 through 6 (with two injections) would be $14,352 (or $3,588/week or $512.57/day); and for Cycles 7 and beyond (one injection) would be $7,176.25 ($1,794.06/week or $256.29/day), using the average weight from MMY2002 study. pERC noted that this is one of the most expensive drugs (per 28-day course) it has ever considered.

Cost-effectiveness estimates: High uncertainty in incremental cost-effectiveness ratio due to high uncertainty in clinical data

The Committee discussed the EGP's overall conclusions on the submitted model. The lack of randomized head-to-head comparative data between daratumumab and current standard of care, the weak clinical justification of the post-progression survival benefit, and the use of propensity score matching without considering several important clinical factors limit the level of confidence in the submitted economic model and economic evaluation report. pERC concluded that at the submitted price, it was highly unlikely that daratumumab was cost-effective. pERC accepted the fact that the EGP could not provide an estimate of the upper bound of the ICER because of the uncertainty in the clinical data available, and agreed with the EGP that the true ICER was not near the lower bound. pERC noted

several limitations in the submitted economic model, mostly due to the lack of comparative data and data with long-term follow-up results. The Committee noted that the majority of the clinical benefit derived in the model occurred in the post-progression state. In other words, accepting the model would require an assumption that patients derived the majority of the benefit of the treatment after they had stopped receiving the treatment. pERC agreed with the EGP and CGP that the clinical plausibility of this assumption was difficult to accept.

The submitter's feedback on pERC's Initial Recommendation states that it is accepted that patients do derive some clinical benefit after they stop taking a drug. The Committee noted that according to the CGP, though it is not clearly known, it seems plausible that patients could derive benefit after they stopped receiving the treatment given the published results. pERC also agreed with the CGP's possible assumptions that may explain the amount of clinical benefit derived after progression may be that the drug is not actually stopped on progression, and rather additional agents are added; or, the progression is biochemical and the drug is continued. According to the CGP, the treatment duration of daratumumab in this clinical setting is not clearly known. However, as reported by the MMY2002 study, the median duration of response was 7.4 months with a PFS of 3.6 months. Therefore, the CGP speculates that the duration of therapy may be between 3 and 8 months, depending on individual cases.

pERC also noted that in the economic model, the submitter included the effect of downstream treatments in the model; however, these costs of the downstream treatments were not included in the model, thus underestimating the ICER.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Drug wastage, pre-medication prior to infusion, unknown and variable duration of treatment

pERC noted that there may be a large prevalent population who would be eligible for treatment with daratumumab. The Committee agreed with PAG in that because treatment is continued until progression, the unknown duration of treatment is a barrier to implementation. Lack of comparative data and long-term data were also noted as barriers to implementation.

The Committee acknowledged PAG's concerns for incremental costs due to drug wastage, specifically in centres where vial sharing would be difficult. Although there are two vial sizes available, dosage is based on weight and there will be some drug wastage, as any unused portion would be discarded.

pERC recognized that additional resources will be required for pre-medication, drug preparation, administration time, and monitoring for multiple severe adverse effects, including infusion reactions.

The Committee noted the factors that most influence the budget impact analysis included body weight (larger budget impact with higher patient weight) and price of pomalidomide (smaller budget impact with higher cost of pomalidomide, since daratumumab was modelled to displace pomalidomide and thus, higher cost of pomalidomide reduces the budget impact of daratumumab). pERC recognized that a key limitation of the budget impact model was not having accurate data for estimating the number and proportion of the multiple myeloma population potentially eligible for daratumumab. This was not further modified or tested by the EGP.

pERC discussed the feasibility of implementing a reimbursement recommendation for daratumumab for the treatment of double-refractory multiple myeloma. pERC agreed with PAG that this would be an add-on therapy, and not a replacement therapy, therefore increasing the budget impact of daratumumab. They 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 resources, and also place a substantial burden on patients and their caregivers. pERC discussed the potential place in therapy for daratumumab and whether it would be considered a last treatment

option for patients. Based on the good performance status of patients included in the non-comparative studies, and the fact that the submitter included subsequent treatment in its submitted economic model, pERC concluded that daratumumab would not be used as a last treatment option in practice. Moreover, pERC recognized that additional downstream resources and costs would be incurred due to the interference of daratumumab with blood compatibility testing. The Committee also noted that there would likely be substantial wastage associated with daratumumab due to the weight-based dosing. It also noted the extremely high cost of daratumumab, and that it was one of the most expensive drugs ever considered by the Committee based on the drug cost alone. As well, pERC noted that, in addition to the high drug costs, there would also be considerably high administrative costs associated with daratumumab due to the intensive preparation and infusion times required.

DRUG AND CONDITION INFORMATION

Drug Information	• IgG1κ human monoclonal antibody that targets the CD38 protein
	• Recommended dose, reviewed by pCODR, is 16 mg/kg body weight administered as an intravenous infusion as follows:
	  • Cycles 1 and 2 (i.e. Weeks 1-8): once weekly
	  • Cycles 3-6 (i.e. Weeks 9-24): once every 2 weeks
	  • Cycle 7 and beyond (i.e. Week 25 and beyond): once every 4 weeks

Cancer Treated	• Multiple myeloma
Burden of Illness	• In 2015, the estimated incidence of multiple myeloma was 2,700, with an estimated 1,400 Canadians dying of the disease • Multiple myeloma is incurable, with the average age of diagnosis being 62 years
Current Standard Treatment	All appropriate multi-agent chemotherapy regimens, including but not limited to: Immunomodulatory drugs (IMiDs): • Pomalidomide • Lenalidomide Proteasome inhibitors (PIs): • Bortezomib • Carfilzomib Other later-generation PIs and IMiDs • Best supportive care
Limitations of Current Therapy	• Multiple myeloma is incurable and an estimated 1,400 deaths were attributable to the disease in 2015. Despite the improvement in clinical outcomes with the use of PIs and IMiDs, patients eventually become resistant to these agents. The prognosis for these patients is poor and treatment options, other than supportive care, are limited

ABOUT THIS RECOMMENDATION

pERC Membership During Deliberation of the Initial Recommendation

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. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
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
Danica Wasney, Pharmacist

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

- Valerie McDonald, who did not vote due to her role as a patient member alternate.

pERC Membership During Deliberation of the Final Recommendation

Recommendations are made by 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
Dr. Marianne Taylor, Oncologist
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Carole McMahon, Patient Member
Valerie McDonald, Patient Member Alternate
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Karen MacCurdy Thompson, Pharmacist
Danica Wasney, Pharmacist

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

- Kelvin Chan and Scott Berry, who were not present for the meeting
- Valerie McDonald, who did not vote due to her role as a patient member alternate.

Avoidance of conflicts of interest

All members of 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 for multiple myeloma, through their declarations, three 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 pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

Use of this Recommendation

This Recommendation from the pCODR Expert Review Committee (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

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